SYNDROMES OF THE HEAD AND NECK

FOURTH EDITION

Robert J. Gorlin
M. Michael Cohen, Jr.
Raoul C. M. Hennekam

Syndromes of the Head and Neck, Fourth Edition

ROBERT J. GORLIN, D.D.S., M.S., D.Sc.
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Syndromes of the Head and Neck

Fourth Edition

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To Marilyn,
Guilan,
and Carol
without whose love and
devotion, this edition
should not have seen
the light of day.

Robert J. Gorlin

Foreword

I have always regarded the concurrence in 1964 of my first faculty appointment in Madison with the appearance of the first edition of Gorlin's magisterial *Syndromes of the Head and Neck* as an especially happy event. Since then I have never been far from one of the subsequent editions in office or clinic or any place else in the world where I have taught or consulted. "*The Syndromes*. . . .", as it is known throughout the world, has become the most useful book in clinical genetics, rivaled perhaps only by McKusick's *OMIM*. The number of contributors to this immensely useful volume is increasing with each edition; however, the judgment, experience, and weight of authority that guarantee the book's value still largely derive from Drs. Gorlin and Cohen, undisputed leaders in the field of oral genetics and oral pathology.

In this edition, they drew on the enthusiasm, experience, and energy of Dr. Raoul Hennekam from Amsterdam. Dr. Hennekam has a well-deserved world reputation as a clinical geneticist. He will assume the helm in future editions.

The millennial date of this fourth edition is a propitious historical landmark, the year 2000 marking also the 200th anniversary of the science of morphology, the 100th of the rediscovery of Mendel's "laws," and the completion of the human genome project. The shaping by Goethe (1796) and Burdach (1800) of morphology as the science of the form, formation, transformation, and malformation of living beings on the basis of historical and developmental considerations dramatically changed the world view of biologists early in the 19th century. It led to the essential, indeed crucial, distinction between structural analogy and homology. Homology became, in Darwin's view, "the most interesting department" of morphology and "may almost be said to be [the] very soul" of natural history. Thus, it was natural selection, not descent, that was the radical innovation in thought in *The Origin of Species*. . . . (1859). Let it be remembered that much, perhaps most of morphology of the 19th century (including modern embryology, the cell theory, pathology, cytology, the study of mitosis, meiosis and chromosomes, evolution, and heredity—the inheritance of form) was the creation of physicians who frequently performed their own autopsies and pathological studies (as do Drs. Gorlin and Cohen) and also studied a multitude of malformed animals and fetuses. Craniofacial anomalies early became a major concern of these physician morphologists who introduced terms still familiar to all of us, such as teratology, otocephaly, anencephaly, and holoprosencephaly. Thus, it is no surprise that Drs. Gorlin, Cohen, and Hennekam, continuing in this richly productive 200-year tradition of craniofacial morphology, have provided some of the most authoritative discussions of these anomalies in the pages of this book.

Mendel was a true child of his age, whose work was initially motivated by a search for the cause of form, i.e., the inherited causes of development. Contrary to the views of many who have not read his original paper of 1865 (1866), Mendel did have a word for what Johannsen later (1909) called "the gene," namely: ". . . .die bildungsfähigen Elemente. . . .," i.e., the form-giving or morphogenetic elements present in haploid form in germ cells. The fact that these elements segregated and freely recombined astounded and delighted him and led him far from his original goal of wanting to understand the causal nature of development and of evolution. It was not until the end of what in biological circles has sometimes been called the Mendelian century that Mendel's original goal was realized in the reunion of all of the branches of morphology through the intermediacy of molecular technology, which at last made it possible to determine the function of these segregating, form-giving elements under normal and abnormal circumstances. And while "*The Syndromes*. . . ." gives hundreds of examples of the abnormal pleiotropic function of genes, including molecular data on many craniofacial syndromes, it must be remembered that nothing can happen in development, whether normal or abnormal, that has

not been made possible by evolution, and that far beyond even the "invention" of the neural crest during the evolution of vertebrates, the beginnings of development are to be found in those pre-Cambrian times, over 600 million years ago, that allowed the emergence of all living metazoans.

This book, more than any other in clinical genetics over the last few decades, has shown us the best results and also the limitations of nosology based on phenotype analysis. During evolution development became severely constrained into a remarkably impoverished set of final morphogenetic outcomes which, if abnormal, must all be highly heterogenous given the ratio of tens of thousands of genes to only a handful of developmentally highly correlated parts of the craniofacial region. The fact of inductive molecular *parsimony*, whereby the same gene acts in different permutations with other transcription or growth factors at different times in several embryonic primordia and perhaps even in later histogenesis of several tissues, explains the phenomenon of pleiotropy that is ubiquitous in clinical morphology. This biologic fact or hypothesis has to be considered in every genetic disorder and is addressed masterfully in "*The Syndromes*. . . .," extending its value far beyond the head and neck into *all* parts of the human body.

The highly successful application of molecular methods to a causal analysis of development and the completion of the human genome sequencing project is expected to redress, at last, the half-century imbalance between genotype and phenotype research—not opposing but complementary scientific efforts—so as to give ever-increasing clarity to the phenomena of heterogeneity, variability, homology, penetrance, and expressivity, issues addressed with ever-increasing urgency in the successive editions of this book. The introduction of many new molecular insights in the Fourth Edition is a harbinger of the future of clinical morphology and a most valuable resource for all of its practitioners. For undertaking and continuing this labor of love, biomedicine owes Drs. Gorlin, Cohen, and Hennekam a profound debt of gratitude.

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Foreword to Third Edition (1990)

Syndromologists, medical geneticists, and (even more so) other health workers have found it increasingly difficult to keep up with the vigorous growth of knowledge about syndromes. The distinguished teratologist Josef Warkany wrote "with the increasing interest in congenital malformations a syndrome fever is spreading through many specialties, and it is difficult for editors of medical journals and readers to separate spurious from durable and meaningful syndromes." That was in 1971 (Congenital Malformations: Notes and Comments). Thus, there is a need for judicious sifting, organizing, and synthesis of the plethora of syndromic literature into meaningful patterns. The first edition of this volume was welcomed by those who were even then beginning to feel this need. Its breadth and depth reflected the encyclopedic knowledge and judgment of Robert Gorlin, an extraordinary phenomenon. And it was by no means limited to the head and neck! To keep up with the burgeoning growth of knowledge, the second edition added another extraordinary repository of syndromic lore, in the form of Michael Cohen. In the present edition, the breadth and depth of the syndrome data base have been further extended by the otolaryngologic knowledge of L. Stefan Levin and by specific chapters from no fewer than 18 collaborators. The result is a truly encyclopedic work, containing descriptions of the phenotypic spectrum, epidemiology, mode of inheritance, and pathogenesis of nearly 700 syndromes. McKusick's Catalogue has more entries, since it covers all Mendelian disorders, not just syndromes, but this volume includes non-Mendelian syndromes as well, and in far more depth. The several computer-aided syndrome-diagnosis systems now available are useful as diagnostic aids, but do not provide as exhaustive descriptions of phenotype or as critical analyses of the literature. This book will be welcomed as an essential component of the knowledge base for the clinical geneticist and others confronted with syndromes. It is an honor to be associated with it, even in this peripheral way. I am certainly

looking forward to having it on my bookshelf, and hope that I will be able to persuade my students to let me read it now and then!

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Foreword to the Second Edition (1976)

The first edition of this book was the pioneering text for this segment of medicine. I vividly recall the excitement upon first reading the book in 1964. At last!—here was a cohesive authoritative text which portrayed the majority of syndromes which had been recognized at that time. Though entitled *Syndromes of the Head and Neck*, it covered all known features of each disorder in a nonspecialized and balanced manner, including the natural history, etiology, differential diagnosis, and pertinent references for each disorder. The field of syndromology has expanded since that time. The number of recognized disorders set forth in the book has more than doubled, and the knowledge has been updated on the original syndromes. A third person, M. Michael Cohen, Jr., has been added to the authorship of this expanded work on syndromes. Thus, this second edition is a most welcome addition for all those who work with, or are interested in, syndromes of malformation. Many children and their parents will be the indirect beneficiaries of this text. For our own patients, we sincerely thank the authors for this monumental work.

David W. Smith, M.D.*
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Foreword to the First Edition (1964)

The authors of this monograph are keen observers and ardent students of disease in the best tradition of Jonathan Hutchinson, Parkes Weber, and other clinicians of an earlier generation. Many of the diseases on which they have concentrated their attention are rare, but for several reasons no less important. Although these diseases occur infrequently, they constitute in the aggregate a significant portion of medicine. Most of them are congenital malformations or disorders loosely called constitutional; many of them are genetic either in the classic Mendelian sense or as chromosomal aberrations. It is a truism that this body of diseases has come to represent a main challenge to medicine now that infectious and nutritional diseases are better understood and controlled. That the disorder from which he suffers is rare is no consolation to its victim. The first step in the understanding of these conditions must be an accurate and full clinical description.

The careful study of exceptional cases can contribute importantly to medicine and to biology in general. Bateson, a famous early geneticist, said "Treasure your exceptions!" In 1657 William Harvey, of blood circulation fame, eloquently expressed the usefulness of the study of rare diseases:

> Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of Nature by careful investigation of cases of rarer forms of disease. For it has been found, in almost all things, that what they contain of useful or applicable nature is hardly perceived unless we are deprived of them, or they become deranged in some way.

Professors Gorlin and Pindborg have done a valuable service to oral pathology and medicine in general by collating their extensive personal experiences and the widely scattered reports of the literature. With skill they have synthesized and interpreted. The fundamental relationship between disorders separately reported, usually under diverse labels, has been carefully explored and convincingly demonstrated in a number of instances. For this, all medicine is in debt of the authors. Their monograph is a particularly valuable addition to the English-language medical

*Deceased

literature because they have mined much ore previously not available. With their linguistic prowess they have been able to study in the original a considerable body of literature previously unknown to most of us. Specialists such as ophthalmologists, dermatologists, and dentists have always been in the enviable position of being able to study disease with simple clinical methods. Fortunately many of these specialists, appreciating the relationship of systemic and constitutional disorders to the manifestations which fall within their purview, have made worthwhile contributions to pathology. With this monograph, Gorlin and Pindborg have joined this company. Their work will be valued, not only by dentists, but by all the numerous medical specialists who are called on to care for patients with these disorders.

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Preface

A number of the chapters have been reviewed by individuals who have far greater expertise than any of the editors. To these individuals, generous with their time, we express our profound indebtedness. We truly appreciate the effort and expertise that they have lent to improve the text.

Alphabetically, they include: Mary Ahrens, Judith Allanson, Susan Berry, Beth Ann Bloom, David M. Brown, Suzanne G. Cassidy, Vazken Der Kaloustian, Charis Eng, Vickie Matthias Hagen, Judith G. Hall, Betsy Hirsch, Ioannis Koutlas, Bonnie LeRoy, Brian Michalowicz, Maximilian Muenke, John M. Opitz, Mary Ella Pierpont, Andrew Read, Nathaniel Robin, Karol Rubin, Heddie O. Sedano, Karel Vrticka, Matthew Warman, and Chester B. Whitley. We are profoundly indebted to the staff of the Biomedical Library of the University of Minnesota. Among these, Delbert Reed is the consummate librarian. He has never failed to exhibit unbridled enthusiasm for any literature search, however hopeless. In Amsterdam, the same job was done by Hannelore De Groot, who always succeeded in finding the publications immediately. We are honored that John Opitz has agreed to write the Foreword to this edition. For continuity with earlier editions, we are reprinting the Forewords from the first edition (Victor A. McKusick), the second edition (David W. Smith), and the third edition (F. Clarke Fraser).

This fourth edition of *Syndromes of the Head and Neck* was written at a point when each new weekly or monthly publication presented us with additional molecular information. It was also written at a time when a spate of new syndromes appeared each month. We tried to be as catholic in our approach as possible, the limiting factor being that the facies must be unusual—hence the title that is so well known that change of the name was not deemed wise. It took approximately five years of almost full-time labor to bring this edition to fruition. Based on our experience, it would have been better to have started the fourth edition upon completing the third, and it is our sincere hope, because of the burgeoning of material, that Raoul Hennekam who will assume the helm for further editions will be able to assign each chapter to a different author who will update the material monthly. We have added new material up to June 2001.

Although we have tried to group syndromes into useful categories, many conditions have facets that span several categories and assignment may appear arbitrary. We have added another chapter: Syndromes Involving the Eye, and have, in part, reassigned some entities to it.

An attempt was made in this edition to address the molecular aspects of the syndromes, if known. In many cases, gene mapping has been accomplished, but the nature of many of the genes has not yet been precisely determined.

Syndrome delineation has burgeoned. The 1964 edition contained 580 pages, the 1990 edition had about 1000 pages. The present edition has about 1275 pages. In 1972, we tabulated 72 syndromes of orofacial clefting. Within the confines of these pages, we have tallied over 350 such syndromes.

Our personal desire for a one-volume text was accomplished by altering typographic style, removing redundant illustrations, and deleting orthodontic measurements in the Appendix. Raoul Hennekam has vastly improved the index, and we have added sections on helpful web sites and computer database systems.

Production of this edition was made smooth by Jeffrey House, Nancy Wolitzer, and Susan Hannan of Oxford University Press. Their suggestions and respect for our opinions have made the task so much easier.

This edition and the second edition of *Hereditary Hearing Loss and Its Syndromes* were made possible by the unlimited generosity of Guilan Norouzi.

For the past one and one-half decades, one of us (RJG) has been fortunate to have the editorial assistance of Carol Bauer Rose. In part she was hired because of her experience in many aspects of book production. Very few know what it is like to devote five years of intense effort toward developing a text without major flaws—at least grammatical ones. Carol has agonized about semicolons and clear phraseology. The scientific errors are ours. We are also grateful to Ruth E. MacLean and Belinda Leeuwenhage for their editorial help on this text.

Minneapolis R. J. G.
Halifax M. M. C.
Amsterdam R. C. M. H.

Contents

Syndromes of the Head and Neck

Chapter 1
Deformations and Disruptions

Craniofacial deformations

Congenital deformations of the head and neck are common, and most resolve spontaneously within the first few days of postnatal life. When they do not, further evaluation may be necessary to plan therapeutic interventions (1,2,4,5,9) that may prevent long-term consequences. The distinction between deformations and malformations and its implications are discussed elsewhere (6,8,9).

Approximately 2% of infants are born with extrinsically caused deformations that usually arise during late fetal life from intrauterine constraint. Approximately 30% of deformed infants have two or more deformations. Deformed infants tend to show catch-up growth toward their genetic potential during the first few postnatal months after release from the intrauterine constraining environment (8). Table 1–1 indicates some of the known causes, both extrinsic and intrinsic, of deformations. Deformations considered here include nasal, auricular, and mandibular deformities, torticollis, nonsynostotic plagiocephaly, craniosynostosis caused by intrauterine constraint, and abnormal fetal presentations, which may result in craniofacial deformation.

Table 1–1. Causes of deformations[a]

Extrinsic
Mechanical
Unstretched uterine and abdominal muscles
Small maternal size
Amnionic tear
Unusual implantation site
Uterine leiomyomas
Unicornuate uterus
Bicornuate uterus
Twin fetuses
Intrinsic
Malformational
Spina bifida
Other central nervous system malformations
Bilateral renal agenesis
Severe hypoplastic kidneys
Severe polycystic kidneys
Urethral atresia
Functional
Neurologic disturbances
Muscular disturbances
Connective tissue defects

[a] From MM Cohen Jr, The Child with Multiple Birth Defects, 2nd ed, Oxford University Press, New York, 1997.

Nasal deformation. Deformation of the nose may be associated with face presentation, transverse lie, oligohydramnios, or severe fetal crowding. In most instances, the nose will be compressed and/or deviated (Fig. 1–1), which may make it appear short. Occasionally the nasal cartilage is dislocated from the vomerine ridge, resulting in nasal asymmetry with slanting of the columella. The naris on the side toward the dislocated cartilaginous septum will appear small (9).

Auricular deformation. Overfolding of the superior rim of the helix and other alterations in the cartilaginous auricle are frequently caused by fetal constraint. The ear may be flattened against the head by oligohydramnios, and prolonged pressure against the auricle may result in overgrowth. Enlarged, flattened ears have frequently been associated with renal agenesis as part of *Potter sequence*. When one ear is exposed to more pressure than the other, they may be asymmetric. Occasionally, with prolonged breech presentation, particularly when associated with tilted head position in utero, the lower auricle may be lifted by pressure from the shoulder (2).

Mandibular deformation. Micrognathia may result from limitation of mandibular growth caused by late gestational constraint, which compresses the chin against the chest. With prolonged compression, there may be a pressure indentation on the superior aspect of the anterior thorax. Marked compression may also lead to pressure necrosis along the edges of the anterior neck creases (Fig. 1–2). Such necrosis may extend

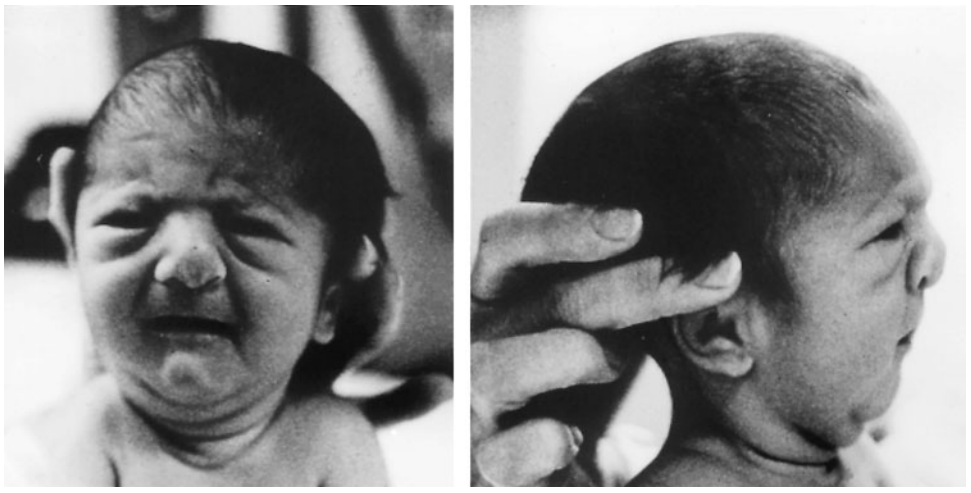
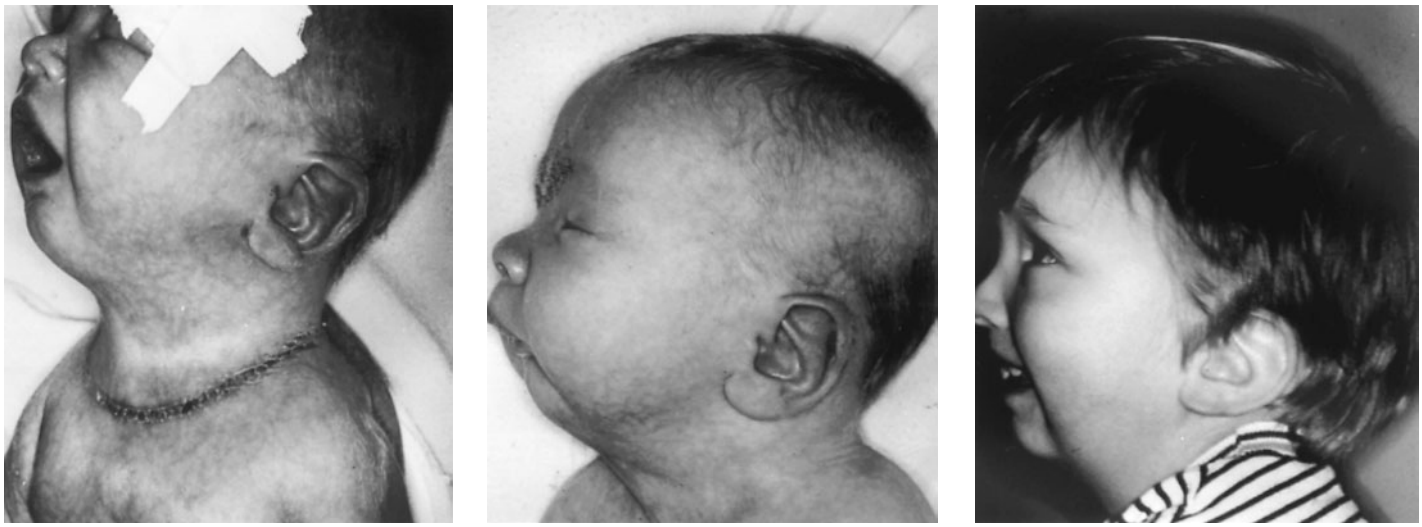


Fig. 1–1. *Craniofacial deformations*. Compression of the face, particularly the nose, from prolonged transverse presentation with the head retroflexed and the face compressed against the lateral wall of the uterus. (From JM Graham Jr, Smith's Recognizable Patterns of Human Deformation, 2nd ed, W.B. Saunders, Philadelphia, 1988.)



A B C

Fig. 1–2. *Craniofacial deformations*. Extensive compression from persistent leakage of amnionic fluid documented by ultrasound from 17 weeks gestation to birth. (A) Marked mandibular deformity at 3 days of age. Note necrosis along neck creases (which healed with scarring). (B) Extensive mandibular deformation still evident at 3 weeks of age. (C) Partial resolution of mandibular deformity by 2.5 years of age. (From JM Graham Jr, Smith's Recognizable Patterns of Human Deformation, 2nd ed, W.B. Saunders, Philadelphia, 1988.)

deeply enough into the dermis to result in scarring. When micrognathia occurs on a deformational basis (rather than on a hypoplastic, malformational basis), there is usually catch-up growth postnatally once the fetus is no longer in the constraining intrauterine environment (6,9).

When mandibular compression is asymmetric, it can produce mandibular asymmetry. Most commonly, this results from the shoulder being thrust up under the mandible with prolonged breech or oblique presentations. A prominent sulcus impression may occur along the neck from shoulder compression (6,9).

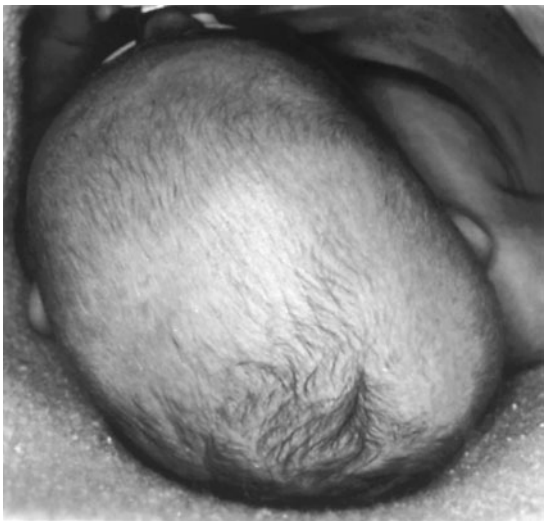
Torticollis. Congenital torticollis usually occurs together with an obliquely shaped plagiocephalic head and mandibular asymmetry. Often this results from the head being caught askew prenatally. Muscular torticollis may result from constraint on one side of the neck causing ischemia to the central portion of the sternocleidomastoid muscle followed by secondary fibrosis. A fusiform fibrous mass may sometimes be palpable within the muscle, a sternocleidomastoid "knot" or "tumor." Asymmetric shortening of one sternocleidomastoid muscle may lead to aberrant head posture. With persistent torticollis and resultant head posture, craniofacial deformation may be progressive (4,5,9).

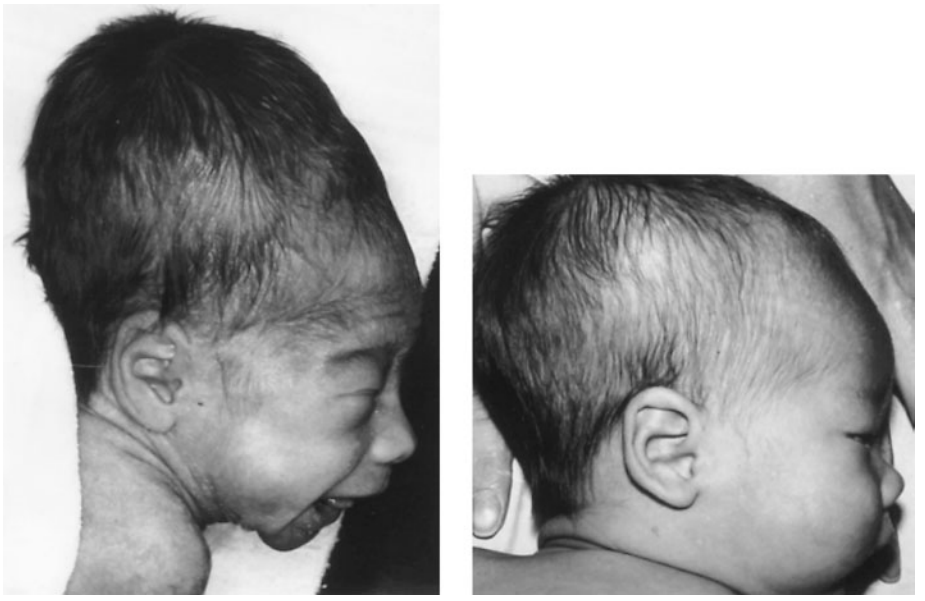
Torticollis-caused plagiocephaly. When persistent sternocleidomastoid torticollis or asymmetric cervical vertebral anomalies result in the head resting in an asymmetric position, oblique molding results in the head being rhomboid shaped, with frontal prominence on the preferred side together with contralateral prominence of the occiput (Fig. 1–3). With marked cranial distortion, the eyes and ears may be asymmetrically placed and the mandible may be asymmetrically deformed. If torticollis remains uncorrected, plagiocephaly may be progressive (4,5,9).

Deformation-induced craniosynostosis and plagiocephaly. Fetal head constraint has been implicated as an important cause for some instances of sagittal, coronal, and metopic craniostenosis. In such instances, craniosynostosis is not associated with other malformations and the condition is not familial. With deformational synostosis, fetal head constraint results in lack of growth stretch across the suture, enhancing liability toward synostosis (7,9,11–13,15). Experimental evidence for this interpretation was provided by Koskinen-Moffett (16), who produced prenatal synostosis of the coronal and squamosal sutures in mouse pups by closing the uterine cervix with a surgical clip to delay birth for several days, which crowded the fetuses.

Plagiocephaly is etiologically and pathogenetically heterogeneous. Well-known types include synostotic anterior plagiocephaly (unilateral coronal synostosis), synostotic posterior plagiocephaly (unilateral lambdoid synostosis), deformational anterior plagiocephaly, and deformational posterior plagiocephaly. Of these, deformational plagiocephaly is common and lambdoid synostosis is rare. Deformational posterior plagiocephaly has increased dramatically since the 1992 recommendation of the American Academy of Pediatrics for supine infant sleeping to reduce the risk of sudden infant death syndrome. Unfortunately, deformational posterior plagiocephaly has sometimes been diagnostically confused with lambdoid synostosis, resulting in unnecessary surgery when helmet

Fig. 1–3. *Craniofacial deformations*. Four and one-half month-old infant with persistent head turn to the left caused by cervical and thoracic vertebral anomalies. Note resultant marked plagiocephaly. (From JM Graham Jr, Smith's Recognizable Patterns of Human Deformation, 2nd ed, W.B. Saunders, Philadelphia, 1988.)





A B

Fig. 1–4. *Craniofacial deformations*. (A) Extensive vertex molding at birth. (B) Self-resolution by 2-3 months of age. (From JM Graham Jr, Smith's Recognizable Patterns of Human Deformation, 2nd ed, W.B. Saunders, Philadelphia, 1988.)

therapy would have been effective if introduced early enough. Surgery may be indicated in nonresponders to helmet therapy and in those who are still asymmetric after 1 year of age. Differentiation of deformational vs. synostotic plagiocephaly has been discussed extensively by Cohen and MacLean (7).

Abnormal fetal presentation. A vertex presentation is most common and transient molding of the head occurs in the birth canal. With prolonged engagement, normal vertex birth molding may be accentuated (Fig. 1–4). The prognosis for a complete return to normal form in such instances is excellent (9).

With prolonged pressure on the vertex region, particularly with a first-born infant, a large fetus, or a small mother, diminished mineralization of the cranium may result. Mild vertex craniotabes occurs in 2% of neonates, with more extensive cranial softening occurring less frequently (Fig. 1–5). The presence of normal cranial bone along the sides of the calvaria helps distinguish craniotabes from defective calvarial mineralization resulting from inherited metabolic or connective tissue disorders such as hypophosphatasia or osteogenesis imperfecta. Vertex craniotabes, resulting from late fetal head constraint, usually resolves spontaneously within the first few postnatal months (10).

Breech presentation is the most common abnormal fetal presentation, occurring in 6% of all pregnancies; one-third of all deformations occur in breech babies (3). In Dunn's series (8), 32% of all deformations in newborns were associated with breech presentation. Genu recurvatum (100%), hip dislocation (50%), postural scoliosis (42%), mandibular asymmetry (20%–25%), torticollis (20%–25%), and talipes equinovarus (20%–25%) are all related to breech presentation.

Prolonged breech presentation may give rise to unusual molding of the fetal head, resulting in dolichocephaly with a prominent occipital shelf (14) (Fig. 1–6). Vaginal delivery of a breech fetus with hyperextended head is associated with significant morbidity and mortality (1). Serious consequences include trauma to the spinal cord or brachial plexus, compression of the vertebral artery with cerebral ischemia, or severance of the pituitary stalk with consequent hypopituitarism. Thus, the current trend is toward cesarean delivery of fetuses with breech presentation.

Transverse lie is less frequent than breech presentation, occurring once in every 300–600 deliveries. It is more common in multiparous women, and it results in problems similar to those associated with breech presentation. Thus, unresolved transverse presentation is also an indication for cesarean delivery. Lateral constraint of the fetus may flatten the face, limit mandibular growth, and cause cephalic retroflexion and truncal scoliosis with positional foot deformities. Figure 1–1 demonstrates remarkable facial compression associated with prolonged transverse lie. Such compression is usually only temporary.

Face and brow presentations (Fig. 1–7) may also temporally compress the presenting part. Face presentations occur about once in 500 births and

Fig. 1–5. *Craniofacial deformations*. Prolonged vertex presentation at least 4 weeks prior to delivery. Large area of craniotabes represented by cross hatching. Self-resolution by 2 months of age. (From JM Graham Jr, Smith's Recognizable Patterns of Human Deformation, 2nd ed, W.B. Saunders, Philadelphia, 1988.)

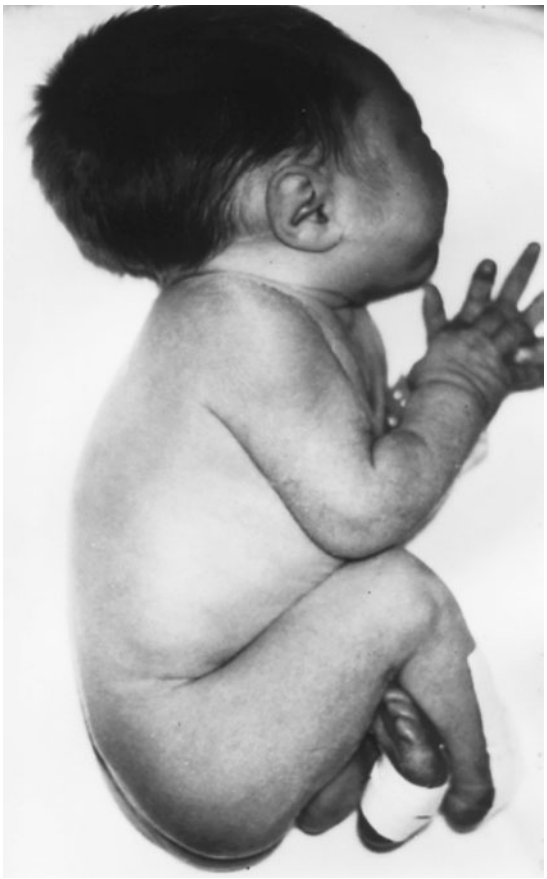
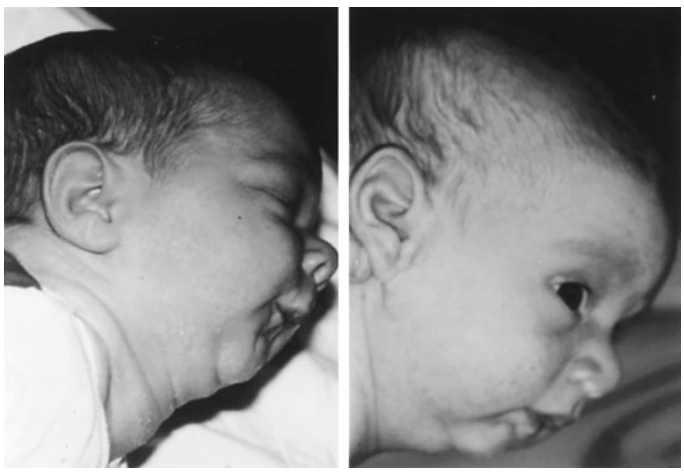


Fig. 1–6. *Craniofacial deformations*. Prolonged breech presentation resulting in prominent occipital shelf. Resultant equinovarus foot deformities treated by taping. (From JM Graham Jr, Smith's Recognizable Patterns of Human Deformation, 2nd ed, W.B. Saunders, Philadelphia, 1988.)

Fig. 1–7. *Craniofacial deformations*. Prolonged face presentation during the last 2 months of gestation. (A) Nasal and mandibular compression. (B) Partial self-resolution by 6 weeks of age. (From JM Graham Jr, Smith's Recognizable Patterns of Human Deformation, 2nd ed, W.B. Saunders, Philadelphia, 1988.)



A B

brow presentations are even less common. Only anterior positions can be delivered vaginally because of the inability of the neck to further extend in the posterior position. Compression of the mandible may temporarily restrict its growth, and compression of the neck against the pubic ramus during vaginal delivery may cause fracture of the trachea or larynx. Thus, cesarean section should be given consideration in this situation. It should also be noted that 90% of babies born in face or brow presentation are infants with major malformations, with anencephaly being the most common. For otherwise normal infants with facial features such as those shown in Figure 1–7, the prognosis for complete return to normal form is excellent.

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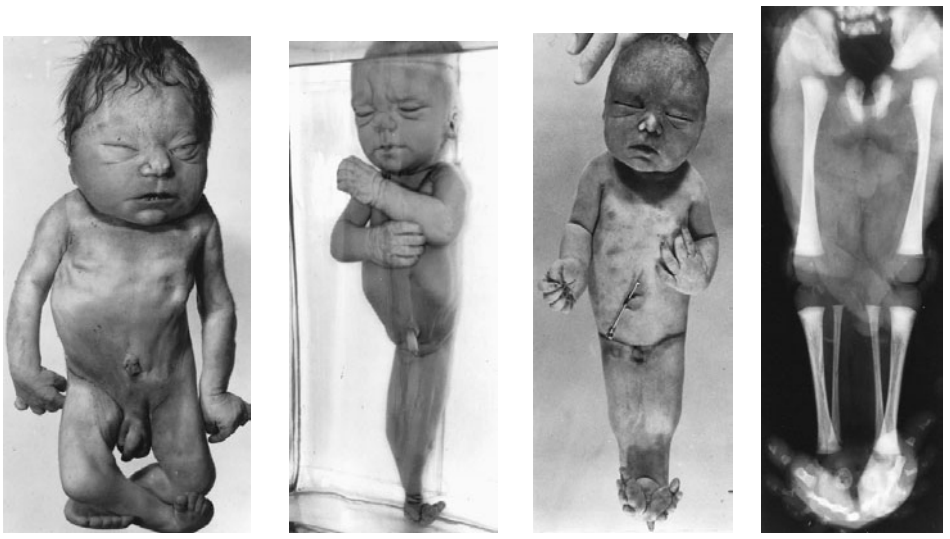
Potter sequence (oligohydramnios sequence)

Potter sequence is characterized by compression deformities of the face and limbs (Fig. 1–8A), pulmonary hypoplasia, wrinkled skin, and growth restriction resulting from any pathologic condition that leads to oligohydramnios (42,95,151), such as bilateral renal agenesis (110,113), cystic dysplasia (10), severe polycystic kidneys (43,60,103,114), urinary tract obstruction (4,79), or amnionic leakage (20,79,150). In addition to diverse renal pathology, more extensive malformations may occur in some instances (35), the severe caudal axis defect sirenomelia (Figs. 1–8B–D) being the most extreme example (15,29,37,52,77,80,103,122,143, 146,158). Several unusual experiments of nature have been recorded in which the extrarenal features of Potter sequence are not manifest (4,79, 94,150) (Fig. 1–9).

Originally described by Potter (113–116) in association with bilateral renal agenesis, Potter sequence is now known to be extremely heterogeneous, both etiologically and pathogenetically. The term "Potter sequence" or "oligohydramnios sequence" best describes the condition, with other terms, such as "Potter syndrome" (44,45,84,89,110,129, 165,167) (the condition is not a true syndrome sui generis, but may occur as a component part of many different syndromes or may occur nonsyndromically), "bilateral renal agenesis" (48,113–115,124,148) (too restrictive), and "renofacial dysplasia" (18,52,58,60,64,105,106,156) (not specific enough), now being obsolete.



A B C D

Fig. 1–8. *Potter sequence*. (A) Potter sequence with compressed facial appearance and limb positioning deformities. (B) Sirenomelia, a severe caudal axis malformation sequence in which kidneys and genitals are missing. Note Potter facies and upper limb deformities. (C, D) Another example of sirenomelia. (A from DW Smith, Recognizable Patterns of Human Malformation, 3rd ed, W.B. Saunders, Philadelphia, 1982. B courtesy of the Warren Anatomical Museum, Harvard University. Montage from MM Cohen Jr, The Child with Multiple Birth Defects, 2nd ed, Oxford University Press, New York, 1997.)

With Potter sequence, malformations of the genitourinary tract, lumbosacral spine, and lower intestinal tract are common (35) and constitute, in Opitz's terminology (107), a developmental field defect. Duncan et al (38) noted the frequent association of müllerian duct anomalies, renal agenesis, and cervical and thoracic vertebral anomalies, and coined the term "MURCS association."

Extensive reviews have been carried out by Curry et al (35), who analyzed 80 cases, Schmidt et al (140), who studied 23 families, and Roodhooft et al (126) and Al Saadi et al (3), who studied 41 and 21 families, respectively. Approximately 80% of Potter sequence cases are nonsyndromic (35), with the remaining 20% occurring in many different syndromes and associations. They may be chromosomal, autosomal dominant, autosomal recessive, X-linked, teratogenic, disruptive, or of unknown origin. They have been reviewed extensively by Gorlin et al (54) and Van Allen (155) and in many specific articles (2,9,11,12,13,21,25, 29–31,33–36,40,41,44,45,49,53,54,57,63,65,68–70,73,75,76,78,83–85, 88,93,98–101,111,112,118,128–130,133,134,138,141,142,145,147,153, 154,163–166) (Table 1–2).

The complex and variable renal pathology found with Potter sequence has been reviewed by Bernstein and associates (9–11). In 80 retrospectively ascertained cases, Curry et al (35) found bilateral renal agenesis in approximately 21%, cystic dysplasia in approximately 48%, obstructive uropathy in approximately 25%, and other forms of renal pathology in the remaining 6%.

The prevalence of bilateral renal agenesis has been reported to vary from 1 in 3000 to 1 in 9000 births, predominating in males by a ratio of 2:1 or 3:1. The prevalence of unilateral renal agenesis at necropsy varies from 1 in 600 to 1 in 1000 (4,27,47,77,110,116,157). Genetic evidence is accumulating to indicate that bilateral renal agenesis and cystic dysplasia should be nosologically grouped together. In several documented instances, bilateral renal agenesis has been observed in one sib and cystic dysplasia with or without unilateral renal agenesis has been found in the other sib (22,27,35,61). Affected sibs with either bilateral renal agenesis or cystic dysplasia have been observed on numerous occasions (7,20,22,23,32,61,89,94,96,97,102,109,124,126,127,132, 135–137,161,162). Autosomal dominant inheritance with reduced penetrance and variable expressivity is consistent with affected families in which a parent with unilateral renal agenesis has children with either unilateral or bilateral renal agenesis (12,16,20,23,59,82,103,134,168); Buchta et al (20) called the condition "hereditary renal adysplasia." In some of the affected families, second- and third-degree relatives as well as first-degree relatives of probands with bilateral renal agenesis had unilateral renal agenesis (12,23,67,82,97). Roodhooft et al (126) ultrasonically investigated the parents and siblings of 41 probands with bilateral renal agenesis and/or cystic dysplasia and found renal abnormalities in 9%. McPherson et al (97) suggested that hereditary renal adysplasia was more common than previously supposed and may account for most recurrences of bilateral renal agenesis, even when the parents are normal. They calculated penetrance to be between 50% and 90%. Offspring and affected or obligate heterozygotes have an empiric risk for bilateral severe involvement of 15%–20%. Other manifestations of the gene may include cryptorchidism in males and müllerian duct abnormalities in females (12,20,23,136).

Al Saadi et al (3) obtained family histories and performed renal ultrasonography on parents and sibs of 21 probands with renal dysplasia. Among the probands were 16 bilateral and 5 unilateral cases. Specifically excluded from this study were cases of bilateral renal agenesis and known syndromes, both chromosomal and nonchromosomal, with renal dysplasia. Empiric recurrence risk calculated from this family study was only 2.1%. Al Saadi et al (3) concluded that multicystic and aplastic types of renal dysplasia are usually sporadic and only rarely familial in contrast to other types of renal dysplasia identified in the literature as familial.

Obstructive uropathy as a cause of Potter sequence is also complex because of clinical and pathologic heterogeneity. Several possible sites for obstruction exist, particularly in the male. The marked male preponderance for obstructive uropathy is related to the more complex development of the male urethra (108). Clinical variation extends from early fetal lethality to survival with minimal morbidity. Recurrence of prune belly secondary to obstructive uropathy has most frequently involved affected brothers (19,51,56,82,123,159). Three affected sibs—two males and one female—have been reported in one instance (50). Affected male cousins (1,51) and three pairs of discordant monozygotic twins (71) have also been observed.

Family studies of probands with vesicoureteral reflux or duplication of the collecting system have shown that affected sibs have the same abnormality as the proband in 26%–34% of cases with reflux (39,72) and in 19% of cases with ureteral duplication (160). Twenty-three percent of parents with children who had ureteral duplication had similar findings (5,160). Finally, six pairs of twins and three pairs of sibs with posterior urethral valves were reviewed by Livne et al (87). Their data suggested that obstructive urinary tract abnormalities may result from an autosomal dominant gene with reduced penetrance.

Prenatal and perinatal factors. Amnion nodosum, breech presentation (40%), intrauterine death (25%), and antepartum hemorrhage (15%) have been found in a large series. Cesarean delivery is required in about 10% of cases. About half the infants are small for date of birth. Respiratory insufficiency is common (6,116,121).

Renal pathology. Renal pathology is quite variable. Bilateral renal agenesis is a valid diagnosis only when no renal tissue is found on gross

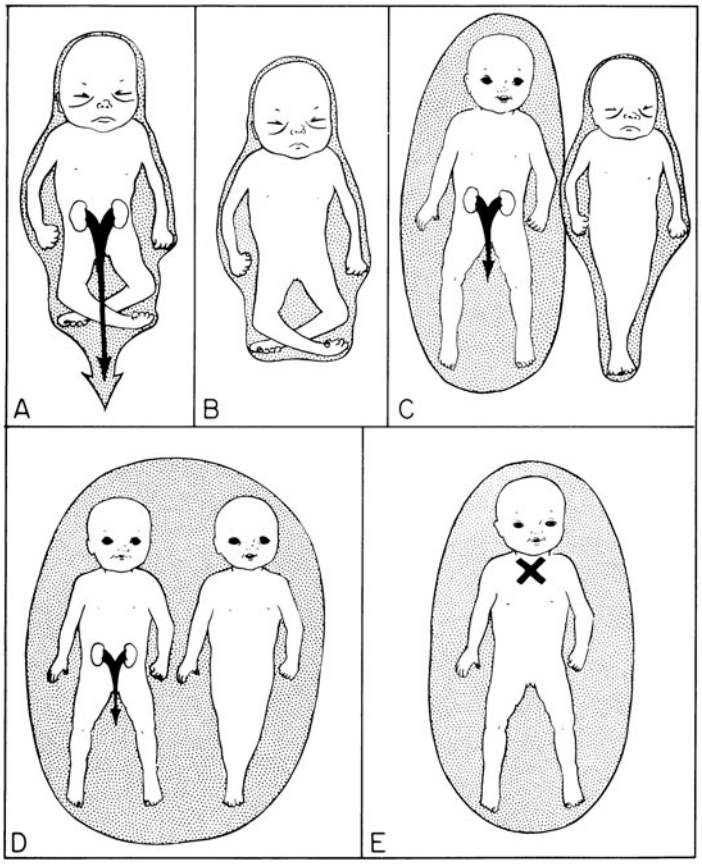


Fig. 1–9. *Potter sequence*. Oligohydramnios has different causes and, except under unusual circumstances, leads to facial and limb deformities of Potter sequence. Normally, small amounts of amnionic fluid cross the amnion as a transudate, but most amnionic fluid results from fetal urination. (A) Amnionic tear with chronic leakage of fluid leading to oligohydramnios, Potter facies, and limb positioning defects. Both kidneys are present and urination is normal. (B) Bilateral renal agenesis. (C) Monozygotic twins with separate amnions. Fetus on the left has kidneys, and enough fetal urine is contributed to amnionic fluid to protect fetus from deformities of Potter sequence. (D) Monozygotic twins sharing common amnionic sac. Note that although the fetus on the right has sirenomelia, Potter deformities are not present because the fetus on the left provides enough urine in amnionic fluid to protect the co-twin from deformities of Potter sequence. (E) Fetus has bilateral renal agenesis and therefore does not contribute fetal urine to amnionic fluid. Potter sequence based on neurologic swallowing deficit; amniotic fluid crossing the amnion remains external to the fetus, protecting it from extrinsic, deforming forces. (From MM Cohen Jr, The Child with Multiple Birth Defects, 2nd ed, Oxford University Press, New York, 2000.)

histopathologic examination. In such instances, the renal arteries and ureters are also absent and the bladder is hypoplastic, rudimentary, or absent (11).

In renal cystic dysplasia, abnormal renal organization may result from arrested development. Pathologic changes include primitive ducts, nests of cartilage, and primitive glomerular and tubular structures with aberrant relationships to one another. Kidneys may be enlarged, of normal size, or reduced in size. When involvement is unilateral, the other kidney is absent. Various abnormalities of the renal arteries, ureters, and bladder are common (10,11).

In infantile polycystic kidney disease, both kidneys are greatly enlarged with minute cysts on the surface. Medullary ductal dilatation is characteristic, and hepatic lesions with an increased number of portal bile ducts are observed (9).

Hypoplastic kidneys are distinguished from cystic dysplasia. The kidneys are extremely small but structurally normal with normal differentiation (35).

With intrauterine obstructive uropathy, the kidneys may be large and cystic, but may also be small, cystic, and dysplastic when destruction is a significant factor. Obstruction may occur in the distal urethra or the prostatic urethra. Atresia of the ureters is noted less commonly at the level of the bladder or the posterior urethral valves. Massive urinary ascites with distended abdomen may occur on occasion (35).

Medullary dysplasia is uncommon, but, when present, is reported to be accompanied by abnormalities of cortical tubular differentiation (35).

When Potter sequence results from amnionic leakage, both kidneys are normal (151).

Craniofacial features. A prominent semicircular skin fold extends from the inner canthus onto the cheek. When this fold is absent, some functioning kidney tissue may be present. Ocular hypertelorism has been observed. The nose may be blunted, with a turned-down nasal tip. A prominent crease is often present on the chin. The ears are low-set, posteriorly angulated, large, and floppy with cartilaginous deficiency. Micrognathia has been observed in most cases. Cleft lip and/or palate have been noted in a few instances (110,113–115).

Skin. The skin is very dry, loose, and wrinkled, giving a prematurely senile appearance (43,48,114). Markedly hypoplastic nails have been observed in some instances (35). Less commonly, neck webbing may be noted (35). Prune belly may be observed in some instances and does not necessarily correlate with the pathologic diagnosis of obstructive uropathy, nor does lack of abdominal wall distention exclude the presence of urinary tract obstruction. The wrinkled, prune-like appearance is found only in those without abdominal distention. Variable degrees of abdominal distention with abdominal muscle deficiency may be observed (35).

Skeletal and limb anomalies. Large fontanels and wide sutures have been observed in some instances (35). Flexion contractures at the knees and hips, spade-like hands, genu varum, and talipes equinovarus are common (106,114). Other findings are quite variable and may include hyperextensibility of the knees and other joints, camptodactyly, hypoplastic arm, hypoplastic leg, especially with obstructive uropathy, thoracic hemivertebrae, ischial and sacral aplasia or hypoplasia, other vertebral anomalies, and sirenomelia (1,4,24,35,46,55,66,86,104,106,108, 114–116,120,152).

Pathogenetic hypotheses about sirenomelia are particularly well reviewed by Stevenson et al (146). Their study indicated that sirenomelia and its commonly associated defects are produced by a vascular steal that diverts blood flow and nutrients from caudal structures of the embryo to the placenta. Arteries below the level of the steal vessel are underdeveloped and tissues dependent on them for nutrient supply fail to develop, become arrested in some incomplete stage of development, or are malformed. Thus, the single lower extremity in sirenomelia arises from failure of the lower limb bud field to be cleaved into two lateral masses by an intervening allantois.

Genital anomalies. Abnormalities may include cryptorchidism (33% of affected males and 100% of affected males with prune belly), gonadal hypoplasia, absent ductus deferens, absent seminal vesicles, rectovaginal fistula, absent uterus, bicornuate uterus, unicornuate uterus, blind-ended vagina, absent vagina, and masculinization of the external genitalia with 46,XX karyotype (4,12,20,26,35,91,115,116,124, 134,137).

Lungs. The lungs are hypoplastic with primitive or absent alveoli (67,114,116).

Gastrointestinal system. Imperforate anus, esophageal atresia, duodenal atresia, malrotation, Meckel diverticulum, and omphalocele have been observed (3,35,162).

Cardiovascular anomalies. Reported congenital heart defects include atrial septal defect, ventricular septal defect, patent ductus arteriosus, hypoplastic left ventricle, pulmonic stenosis, tetralogy of Fallot, pulmonary atresia, abnormal tricuspid valve, coarctation of the aorta, and single umbilical artery (3,35,162).

Table 1–2. Syndromes in which *Potter sequence* has been reported

Syndromes	Renal pathology	References
Chromosomal		
46, XX, −3, +der(3)t(3;11)(p25;ql3.2)mat	Hypoplastic kidney	Curry et al (35)
Deletion short arm 4	Bilateral renal agenesis	Mikelsaar et al (100)
Deletion short arm 5	Bilateral renal agenesis	Egli and Stalder (40)
Duplication long arm 6	Unilateral renal agenesis, unilateral cystic dysplasia	Curry et al (35)
Trisomy 7	Cystic dysplasia, enlarged kidneys	Pflueger et al (111)
Trisomy 8	Cystic dysplasia, enlarged kidneys	Juberg et al (73)
Trisomy 9	Other	Curry et al (35)
Trisomy 13	Cystic dysplasia, small kidneys	Gilbert and Opitz (53)
Deletion long arm 15	Cystic dysplasia, small kidneys	Clark (30)
Monosomy 16 mosaic	Obstructive uropathy	Harley et al (65)
Trisomy 18	Obstructive uropathy	Frydman et al (49)
Duplication short arm 20	Cystic dysplasia, small kidneys	
Trisomy 21	Bilateral renal agenesis	Egli and Stalder (40)
Duplication long arm 22	Bilateral renal agenesis, obstructive uropathy	Egli and Stalder (40)
Turner syndrome	Cystic dysplasia, small kidneys, obstructive uropathy	Lubinsky et al (92); Wolf et al (164)
XYY	Cystic dysplasia, small kidneys	Côté et al (33); Machin (93); Sutherland et al (148)
Familial marker chromosome	Bilateral renal agenesis	Ferrandez and Schmid (44)
Autosomal dominant		
Adult type polycystic kidney disease	Other	Proesmans et al (119); Shokeir (142)
Anal, ear, renal, and radial anomalies	Obstructive uropathy, other	Kurnit et al (85)
Beckwith-Wiedemann syndrome	Obstructive uropathy	Knight et al (78)
Branchio-oto-renal syndrome	Bilateral renal agenesis, cystic dysplasia, small kidneys	Fitch and Srolovitz (46); Melnick et al (99); Carmi et al (25)
EEC syndrome	Obstructive uropathy	Ivarrson et al (70)
Müllerian duct and renal anomalies	Renal agenesis	Biedel et al (12); Schimke and King (134)
Autosomal recessive		
Abnormal renal tubular differentiation, microcephaly, and joint hypermobility	Obstructive uropathy	Allanson et al (2)
Acrorenal mandibular syndrome	Bilateral renal agenesis	Halal et al (63)
Bilateral renal agenesis, lens prolapse, and cataracts	Bilateral renal agenesis	Biedner (13)
Cerebro-oculo-facio-skeletal syndrome	Bilateral renal agenesis	Preus et al (118)
Cryptophthalmos syndrome	Bilateral renal agenesis	Burn and Marwood (21); Codère et al (31); Kahler et al (75)
Cystic dysplasia, CNS malformations, and liver abnormalities	Cystic dysplasia, small kidneys	Miranda et al (101)
Elejalde syndrome	Cystic dysplasia, enlarged kidneys	Elejalde et al (41)
Familial renal tubular dysgenesis	Other	Saunders et al (133)
Glutaric aciduria, type II	Cystic dysplasia, enlarged or small kidneys	Kahler et al (76)
Infantile polycystic kidney disease	Other	Bernstein (9)
Meckel syndrome	Cystic dysplasia, enlarged kidneys	Mecke and Passarge (98)
Medullary dysplasia and cerebral dysgenesis	Other	Bernstein and Kissane (11)
Mesomelic dysplasia	Other	Rutledge et al (128)
Prune belly, pulmonic stenosis, retardation, and hearing deficit	Obstructive uropathy	Lockhart et al (88)
Renal cystic dysplasia and cerebellar dysgenesis	Cystic dysplasia, small kidneys	Kornguth et al (83)
Renal dysplasia and asplenia	Cystic dysplasia enlarged or small kidneys	Crawford (34)
Renal, genital, and middle ear anomalies	Bilateral renal agenesis	Schmidt et al (138); Winter et al (163)
Saldino-Noonan syndrome	Cystic dysplasia, enlarged kidneys	Spranger et al (145); Saldino and Noonan (130)
Smith-Lemli-Opitz syndrome, type II	Renal agenesis, cystic dysplasia	Curry et al (36)
Thymic aplasia, growth retardation, fetal death	Other	Shepard et al (141)
X-linked		
Lenz microphthalmia syndrome	Bilateral renal agenesis	Hoefnagel et al (68)
Teratogenic		
Diabetes mellitus	Bilateral renal agenesis or cystic dysplasia with small kidneys or obstructive uropathy	Grix et al (57)
Thalidomide	Bilateral renal agenesis or obstructive uropathy or other pathology	Pliess (112)
Disruptive		
Amnion rupture sequence	Normal kidneys	See amnion rupture sequence section
Unknown genesis		
Agnathia, tracheoesophageal fistula, duodenal atresia, and renal agenesis	Bilateral renal agenesis	Saito et al (129)
Congenital cystic adenomatoid malformation and bilateral renal agenesis	Bilateral renal agenesis	Krous et al (84)
Ear anomalies, cataracts, and cystic dysplasia	Cystic dysplasia, small kidneys	Wright et al (165)
Renal agenesis, cardiac anomalies, and skeletal defects	Bilateral renal agenesis	Holzgreve et al (69)
Renal dysplasia, mesomelia, and radiohumeral synostosis	Cystic dysplasia, small kidneys	Ulbright et al (155)
Renal dysplasia, pancreatic fibrosis, meconium ileus, and situs inversus	Cystic dysplasia, small kidneys	Yoshikawa et al (166)
Renal hypoplasia and ectrodactyly	Renal hypoplasia	Fitch and Lachance (45)
VATER association	Bilateral renal agenesis or cystic dysplasia with small kidneys or obstructive uropathy, or other pathology	Uehling et al (154)

Other findings. Other findings may include brain malformations, diaphragmatic hernia, asplenia, polysplenia, adrenal hypoplasia, and accessory adrenal glands (3,35).

Diagnosis, differential diagnosis, and laboratory aids. Because of the heterogeneous causes of Potter sequence, diagnosis and recurrence risk counseling should be based on (*a*) careful clinical examination, (*b*) complete autopsy with special attention to renal histopathology, (*c*) chromosome analysis, (*d*) family history, and (*e*) renal ultrasound examination for parents of infants with renal agenesis and/or cystic dysplasia and more distant relatives if indicated by history or by demonstrated parental involvement based on ultrasound. Prenatal ultrasonography has identified oligohydramnios (35), renal agenesis and/or cystic dysplasia (8,28,37,62,74,125,139,140), and obstructive uropathy (17,131,144).

Syndromes with Potter sequence are listed in Table 1–2. The association of ear anomalies with genitourinary defects independent of Potter sequence has been discussed by several authors (14,90,149,155).

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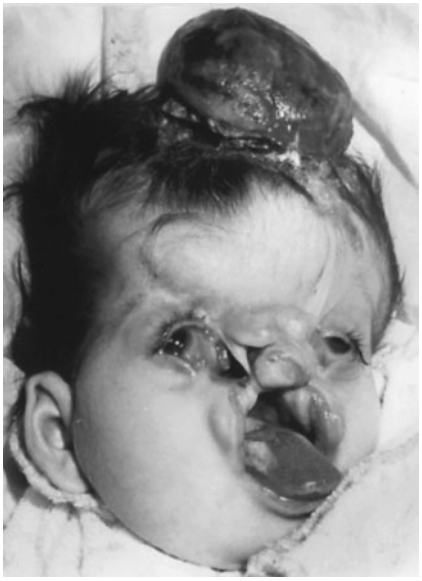
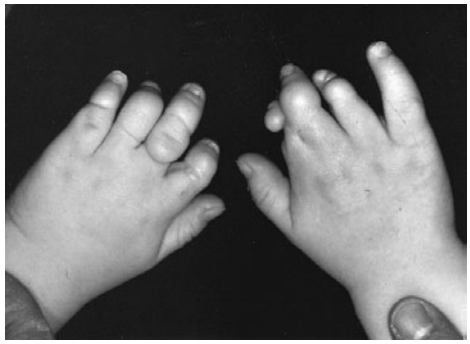
Amnion rupture sequence

Amnion rupture sequence may result in limb reduction defects, amputations, ring constrictions, distal syndactyly, talipes equinovarus, short umbilical cord, craniofacial disruptions and clefts, neural tube defects, limb/body wall deficiency, gastroschisis, extrathoracic heart, scoliosis, growth restriction, and various other anomalies (Figs. 1–10 to 1–14). Severity of amnionic rupture sequence varies from a single ring constriction or amputation to such severe involvement that viability

Fig. 1–10. *Amnion rupture sequence*. (A) Agenesis of membranous skull bones with protrusion of cranial contents. Bilateral facial clefts extending through premaxilla, lips, lateral nose, medial orbits, and skull. (B) Variations in hand anomalies. Note circumferential creases, syndactyly. (C) Amputations of variable extent. (A from MS Granick et al, Plast Reconstr Surg 80:829, 1987).



A



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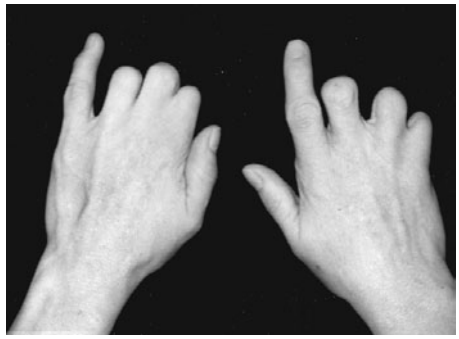

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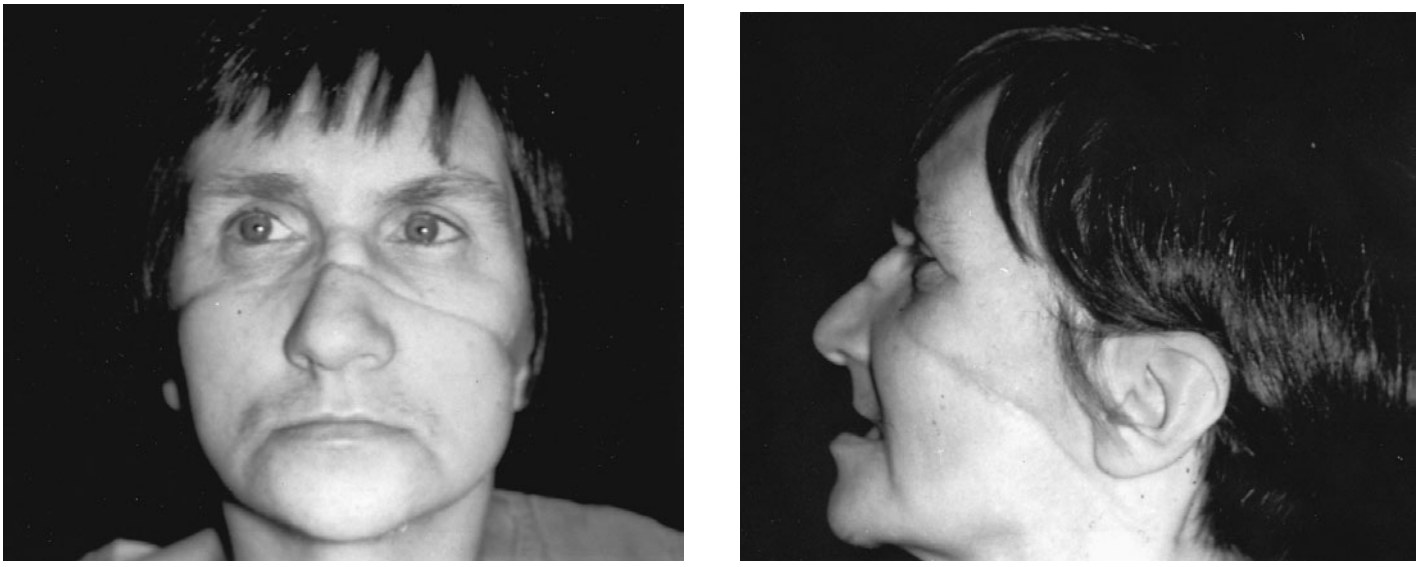


A B

Fig. 1–11. *Amnion rupture sequence*. (A, B) Amniotic band across nose to cheek area.

is not possible. The condition has also been known as amnionic band syndrome, aberrant tissue band syndrome, amnionic band lesions, and ADAM complex (4,6,7,23,26,43,45,51,62). Large series have been reported by numerous authors (1,4,6,7,23,26,45,54,57–59). Craniofacial involvement has been emphasized in several publications (2,23,26, 28,37). A good review is that of Christianson et al (7a).

Amnionic rupture may lead to all three basic types of anomalies—disruptions, deformations, and malformations (60). Disruptions are caused by adhesions, by tearing, and by constriction by amnionic bands. Shepard et al (55) indicated that facial clefting, anteriorly located encephaloceles, and pseudoanencephaly might be caused by membranes adhering to the perforating buccopharyngeal membrane and lateral edges of the closing neural folds between 23 and 35 days of development. If bands are present during the embryonic period, they may interfere with normal embryogenesis, resulting in malformations. Deformations result from oligohydramnios, which leads to intrauterine crowding and tethering of fetal parts. Severe constraint leads to vascular engorgement, hemorrhage, edema, and tissue necrosis resulting in severe disruptions such as limb/body wall defects. Finally, some malformations that cannot be explained by bands, constraint, or compression may occur with amnionic rupture sequence anomalies. In such instances, disruptive and nondisruptive abnormalities may have a common primary etiology in some cases and may occur by chance in others (1,19,22,23,27,32,39,47,57–59). Herva and co-workers (17,18) suggested that many severe cases were based not on a single rupture of the amnion but by a defective early germinal disc.

Fig. 1–12. *Amnion rupture sequence*. Bizarre facial clefting and asymmetric encephaloceles. Note amputation of thumb and index finger. (From MM Cohen Jr, The Child with Multiple Birth Defects, 2nd ed, Oxford University Press, New York, 1997.)

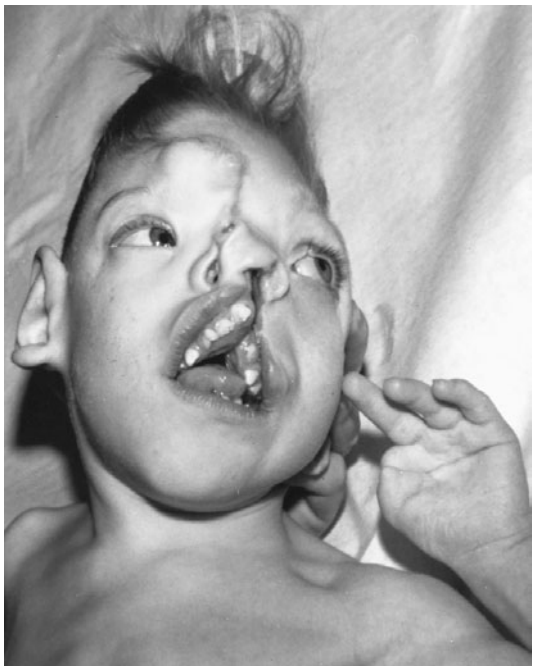
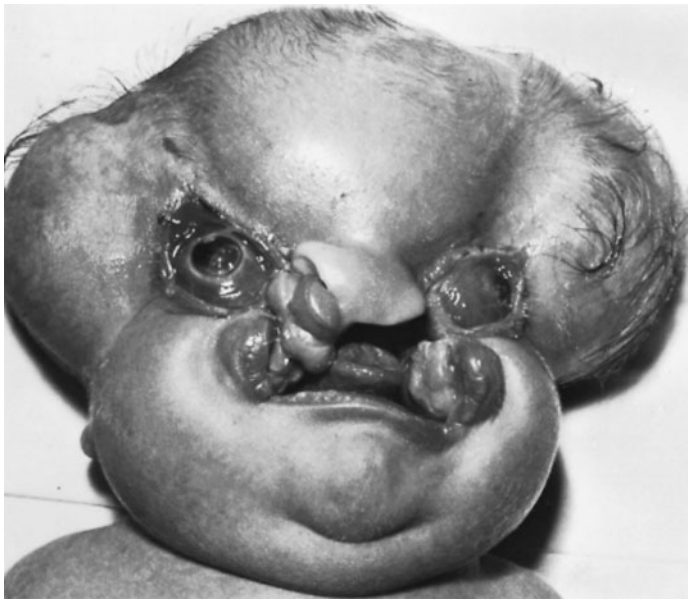


Fig. 1–13. *Amnion rupture sequence*. Cloverleaf skull in infant with bilateral oblique facial clefts. Patient also had amputation of digits. (From A Schuch and HJ Pesch, Z Kinderheilkd 109:187, 1971.)



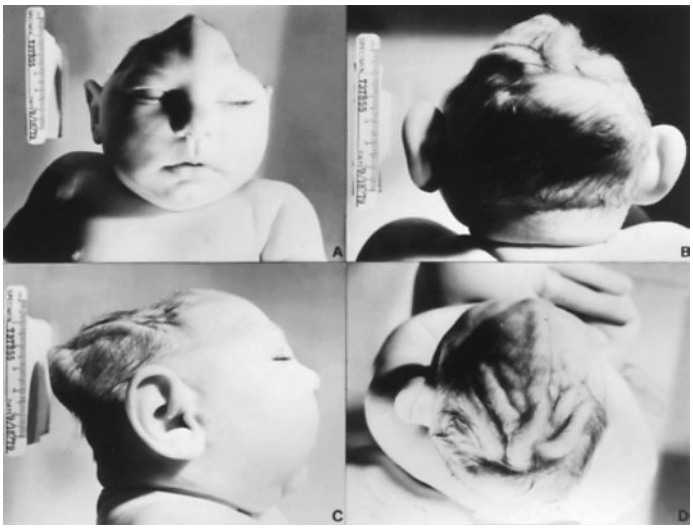


Fig. 1–14. *Fetal brain disruption sequence*. (A–D) Severe microcephaly, ridged and overriding sutures, collapse of skull, prominent occipital bone, and scalp rugae. (From LJ Russell et al, Am J Med Genet 17:509, 1984.)

Baker and Rudolph (1) estimated that congenital ring constrictions and amputations occurred with a frequency of 1 in 10,000 live births. Herva et al (18) noted a cluster of severe amnionic band cases (9 in 17 months) in Finland. Ossipoff and Hall (45) reported that 1 in 1300 pregnancies had amnionic rupture sequence, and Byrne et al (6) gave a frequency of one in 5000–15,000 births, but indicated that the condition was relatively common among abortuses. On the basis of ultrasound at 18 weeks in utero, Papp et al (48) reported amnionic bands without signs of amnionic rupture or other fetal malformations in 5 of 12,131 consecutive pregnancies. They suggested that "innocent bands" may exist. Kalousek and Bamforth (24) found that amnion rupture sequence was common in previable fetuses, the prevalence being 1 in 56.

The best epidemiologic study is that of Garza et al. (11). Using amputation or ring constriction as a minimal criterion, among 388,325 live births, the birth prevalence for amnionic rupture sequence was 1.17 per 10,000. The prevalence for males was 0.91 and for females was 1.44. Defects occurred 1.76 times more often among blacks than among whites. Infants of young, black multigravidas showed the highest rate (6.2), and infants of older black multigravidas showed the lowest rate (0.5). Maternal age effect was not observed in black primagravidas or in white mothers. Birth weight was below 2500g in 49% of amnionic rupture sequence cases compared with 6.8% among all live births in the Atlanta area. The known case fatality rate was 30%.

The overwhelming majority of cases are sporadic. However, a few examples have been familial (9,32,33). Although most reported identical twins have been discordant (8,25,31,45,57), concordant twins have also been noted (10,31,64). Gellis (12) reviewed two families in which father and son had ring constrictions on the terminal phalanges of the same fingers. Such cases are probably best understood on the basis of Streeter dysplasia of genetic origin. Amnionic disruption sequence has been associated with amniocentesis (41).

Limb defects. Limb defects are the most commonly observed abnormalities with amnionic rupture sequence (Fig. 1–10B,C). Findings may include ring constrictions, lymphedema below the ring constriction, congenital amputations of one or more limbs or digits, distal syndactyly, and talipes equinovarus (1,7,21,42,44,50,57). Less common and more unusual abnormalities have included absent limb, oligodactyly, arthrogryposis, single forearm bone, single lower leg bone, radial and ulnar hypoplasia, ectrodactyly, and preaxial polydactyly (13,58). Proximal syndactyly has also been noted (14). Hall (16) noted a transposed arm secondary to amnionic band disruption.

Craniofacial anomalies. With increasing severity of disruption, craniofacial anomalies may include severe microcephaly with deficiency of the anterior calvaria; asymmetric, usually anteriorly located, and sometimes multiple encephaloceles, bony orbital clefts, coloboma of eyelids, ectropion, lacrimal outflow obstruction, globe involvement, and microphthalmia; distortion and disruption of the palpebral fissures; various nasal disruptions; cleft lip, cleft palate, and bizarre facial clefts; and aberrant tissue bands about the face (Fig. 1–10A) (6a,29,30). Potter deformities (Fig. 1–11) and anencephaly have been observed. Various malformations have been reported including holoprosencephaly, Dandy-Walker malformation, septo-optic dysplasia, cloverleaf skull, hydrocephaly, ocular hypertelorism, uveal coloboma, choanal atresia, unilateral proboscis, Robin sequence, and other malformations (2–4,7,19,20,22,23,26,28,35,37,46, 51,53,58,59). Neurologic manifestations in survivors have been discussed by Chen and Gonzalez (7).

Thoracic, abdominal, and other defects. Body wall deficiency may include thoracoschisis, abdominoschisis, thoracoabdominoschisis, ectopia cordis, gastroschisis, omphalocele, and even extrophy of the bladder. Many other malformations have been reported including various cardiovascular anomalies, abnormal lung lobulation, absent or abnormal diaphragm, abnormalities of intestinal rotation, anal atresia, absent gonads, and anomalous external genitalia (19,22,23,39,47,56,58,59). Scoliosis may be observed (39). Low-frequency malformations have been tabulated by several authors (22,58,59). Placenta and membranes have been discussed by Van Allen and Myhre (58). Sachdev et al (52) reported a case of amnionic rupture sequence associated with an incompetent cervix.

Differential diagnosis. Amnionic band defects may mimic *frontonasal dysplasia*, ocular hypertelorism, branchial arch dysplasia, *Meckel syndrome, cryptophthalmos*, arthrogryposis, pterygium-related entities, scalp defect/limb reduction, and ectrodactyly (15). Genetic type ring constrictions of the terminal phalanges (12) may mimic amnionic band constrictions and amputations. Differences between amniogenic and genetic or teratogenic limb anomalies have been discussed by Baker and Rudolph (1). On occasion, postnatal hair strangulation of toes during infancy may mimic amnionic band ring constrictions or amputations of digits (40). Amnionic bands have been observed with severe *osteogenesis imperfecta* (62,63), *type IV Ehlers-Danlos syndrome* (63), and *epidermolysis bullosa* (36). One must exclude *oromandibular limb hypogenesis disorders*.

Laboratory aids. Elevated amnionic α-fetoprotein levels are often found (5). Prenatal diagnosis by ultrasonography is possible in patients with severe craniofacial defects (7,31,34,38,49,61).

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Fetal brain disruption sequence

In 1984, Russell et al (3) reported three infants with severe microcephaly, overlapping sutures, prominence of the occipital bone, and scalp rugae. Four additional cases were reported by Moore et al (2).

The fetal brain disruption sequence is postulated to arise from partial brain disruption during the second or third trimester with subsequent skull collapse secondary to decreased intracranial pressure. Possible mechanisms include interruption of the blood supply to selected areas of the brain such as disruption secondary to co-twin demise, prenatal viral infection, and hyperthermia.

Severe microcephaly with severe to profound mental deficiency is characteristic. Diminished intracranial pressure leads to calvarial collapse with overlapping sutures, scalp rugae, and prominent occipital bone (Fig. 1–14).

Differential diagnosis. *Cutis verticis gyrata* occurs as a separate condition, typically having its onset after puberty; collapse of the calvaria does not occur, although microcephaly may be present. Associated endocrine problems are common. Scalp rugae have been observed with severe microcephaly and with hydranencephaly. The fetal brain disruption sequence differs from atelencephaly (1).

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Chapter 2
Teratogenic Agents

Growth and development of the embryo can be adversely affected by a wide variety of environmental agents (*teratogens*). These include intrauterine infections, various chemical agents and medications, radiation, and maternal metabolic disorders. Prior to discussion of specific teratogens, it would be logical to familiarize the reader with some of the general principles of teratology.

The first two weeks of life, that is, the time prior to organogenesis, appear to be a relatively safe time for the embryo regarding teratogenic exposure. The next 45 days, however, are especially dangerous, for it is during this period that most organs develop. After an organ has developed, unless there is disruption, the teratogen cannot cause a malformation. Thus, most major malformations, such as amelia, cleft lip/palate, microtia, and congenital heart anomalies, arise during the first 60 days of embryonic development. One exception is deleterious defects due to alcohol consumption which can arise during the entire pregnancy. Craniosynostosis and hearing loss appear to develop after the first 60 days of conception. The same teratogen can cause different defects at different times of exposure. For example, exposure to thalidomide around the 33rd postconceptual day causes microtia and facial palsy; a bit later exposure results in aplasia of arm bones, and around the 55th day, thalidomide exposure makes the thumb look like a finger. Exposure to rubella after the 55th day causes hearing loss and retinopathy; earlier it induces cataracts and congenital heart anomalies. Isotretinoin exposure in the embryonic period causes epicanthic folds and microtia, but after fetal exposure, no anomalies of the pinnae are noted.

Most, but not all, teratogens have a threshold dose below which no identifiable effects or malformations can be detected. Beyond the threshold dose, some teratogens exhibit a dose–response effect, i.e., the higher the dose, the greater the response. However, in humans this may not be easily observed. Some agents, such as isotretinoin, have a narrow therapeutic dose range. Alcohol, by contrast, has teratogenic effects throughout pregnancy. Still other medications such as anticonvulsants have produced very inconsistent dose-effect responses.

Most teratogens produce a characteristic, that is, clinically recognizable, pattern of abnormalities. Apart from causing retarded growth, most cause specific malformations. Pathogenesis for most teratogens is unknown, but it is likely that a number of them act as ligands, binding cellular or nuclear receptors. Determination of which organs will be affected by which teratogens probably reflects the tissue- and time-specific distribution of matching receptors during the period of exposure. as demonstrated in the case of vitamin A congeners. Other agents probably interfere with cell migration division, differentiation, and death. Altered epithelial-mesenchymal interaction also appears to be a factor.

Teratogens are often species specific; what is teratogenic in mice is not necessarily teratogenic in humans or other animals. For example, cortisone produces cleft palate with high frequency in certain strains of mice but not in others, whereas rats and humans are not susceptible. Thalidomide is not teratogenic in mice, rats, dogs, cats, or guinea pigs, but exposure in rabbits produces injury. Higher apes and humans are highly susceptible.

Alcohol embryopathy

Of all teratogens, alcohol has surely received the greatest attention, for it is the most common recognizable cause of mental and growth retardation in children (43). Although it must be the most venerable of teratogens, its role was not recognized until 1968 by Lemoine et al (38), and Jones et al (31) first clinically defined fetal alcohol syndrome (FAS) in 1973. A less severe manifestation has been termed "fetal alcohol effect" (FAE), but because this is an imprecise term, we discourage its use (1). The structural and functional effects on the embryo are dose related, with up to one-half of affected infants being born to women who drink 2 oz. or more of absolute alcohol per day. It has been estimated that 1 in 30 pregnant women abuse alcohol and that about 6% of these women have children with clinically recognizable FAS (3,9,15). Moderate drinkers, i.e., those who drink from 1 to 2 oz. of absolute alcohol per day, have children with functional and growth disturbances without other morphologic changes (Table 2–1A). Furthermore, the risk of spontaneous abortion is increased for those who drink increased amounts of alcohol during pregnancy. Binge drinking during the first trimester may cause fetal death. Fetal alcohol syndrome has been estimated to occur in at least 2 per 1000 livebirths (53). In the United States this would amount to more than 7000 affected infants annually. There appears to be no safe period for excess alcoholic consumption during pregnancy (2,4,29,30). An excellent follow-up is that of Autti-Ramo et al (6a).

The risk of abortion is doubled if one oz. of alcohol is consumed twice a week (34). Clinical findings of FAS include pre- and postnatal growth retardation, central nervous system dysfunction, and characteristic facies. Birth weight is usually less than 2500 g and subsequent growth is deficient (7). Facial abnormalities include small head circumference, epicanthic folds, short palpebral fissures, ptosis, strabismus, optic nerve hypoplasia, short nose with anteverted nostrils, broad low nasal bridge, mild midfacial hypoplasia, indistinct philtrum, thin vermilion of upper lip, and small mandible (25a,27) (Fig. 2–1; Table 2–1B). Dentition is somewhat delayed. In some surveys, there appears to be an increase in the occurrence of cleft palate (as much as 15%); the heavier the consumption, the greater the frequency of cleft palate (56). Other studies have found an increase in cleft lip/palate but not in cleft palate (45a). Cephalometric study shows upper and midfacial asymmetry and a long face (21,23,27). These changes become evident only if maternal use exceeds four oz. of absolute alcohol per day (17,42). The characteristic facies tends to disappear with age (58,64).

Hypoplasia of the optic nerve head and increased tortuosity of retinal vessels are extremely common (65). Microphthalmia is rare (6). A tendency toward both conductive and sensorineural hearing loss has been noted (13).

Central nervous system problems are increased, and can take the form of hyperactivity, mild to moderate mental retardation, attention deficit, sleep disorders, motor and neuropsychological deficits, and brain malformations, which include microcephaly, hydrocephalus, lissencephaly, and neural tube defects (10,24,45,61,62). Abnormal neuronal migration results in neurological heterotopias, polymicrogyria, pachygyria, agenesis and hypoplasia of the corpus callosum, ventriculomegaly, small brain stem, and defects in the limbic system (16,28,32,46). Glial cell proliferation is increased (23a). Holoprosencephaly is increased in infants of mothers who drink heavily (42). Seizures are likely to occur with elevated frequency of alcohol consumption, as is maladaptive adult behavior. Handicaps range from mild to severe mental retardation, to fine motor dysfunction (tremulousness, poor eye–hand coordination, and various self-stimulating behaviors) (12,59). Hyperactivity is common. In the neonate, such signs as

Table 2–1A. Principal features of fetal alcohol syndrome observed in 245 persons affected

Feature	Manifestation
Central nervous system dysfunction	
Intellectual	Mild to moderate mental retardation[a]
Neurologic	Microcephaly[a]
	Poor coordination, hypotonia[b]
Behavioral	Irritability in infancy[a]
	Hyperactivity in childhood[b]
Growth deficiency	
Prenatal	<2 SD for length and weight[a]
Postnatal	<2 SD for length and weight[a]
	Disproportionately diminished adipose tissue[b]
Facial characteristics	
Eyes	Short palpebral fissures[a]
Nose	Short, upturned[b]
	Hypoplastic philtrum[a]
Maxilla	Hypoplastic[b]
Mouth	Thinned upper vermilion[a]
	Retrognathia in infancy[a]
	Micrognathia or relative prognathia in adolescence[b]

[a]Feature seen in >80% of patients.
[b]Feature seen in >50% of patients.
(From SK Clarren and DW Smith, N Engl J Med 298: 1063, 1978.)

Table 2–1B. Associated features of fetal alcohol syndrome observed in 245 persons affected

Area	Frequent[a]	Occasional[b]
Eyes	Ptosis, strabismus, epicanthal folds	Myopia, clinical microphthalmia, blepharophimosis
Ears	Posterior rotation	Poorly formed concha
Mouth	Prominent lateral palatine ridges	Cleft lip or cleft palate, small teeth with faulty enamel
Cardiac	Murmurs, especially in early childhood, usually atrial septal defect	Ventricular septal defect, great-vessel anomalies, tetralogy of Fallot
Renogenital	Labial hypoplasia	Hypospadias, small rotated kidneys, hydronephrosis
Cutaneous	Hemangiomas	Hirsutism in infancy
Skeletal	Aberrant palmar creases, pectus excavatum	Limited joint movements, especially fingers and elbows, nail hypoplasia, especially 5th, polydactyly, radioulnar synostosis, pectus carinatum, bifid xiphoid, Klippel-Feil anomaly, scoliosis
Muscular		Hernias of diaphragm, umbilicus or groin, diastasis recti

[a]Reported in between 26% and 50% of patients.
[b]Reported in between 1% and 25% of patients.
(From SK Clarren and DW Smith, N Engl J Med 298:1063, 1978.)

Table 2–2. Cardiovascular anomalies associated with selected teratogens

Agent	Anomalies reported
Alcohol	Frequent: VSD, ASD, tetralogy of Fallot, PDA Occasional: Pulmonic stenosis, subaortic stenosis, endocardial cushion defects, dextrocardia, double outlet right ventricle, coarctation of aorta, peripheral pulmonary stenosis, cardiomyopathy, patent foramen ovale, persistent left superior vena cava
Phenytoin	VSD, ASD, pulmonic stenosis, tetralogy of Fallot, valvular pulmonary stenosis, coarctation of aorta, endocardial cushion defects, aortic stenosis, superior vena cava duplex
Trimethadione	VSD, ASD, PDA, aortic stenosis, pulmonic stenosis, hypoplastic left heart, endocardial cushion defect, transposition of great vessels, tetralogy of Fallot
Valproic acid	VSD, PDA, coarctation of aorta, hypoplastic left heart, peripheral pulmonic stenosis, levocardia, right bundle branch block
Coumarin	PDA, peripheral pulmonic stenosis, transposition of great vessels, total anomalous pulmonary venous return

ASD, atrial septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

poor sucking, abnormal muscle tone, irritability, and hyperacusis are frequently noted (52). Linguistic deficits, problems of socialization and memory, sleep disturbances, impulsiveness, and personality disorders are increased (26,45,49,60,62,63).

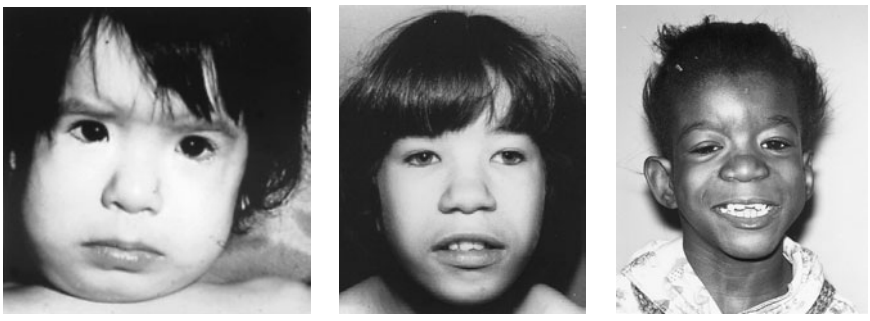
Cardiac anomalies include atrial and ventricular septal defects. In those infants with severe FAS, over 60% have congenital heart anomalies (30,50,54), and the occurrence of *DiGeorge syndrome* is increased (Table 2–2).

Skeletal anomalies include retarded bone age, copper-beaten skull, an increase in radioulnar and cervical vertebral fusions, radioulnar synostosis, hip dislocation, carpal fusion, pseudoepiphyses of metacarpals, hypoplastic distal phalanges, clinodactyly of V, and stippled epiphyses of the lower extremities (14,20,37,40,44,57).

Terminal transverse defects of the limbs occur more frequently (6,22,52), as does nail dysplasia (19). Palmar creases are altered. There is also an increase in embryonal tumors (8,11,18,25,33,55,68).

The pathophysiologic basis for alcohol embryopathy appears to be related to genetic polymorphisms for alcohol dehydrogenase, which converts alcohol to acetaldehyde, and for acetaldehyde dehydrogenase, which converts acetaldehyde to acetate. Technically, FAS may be an acetaldehyde embryopathy (36,41).

There is an excellent mouse model for alcohol embryopathy (66,67). Kotch and Sulik (35), through exposing pregnant mice to ethanol in vivo, noted excessive cell death in selected cell populations in 8-day embryos, especially those at the rim of the anterior neural plate (67). Exposure at day 7 resulted in holoprosencephaly and anencephaly, and at day



A B C

Fig. 2–1. *Fetal alcohol syndrome.* (A) Note narrow palpebral fissures, indistinct philtrum, hirsutism, short nose, and thin upper lip. (B) Older child showing similar facies. (C) Note similar features. (A from KL Jones and DW Smith, Lancet 2:299, 1973. B courtesy of F Majewski, Düsseldorf, Germany. C courtesy of RE Wood, Richmond, Virginia.)

8 and 1/2 it resulted in exencephaly, facial clefts, and DiGeorge sequence, the differing patterns of malformation depending on the changing pattern of premature cell death.

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Angiotension-converting enzyme (ACE) inhibitor embryopathy

Captopril and similar compounds (Capoten, Monopril, Prinivil, Vasotec, Lotensin, Accupril, etc.) have been used in the United States and in Europe with and without the addition of diuretics for control of hypertension. They cross the placenta and are renally excreted. These angiotensin-converting enzyme (ACE) inhibitors have also been shown to impede diabetic nephropathy, both types 1 and 2.

There is some evidence that this group of drugs is fetotoxic; Pryde et al (7) summarized 31 examples in humans, and Barr and Cohen (2) reviewed the literature. The most common findings are second- and third-trimester onset of oligohydramnios and growth restriction followed by profound hypotension and anuria, pulmonary hypoplasia, and renal tubular dysgenesis. The calvaria is delayed in development (1–8).

References [Angiotension-converting enzyme (ACE) inhibitor embryopathy]

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Chorionic villus sampling embryopathy

Chorionic villus sampling (CVS), performed at about 56–66 days of gestation, has been carried out in about 150,000 women during the last decade. In 1991, several case reports were published which suggested that an increased number of infants with transverse limb deficiencies were born to mothers who had CVS (2,4,7). Most reports discussed absence of parts of the fingers or toes. Firth et al (4) and Chen et al (3) also noted associated defects of the tongue and lower jaw (*oromandibular-limb hypogenesis*). In a later report, the same group found this association in 19 of 75 cases (5). These reports engendered a large number of cohort and case–control studies that both supported and contradicted the association (1,4,6,8,9). Ultimately, the World Health Organization (12) suggested that CVS be delayed until weeks 9–12 since a temporal relationship had been indicated. In 1995, a U.S. population–based, multistate case–control study suggested that the odds ratio for all types of limb deficiency after CVS from 8 to 12 weeks gestation was 1.7, while for specific types, such as transverse deficiency, the odds ratio was 6.4. The absolute risk for this type of anomaly was 1 in 2900 births (0.03%)—i.e., a sixfold increase for transverse deficiency (9). Botto et al (1) found that the relative risks for any digital deficiency in two studies were 10.6 and 6.1, respectively. For severe transverse digital deficiencies, the relative risks were 30.5 and 10.7, respectively. Severe deficiencies were found in <25% of all digital deficiencies. The earlier the chorionic villus sampling, the more severe the deficiency.

Stoler et al (11) found an increased frequency of gastroschisis, club foot, and intestinal atresia. A similar body of literature regarding amniocentesis is available (10).

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Cocaine embryopathy

Cocaine is used so often in conjunction with alcohol, cigarettes, marijuana, opiates, and illicit drugs that it has been difficult to separate its effects from those of other substances (8). An estimated 50% of cocaine users take only cocaine; the remainder take other drugs as well (18). Cocaine readily crosses the placental barrier.

Cocaine use is widespread. By 1985, approximately 25 million Americans had used cocaine, and about 5 million used it regularly. In 1986, it was estimated that 10% of pregnant women in Detroit used it (11). In 1992, 6% of babies born at a private suburban hospital had cocaine metabolites in the meconium (18). Similar data were evident in Boston (8). In mothers who use cocaine, preterm labor is increased (14).

Birth weight, length, and head circumference are generally below the 25th centile (2,10,12,17,19). Microcephaly is evident in about 30%, and about 25% have intrauterine growth retardation (2,11,14). In another study, no such effects were found (3). The facies is characterized by bitemporal narrowing, low hairline, horizontal supraorbital ridge, prominent glabella, short palpebral fissures, and short nose with anteverted nares (1,9,13,16).

Infants exposed prenatally to cocaine exhibit long-term depression of interactive behavior (3). Midline prosencephalic development and neuronal migration are also affected. Agenesis of the corpus callosum and septum pellucidum, septo-optic dysplasia, schizencephaly, and neuronal heterotopias have been described (6), as well as microphthalmia, optic hypoplasia, retinal dysgenesis, and retinal colobomas (7). Porencephaly and brain hemorrhage of various types have been reported (5,14).

The incidence of various major cardiac anomalies is increased (14,15), as are urinary tract anomalies (4). Limb reduction defects and intestinal atresias have been attributed to the vascular disruption effects of cocaine (1,13,16,18). Maternal hair tests have been employed to determine use during pregnancy (13a).

References (Cocaine embryopathy)

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Cyclophosphamide (Cytoxan) embryopathy

Cytoxan, an alkylating agent used in treating cancer and autoimmune disease, has been cited as being teratogenic but not producing a specific phenotype (1–4). Variable findings have included growth deficiency and developmental delay, craniosynostosis, microcephaly, blepharophimosis, unusual pinnae, flat nasal bridge, and various extremity anomalies (hypoplastic radius and/or thumbs, hypoplastic middle phalanx of fifth fingers, absent fingers/toes).

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Cytomegalovirus and toxoplasmosis embryopathies

Cytomegalovirus (CMV), which is contracted through transplacental transmission, is the most common cause of congenital infections, occurring in 0.5%–2.5% of all live births. It has been estimated that about 1 in every 3000 infants born in the United States suffers brain damage due to CMV exposure in utero. Conversely, when exposed early in pregnancy, the frequency of brain damage due to cytomegalic meningoencephalitis in the newborn has been estimated to be about 80%. In addition, intrauterine growth retardation (35%), pneumonitis (25%), hepatosplenomegaly (90%), thrombocytopenia (70%), jaundice (50%), and hemolytic anemia (50%) may be seen in the neonatal period.

Because the CMV causes cellular necrosis, infections such as necrotizing meningoencephalitis eventuate in microcephaly (40%), periventricular calcifications (25%), metaphysitis (25%), mental retardation, seizures, sensorineural hearing loss, and motor deficits (1,5,6). Obstuctive hydrocephalus may occur. Cytomegalovirus infections of the eye result in chorioretinitis and optic atrophy.

Similarly, about 6 in 1000 pregnancies in the United States are associated with primary maternal infection with toxoplasmosis. In about half the cases, the untreated mother gives birth to a congenitally infected infant, about 75% being asymptomatic, 10% being stillborn, and 10% being severely affected. It has been estimated that 70%–85% of women of childbearing age in the United States lack antibodies and are susceptible to primary infection. Prematurity occurs in 25% of infants exposed to CMV. Although malformations do not occur, hydrocephalus (5%) and microcephaly (5%) may result from chronic destructive meningoencephalitis and, as in the case of CMV, chorioretinitis may progress to loss of vision. Cerebral calcifications may be seen in about 10% of affected infants.

In those with severe toxoplasmic infections, about 80% have some degree of mental retardation, 70% have seizures or spasticity, and 50% have chorioretinitis. About 15% of this group will manifest sensorineural hearing loss (1–4,7). The mildest expression is chorioretinitis.

Severity of infection reflects time of infection—the earlier in pregnancy it occurs, the more severe the infection. Those who acquire the infection in the last trimester are often asymptomatic.

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Diabetic embryopathy

It has been well demonstrated that children born to insulin-dependent diabetic mothers have a two- to threefold increased risk of congenital malformations and/or spontaneous abortion (7). One case–control study indicated a relative risk of about 8, with a relative risk of 15 for major central nervous system injury and 18 for cardiovascular system injury (2). Injuries to the fetus occur before the seventh week of gestation (8).

While the spectrum of injury is broad, the most frequently noted anomalies are those of the cardiovascular, genitourinary, and central nervous systems. In addition, infants with caudal regression developmental field defect and femoral hypoplasia–unusual facies syndrome are born to diabetic mothers with greater frequency. The term "axial mesodermal dysplasia" refers to a condition with signs of oculoauriculovertebral dysplasia (but without facial asymmetry) and caudal "regression" (12). Oculoauriculovertebral abnormalities are more common in children of diabetic mothers (4).

About 3% of these children have anomalies of the pinnae, heart, vertebrae, and central nervous system (5). Anomalies of the central nervous system include spina bifida and anencephaly. Ear anomalies, found in

2% of affected infants, include ear tags, microtia or anotia, and hirsutism (3,4,10). Caudal dysplasia is found in about 1%–2% (6,7,14,15). Conversely, about 15% of infants with caudal dysplasia are born to diabetic mothers. Malformations of the ribs and vertebral column occur with greater frequency (9,11). About 25% of those with femoral hypoplasia–unusual facies syndrome have diabetic mothers (5). Holoprosencephaly also occurs more frequently (1).

Cardiac anomalies include ventricular septal defect (VSD), transposition of great vessels, single umbilical artery, and situs inversus. Increased numbers of gastrointestinal anomalies include malrotation of bowel and anal or rectal atresia; and increased numbers of genitourinary abnormalities include renal agenesis, hypospadias, and cryptorchidism (14).

Sadler et al (13) have suggested that the pathogenesis involves a primary insult to developing somite mesoderm and associated neural crest cells.

References (Diabetic embryopathy)

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Diethylstilbestrol embryopathy

Diethylstilbestrol (DES) was used to reduce spontaneous abortion and preterm delivery in at least 4 million pregnancies from 1948 to 1970 (8). Herbst et al (6) first pointed out in 1971 the tendency of female offspring exposed in utero to develop vaginal adenocarcinoma (mesonephroma). While vaginal adenosis is common, seen in possibly 75% of females exposed to DES before the ninth week of gestation, the frequency of adenocarcinoma of the vagina and cervix is very low—1 in 10,000. Another study estimates the risk to be 1 in 1000 (7).

Exposure to DES during the fourth to 12th week of gestation is teratogenic. In addition to being predisposed to vaginal adenosis, most female infants exposed prenatally to DES have persistence of müllerian mucosa over the upper vagina, cervix, and tubular walls. The uterus may be hypoplastic and T-shaped. The fallopian tubes are often short and narrow with absent fimbria (3). The vagina may show transverse ridges, and the cervix may be hooded or collared.

A follow-up study in 1977 of male and female offspring of mothers exposed to DES during pregnancy showed that 18% of female infants exposed to DES had oligomenorrhea compared to 10% of the control group (1), and fertility was diminished (18% vs. 33%). Circumferential or transverse ridges of the vagina and cervix were found in 40% of DES-exposed females in contrast to none in the control group. Adenosis was noted in 67% of the DES group and 3.5% in the control group. Dysplastic lesions of the vagina and cervix were noted in the exposed group, but not in the controls. Although the age range for adenocarcinoma has been 7–42 years, most cases have occurred in females between 15 and 27 years of age. Risk factors include DES taken before the 13th week of pregnancy and birth weight below 2500 g. Survival seems to be related to histologic pattern (women with a tubulocystic pattern fare better than those with a papillary pattern) and degree of nuclear atypia (2,5,6,9–13) (Fig. 2–2). Adenosis was greater in females exposed during the first two months (75%) than in those exposed during the 17th week or later (7%). Fertility does not appear to be decreased (8).

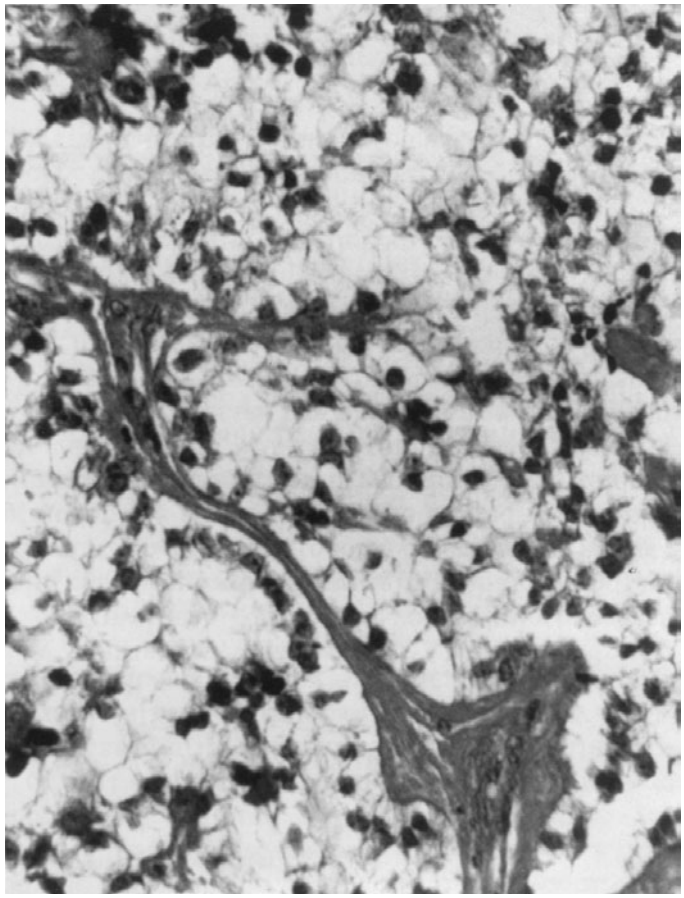

Fig. 2–2. *Diethylstilbestrol embryopathy.* Clear cell adenocarcinoma following DES therapy.

Male infants may have micropenis, hypospadias, cryptorchidism, small testes with indurated capsule, epididymal cysts, and impaired sperm production. About 13% of males have difficulty urinating compared to 2% of a control group (4). There was no increase in the incidence of cancer (8).

About 25% of males had epididymal cysts, hypotrophic testes, and capsular induration compared with 6% of control males. Furthermore, about 25% of the DES-exposed males had an ejaculate volume of <1.5 ml as opposed to 0% in the control group. Also lower were sperm density and total motile spermatozoa. Cancer was not observed in either group (1).

References (Diethylstilbestrol embryopathy)

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Fluconazole embryopathy

Fluconazole is a bis-triazole antibiotic effective against fungal pathogens. In 1992, Li et al (2) were the first to report an infant exposed in utero to fluconazole. The baby exhibited a pattern of malformations consistent with the *Antley-Bixler syndrome* of bony synostosis and characteristic craniofacial abnormalities. Similar cases have since been described (1,3). Findings in four cases included brachycephaly, depressed nasal bridge, dysplastic pinnae, midfacial hypoplasia, pear-shaped nose, proptosis, large anterior fontanel, and craniosynostosis. These patients also exhibited femoral bowing, radiohumeral synostosis, femoral fracture, long palms and fingers, rocker-bottom feet, cardiac defects, and early death. Patients with Antley-Bixler syndrome characteristically have frontal bossing, choanal atresia, and camptodactyly.

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Folate antagonist (aminopterin, methotrexate) embryopathy

Folic acid antagonists have been recognized as having human teratogenic potential since the 1950s, when studies of aminopterin (4-aminopteroyl glutamic acid), which had been employed as an abortifacient, revealed serious congenital malformations (10,11,15,26,27). The embryopathy was first described by Thiersch (26) in 1950. The compounds aminopterin and its methylated derivative, methotrexate, are currently used as chemotherapeutic agents. Their action reduces DNA synthesis through competitive inhibition of folic acid reductase. Over 60 pregnancies have been documented in which there has been exposure to folate antagonists, but information is incomplete with regard to the frequency with which this exposure occurred (10,16,25). Nonetheless, increasing use of these agents for treatment of psoriasis and rheumatoid arthritis raises a legitimate concern for woman exposed to folate antagonists (4,6).

A somewhat similar pattern of anomalies (pseudo-aminopterin embryopathy) has been reported in several children for whom no prenatal antifolate exposure has been identified [7,20 (case 3),28]. The susceptible period appears to be during the eighth to ninth week of gestation (5,15,16,20,22). Specific attack rates associated with particular drug levels are not available.

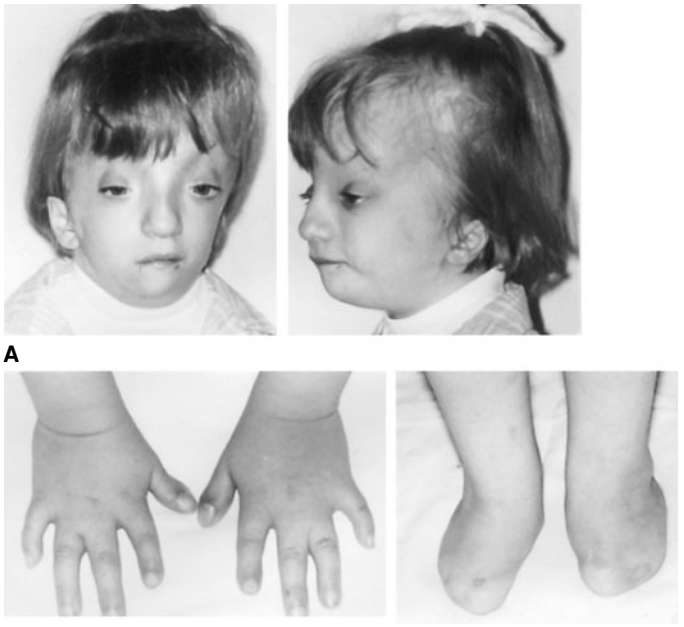

Fig. 2–3. (A) *A folic acid antagonist-induced syndrome* caused by methotrexate, a methyl derivative of aminopterin. (B) Brachydactyly and soft tissue syndactyly involving digits 3 and 4 of the hands together with absence of toes. (From MM Cohen Jr, MacLean RE, Craniosynostosis: Diagnosis, Evaluation, and Management, 2nd ed, Oxford University Press, New York, 2000.)

Clinical findings. Findings from approximately 20 well-documented cases indicate that growth deficiency of prenatal onset may occur. Craniofacial abnormalities include hydrocephalus, abnormal calvaria with widely patent cranial sutures, craniolacunae, abnormal skull shape, and, sometimes, craniosynostosis (16). Less frequently, neural tube defects have been reported (26,27). Dysmorphic facial features include hypertelorism, dysmorphic pinnae, large nose, and striking micrognathia (3,9, 14,16,19,20,22–24) (Fig. 2–3). Cleft palate is increased in frequency (5).

Mental development has been extremely variable, ranging from normal intelligence to low IQ. Some patients have delayed speech development.

Other skeletal defects include short stature, absence or hypoplasia of digits, stenotic changes in long bones, and rib anomalies. Syndactyly and talipes equinovarus have also been reported (1,2,8,12,13,17,18,21) (Fig. 2–3).

Differential diagnosis. Differential diagnosis includes various genetic syndromes associated with *craniosynostosis* and other anomalies of the developing calvaria. Conditions causing micrognathia with cleft palate including the whole range of disorders associated with *Robin sequence* and skeletal defects should be considered. In cases with limb reduction defects and/or syndactyly, the *oromandibular limb-hypogenesis* group of disorders may be suggested.

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Hydantoin embryopathy

As discussed elsewhere in this section, hydantoin (phenytoin, Dilantin), employed as an antileptic, is usually used in combination with other agents for control of seizures (7,27). The first suggestion that the hydantoins were teratogenic was made by Janz and Fuchs (17) in 1964. In 1976, Hanson et al (15) estimated that about 6000 babies were exposed annually.

When taken during pregnancy, hydantoin increases the risk for congenital malformations by two- to threefold—i.e., about 5%–10% of exposed fetuses manifest hydantoin embryopathy (12) while 30% exhibit some changes (16,18,28). Similar data were reported by Majewski et al (22).

The role of genetic factors in hydantoin embryopathy has been confusing (8); in some cases, the effects have been dissimilar. Affected sibs have been noted (5,10,12,29). Genetic susceptibility may be a factor as arene oxide metabolism has been linked to hydantoin embryopathy (9,24,26). Dean et al (7a) found that mothers of children with hydantoin or valproate embryopathy more often have mutations in the *MTHFR* gene.

Among those with features of the syndrome, the findings most often include prenatal and postnatal growth retardation (45%), microcephaly (30%), mental retardation (25%), sutural ridging (10%), cleft lip and/or palate (5%), small nose with low broad nasal bridge (20%), ptosis of eyelids (10%), epicanthic folds (15%), strabismus (15%), wide mouth, short neck with mild webbing, congenital heart disease (especially VSD) (10%), and digital anomalies (35%) (9a,22a). Renal malformation and hypospadias are not rare (11,13,23,30) (Fig. 2–4A,B).

The digital anomalies are characterized by nail hypoplasia and/or hypoplasia of distal phalanges (especially of digits 4 and 5) (15%) and digitalization of thumbs (10%) (Fig. 2–4C,D). An increased number of fingerprint arches has been found (14,31). The incidence of hernia, both umbilical and inguinal, is increased (25%), and about 30% have shawl scrotum.

Embryonal neoplasms include neuroblastoma, ependymoblastoma, ganglioneuroblastoma, melanotic neuroectodermal tumor of infancy, Hodgkin lymphoma, cystic hygroma, mesenchymoma, and Wilms tumor (1,2,3,6,19–21,25). Epoxide hydrolase deficiency is seen in those prone to have affected children (4).

Probably many cases are associated with subtle manifestations. Differential diagnosis includes *alcohol embryopathy* and embryopathy due to other anticonvulsant agents. *Coffin-Siris syndrome*, if indeed it exists, must be excluded.

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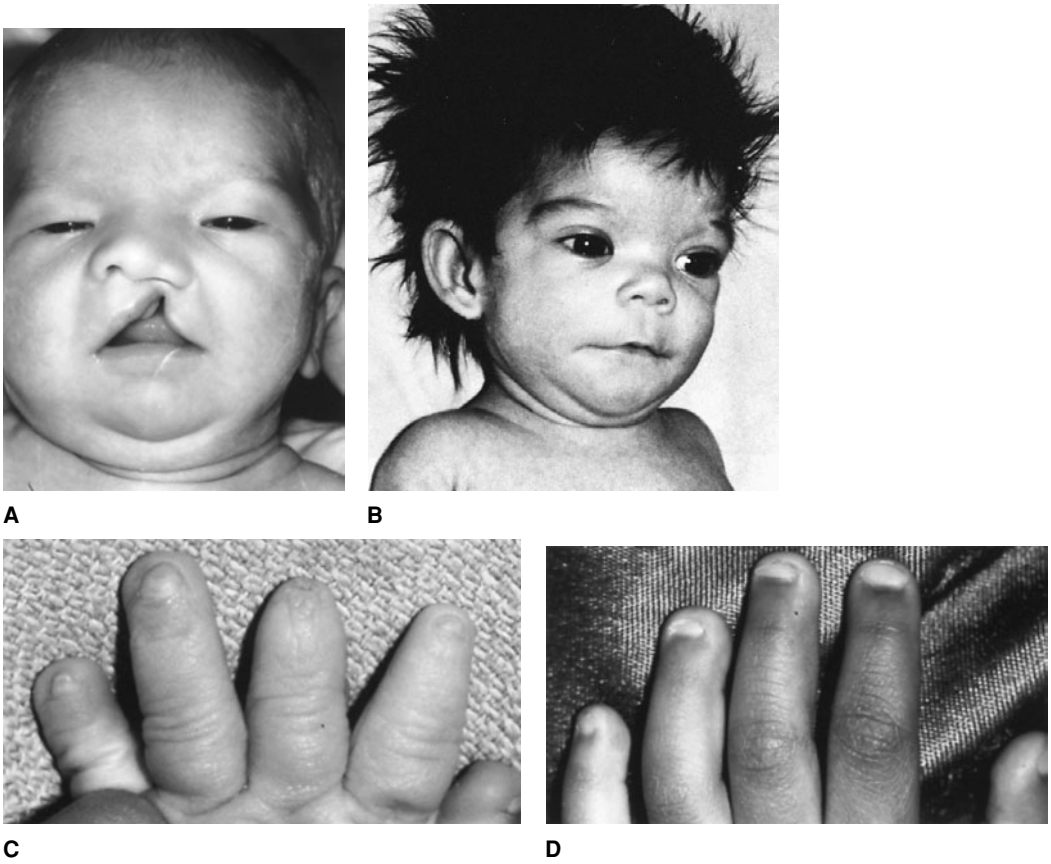

Fig. 2–4. *Hydantoin embryopathy*. (A) Cleft lip. (B) Small nose, low nasal bridge, hypertelorism, and strabismus. (C,D) Nail hypoplasia. (A,D courtesy of JW Hanson, Iowa City, Iowa. B courtesy of R Hill, Houston, Texas.)

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Hyperthermic embryopathy

Hyperthermia, i.e., body temperature of at least 38.9°C, has been described as an antimitotic teratogen following exposure between weeks 4 and 16. While it has been clearly demonstrated that hyperthermia is teratogenic in many species of animals, producing anencephaly, exencephaly, holoprosencephaly, neuronal heterotopias, microcephaly, microphthalmia, cleft lip and/or palate, and arthrogryposis, its role in human teratogenesis is less than clear (1,2). This debate has been elegantly presented by Warkany (10). Most case reports have been related to infections or sauna bathing. Smith et al (7) described several retrospective examples of exposure from 4 to 6 weeks gestation, showing severe mental retardation, seizures, hypotonia, microphthalmia, midface hypoplasia, and mild distal abnormalities. When exposure occurred from the 7th to the 16th week, the infants had neurogenic arthrogryposis and, during the time of neural tube closure (21–28 days), neural tube defects (anencephaly, myelomeningocoele, occipital encephalocele) (3–6). During the latter half of gestation, anomalies were not increased. Superneau and Wertelecki (9) suggested that oromandibular-limb hypogenesis might be the result of hyperthermia.

Cell death is a major factor in heat-induced teratogenesis, mitotic cells being most susceptible (8).

One must exclude Native American (Lumbee) myopathy. This consists of developmental delay, short stature, ptosis, cleft palate, myopathic facies, scoliosis, congenital joint contractures, early death, and autosomal recessive inheritance (CM Powell, personal communication, 2000).

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Maternal phenylketonuria embryopathy

Individuals with phenylketonuria, when placed on a phenylalanine-free diet, lead a reasonably normal life. However, females with this autosomal recessive metabolic disorder who are not diet protected during their pregnancy nearly always have infants with intrauterine and postnatal growth retardation, microcephaly, mental retardation, congenital heart anomalies, dislocated hips, and other problems (1–3,8,12,17). The infants of phenylketonuric mothers are heterozygotes and, because phenylketonuric heterozygotes are normal, the anomalies in the fetus have been attributed to the maternal metabolic disturbances. When maternal phenylalanine levels exceed 20 mg/deciliter, 95% of affected infants have mental retardation, 73% have microcephaly, 40% have intrauterine growth retardation, and 14% have cardiac anomalies (10–13,15,18). When blood levels are maintained at 120–360 μmol/liter prior to the eighth week, infants suffer no congenital heart disease and their intelligence is normal (7–9). Although 25% of pregnancies in women with phenylketonuria were reported to be spontaneously aborted in 1967 (16), a recent international collaborative study recorded a rate of 15% (5), a not unusual level. A 1997 collaborative study suggested that the mother begin the phenylalanine-free diet prior to conception and maintain it throughout pregnancy (16).

A somewhat unusual facies includes epicanthic folds, wide outer canthus, hypoplastic maxilla, wide flat nasal bridge, anteverted nostrils, long smooth philtrum, and thin upper lip (16), reminiscent of that seen in fetal alcohol syndrome (11).

When the diet is essentially phenylalanine-free prior to and during pregnancy but supplemented with tyrosine, children are unaffected (4,6,14). This regimen, however, is extremely difficult to achieve and maintain. Fisch et al (4) have suggested that affected individuals use in vitro fertilization followed by embryonic transfer to a surrogate mother.

Pathogenesis is still unknown, but it may be related to inhibition by phenylalanine of large neutral amino acid transport across the placenta or by direct toxicity of phenylalanine to various organs. At least 250 mutations are known and almost all individuals are doubly heterozygous for the mutations (11).

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Misoprostol embryopathy

Misoprostol, a synthetic analog of prostaglandin E_1, has been employed as an abortifacient in Brazil for about 15 years (1a,3,5–7,11,12). It increases the amplitude and frequency of uterine contractions and stimulates uterine bleeding. When taken during the second month of gestation, it can produce cranial nerve disorders in the fetus, principally affecting cranial nerves VI and VII, and can cause transverse amputations and talipes.

Misoprostol, which is bought over the counter, is used by 50%–75% of women who attempt abortion in Brazil. However, the drug is not very effective and 80% who use the agent continue to term. Fonseca et al (4) reported a localized defect of the cranium and overlying scalp in five babies. Collins and Mahoney (2) described a male baby with hydrocephalus, digital anomalies, and equinovarus deformities. Wood et al (15) found hydrocephalus and growth retardation. Gonzalez et al (5–7) and Pastuszak et al (12) have described 51 children exposed to misoprostol, 22 of whom had *Moebius sequence*, 11 had hydrocephalus, 11 had talipes equinovarus, and 7 had syndactyly of fingers. They posited that the uterine contractions cause vascular disruption, including brain stem ischemia. Some infants have Arnold-Chiari anomaly.

Lipson et al (9) found that rats with abdominal trauma and clamping of the uterine artery produced pups with changes similar to those of misoprostol embryopathy. There is good evidence that occlusion of the subclavian artery will produce Moebius sequence (1,8,10–14).

References (Misoprostol embryopathy)

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Primidone embryopathy

Primidone, a relative of phenobarbitol, was introduced in the early 1950s for prevention of generalized tonic–chronic seizures. The first example of embryopathy was reported by Seip (8) in 1976. About 35 examples have been reported to date (1–10). Patient 1 of Myhre and Williams (4) may have had Noonan syndrome (1); however, a similar phenotype was noted by Krauss et al (3).

The clinical features include pre- and postnatal growth delay, and abnormal facies characterized by metopic ridging, thick nasal root, anteverted nares, up-slanting palpebral fissures, thin vermilion, and micrognathia. Microcephaly, jitteriness, hirsutism, hypoplastic nails, and cardiac defects [coarctation of aorta, VSD, patent ductus arteriosus (PDA), pulmonary artery hypertension, mitral valve deformity, biventricular hypertrophy] were also found.

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Radiation embryopathy

In utero radiation was known as early as the 1920s to be associated with microcephaly, mental retardation, and stunted growth, especially in infants exposed between the 8th and 15th week of gestation. In survivors of the atomic bombings of Hiroshima and Nagasaki, there has been a progressively increased frequency of malignant neoplasms, especially leukemias and lymphomas, but in subsequent pregnancies, there had been no increased rate of spontaneous abortions, stillbirths, or chromosomal abnormalities.

An estimated 0.1% rate of leukemia has been found in individuals who were within 1500 meters of the atomic bomb epicenter. Among 1600 offspring whose mothers were exposed to the bomb, the rate of mental retardation was about 2.5% at dose levels of 10–49 rads and 18% at 15–99 rads, the most critical period being between the 8th and 15th week following fertilization (5–7). Significant exposures between the second and fourth week usually resulted in spontaneous abortion. Doses of <5 rads are probably not teratogenic and an excess of 25 rads is required for evidence of obvious teratogenesis (3,4). Following exposures of 100 rads or more, infants are prone to microcephaly, hydrocephalus, microphthalmia, optic atrophy, retinal dysplasia, and cataracts (1,2a).

Data regarding the nuclear accident at Chernobyl are too confusing to assess (2).

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Retinoid embryopathy

During embryogenesis, retinoids are involved in morphogenesis of many organs: brain, craniofacies, heart, limbs, and axial skeleton, functioning as ligands bound to nuclear receptors of the steroid–thyroid hormone receptor superfamily. These receptor complexes function in transcription factor activation involved in embryologic development.

Although intake of excess vitamin A has been reported to cause embryologic damage (17a,20,22), teratogenic exposure from ingestion of isotretinoin or etretinate concerns us here. The first reports of isotretinoin teratogenicity were those of Rosa (18) in 1983 and Braun et al (3) in 1984. Isotretinoin (13-*cis*-retinoic acid), an active congener and metabolite of vitamin A, is taken orally for treatment of severe cystic acne. Unlike retinyl esters, isotretinoin is not stored in adipose tissues; its elimination half-life is less than one day. During the first trimester, it is a rather powerful teratogen, although a precise critical period has not been established. It has been estimated that about 25% of affected pregnancies reaching 20 gestational weeks have a major malformation (23,25). A mouse model has been studied (9). As with other powerful teratogens, there is a significant increase in the rate of spontaneous abortion and premature delivery (20%–25%) (17).

Etretinate has been used for severe psoriasis. In contrast to isotretinoin, etretinate accumulates in the body with an elimination half-life of about 120 days. Pregnancy should not be attempted until 2 years post-treatment (8). Among 75 pregnancies in which exposure to etretinate occurred, 6 had one or more typical manifestations. Five of 14 induced aborted fetuses had the typical stigmata (8). Over 100 cases of isotretinoin embryopathy and over 20 examples of etretinate embryopathy have been reported, mostly from North America (11,27). Acitretin can also produce an embryopathy (6).

Clinical findings. Exposure of the embryo to retinoids during the first 10 weeks may result in malformations of the brain, craniofacies, heart and major arteries, and thymus. Brain anomalies (noted in 70%) have included hydrocephalus, microcephaly, ventriculomegaly, malformations of the cerebellum and brain stem, and various cranial nerve deficits (16). Intellectual deficits were found in a series of 5-year-olds, with over 50% being in the subnormal range (1).

The skull tends to be somewhat triangular, with narrowing of the frontal area and a large occiput. Hair whorls tend to be misplaced. Abnormalities of the pinnae, seen in 70% of affected infants, range from pretragal pits to anotia with imperforate auditory canals. Those parts of the pinna derived from the second branchial arch are more susceptible than those derived from the first arch (7). The pinnae are asymmetrically microtic (4) (Fig. 2–5). Occasionally, only a tragus and slit-like canal are present. The

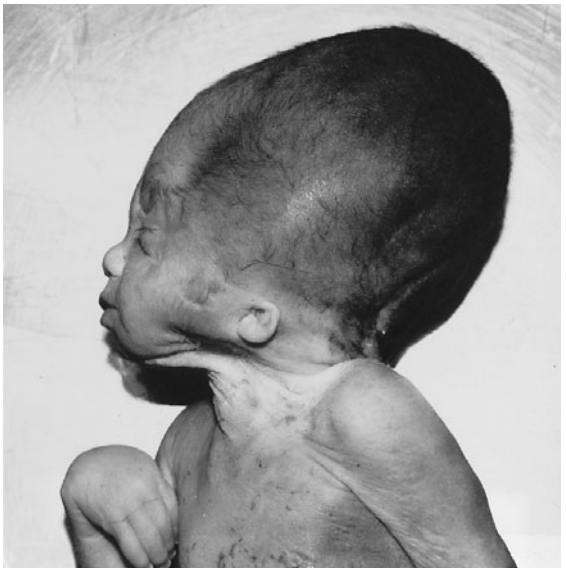

Fig. 2–5. *Retinoid embryopathy.* Note abnormal ears. (Courtesy of L Van Maldergem, Loverval, Belgium.)

ossicles of the middle ear are less frequently affected, and the inner ear, only rarely. Facial nerve paralysis on the side of the more severely affected ear may be seen. The nasal bridge and midface are often depressed. Cleft palate is found in about 15% of affected individuals (12,14,15), and the mandible is small in 35% (19). The eyes are occasionally microphthalmic (20).

Cardiac anomalies include common truncus, transposition of great vessels, atrial septal defect (ASD), VSD, tetralogy of Fallot, and aortic arch malformations. Classic DiGeorge anomaly (conotruncal malformations, thymic and parathyroid hypoplasia / aplasia) are seen in over 35% of cases (13). Retinal or optic nerve abnormalities are found in 20%. Various thymic abnormalities, such as T-cell immunodeficiency and ectopic thymic tissue in the lateral neck, occur in about 35% of affected individuals (5,13).

The external ear, palatal, mandibular, and cerebellar abnormalities can be explained by excessive cell death in the rhomboencephalic neural folds prior to the time of their emigration into the first two arches. The thymic and conotruncal abnormalities could be similarly explained as the result of a deficiency of crest cells going to the third and fourth arches (2,10,14,24,26,28).

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Rubella embryopathy

Rubella (German measles) was one of the first known teratogens, its effects having been demonstrated by the Australian ophthalmologist Gregg (3) in 1941. An excellent history of our understanding of rubella embryopathy is that of South and Sever (9). In a 1964 rubella epidemic of almost 2 million cases in the United States, an estimated 20,000–30,000 babies were damaged by the epidemic (7). Rubella contracted prior to the 11th week has a complication rate of close to 100% (principally sensorineural hearing loss and congenital heart disease), and about 35% of those infected during the 13th–16th week have complications (primarily hearing loss) (4–6,7,9,12). After 16 weeks, no stigmata attributable to rubella can be found (4). A superb survey of the teratogenic effects of rubella can be found in Webster (13).

Various studies have demonstrated that spontaneous abortion occurs in about 10% of affected pregnancies and stillbirth in about 5%, and most affected fetuses have intrauterine growth retardation (6). Approximately one-third of liveborn infants who also have thrombocytopenic purpura die during the first year of life. Major abnormalities, largely those of the eye, ear, and heart, occur in about 25% of infants exposed to rubella (1). The most commonly noted abnormalities are sensorineural hearing loss (unilateral or bilateral), mental retardation, various eye anomalies (cataract, microphthalmia, iris hypoplasia, strabismus, glaucoma, nystagmus, retinopathy, mesodermal dysgenesis), and cardiovascular anomalies (pulmonary artery stenosis, pulmonary valvular stenosis, aortic valvular stenosis, ventricular septal defect, and patent ductus arteriosus) (Table 2–3C). Diabetes mellitus develops in about 30% of adults who had rubella embryopathy. Progressive rubella panencephalitis, a "slow" virus presentation, is rare (9) (Fig. 2–6).

Cataract and glaucoma and cardiac malformations can occur in infants exposed through 12 weeks, with peripheral pulmonary stenosis occurring through 24 weeks and hearing loss through 28 weeks (9). When

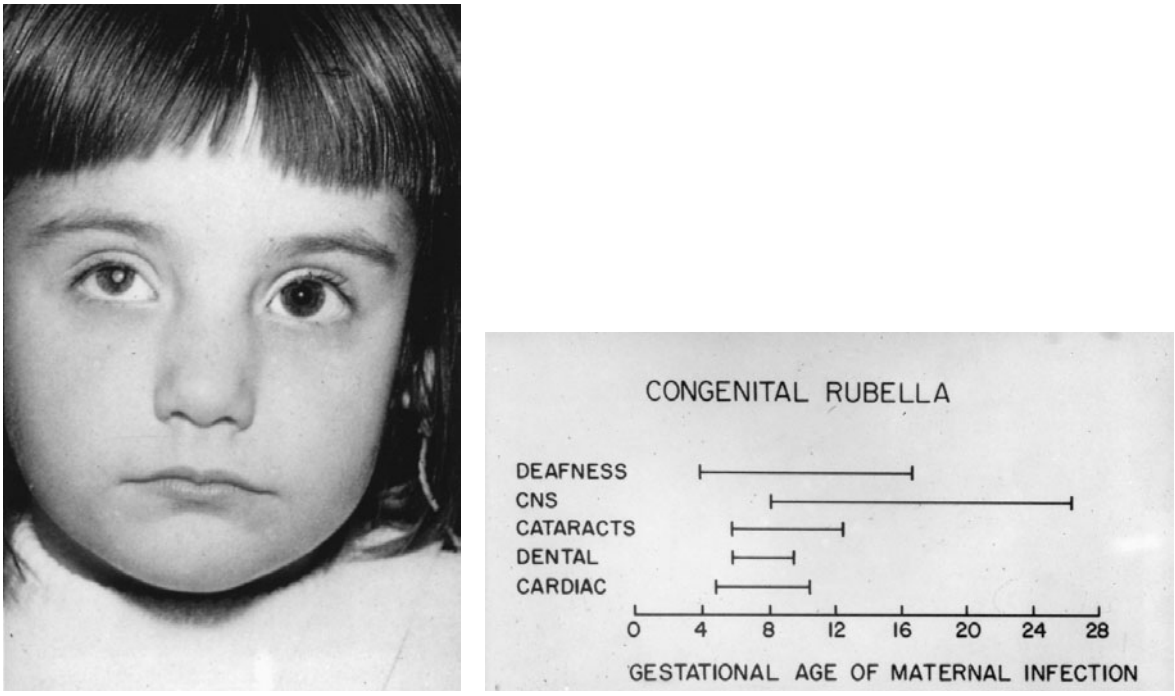

Fig. 2–6. *Rubella embryopathy.* (A) Congenital cataract. (B) Relationship of gestational age at time of maternal rubella infection to anomalies observed.

contracted during the last trimester of pregnancy, the brain is apparently not affected.

Enamel dysplasia of the primary teeth was found in 20% of infants (2).

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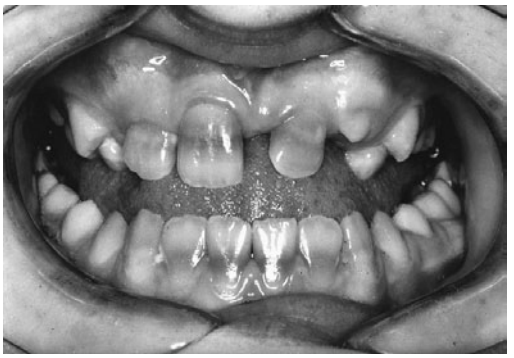
Tetracycline embryopathy

Discoloration of the deciduous or permanent teeth may result from ingestion of tetracycline by the pregnant female or by the child. Chlortetracyclines were first introduced in 1949. Since then, many homologues have become available. These yellow antibiotics fluoresce yellow under ultraviolet light, and darken in color with oxidation. The affinity of tetracycline for bone and for teeth was first demonstrated in 1956 by Schwachman and Schuster (5).

The state of tooth development determines the location and distribution of the staining. Calcification of the deciduous teeth begins during the fourth month of gestation, and the crowns of the permanent dentition begin to calcify shortly before birth, with completion occurring by the eighth year of life. Discoloration depends upon dose, time, length of administration, and the homologue of the tetracycline employed; for example, oxytetracycline stains to a lesser degree than tetracycline (1). Anterior deciduous teeth (incisors and canines) are stained from four months in utero to nine months postpartum, and anterior permanent teeth are stained from 3 months postpartum to seven years of age. Dosages of 20–25 mg/kg or greater over a period of as little as three days can produce discoloration (4).

In the 1960s, the frequency of staining peaked at about 25% among children seen in pediatric practice. However, on microscopic examination at least 50% of extracted first permanent molars from children 7–15 years of age showed at least one deposit (6). The permanent teeth were especially stained if tetracycline therapy was continued for years, such as in cystic fibrosis. The dentin is more heavily stained than the enamel (11). Tetracycline forms an orthocalcium phosphate complex with dentin and enamel that is then oxidized by ultraviolet light (7).

Fig. 2–7. *Tetracycline embryopathy.* Note dark discoloration of anterior teeth.



The deciduous teeth present a yellow to brownish discoloration of the crown located primarily near the gingival third of the incisors, and the occlusal and incisal third of the molars and canines, respectively (Fig. 2–7). In premature infants, a larger surface is stained, and enamel hypoplasia is often found. The bright yellow color which is striking upon eruption of deciduous teeth becomes brown after exposure to light. As the teeth become brown, fluorescence under ultraviolet light progressively declines (2,3,6,8,10).

Ground sections reveal a zonal pattern of staining that forms bands in the dentin corresponding to the time of administration of tetracycline, the fluorescent bands running parallel to the dentinoenamel junction following the incremental lines of growth (9) (Fig. 2–8). Decalcified sections show an increase in interglobular spaces indicating hypomaturation.

Fig. 2–8. *Tetracycline embryopathy.* Ground section of premolar tooth under ultraviolet light showing periodic deposits. (From N Kotsanos, Br Dent J 152:91, 1982.)

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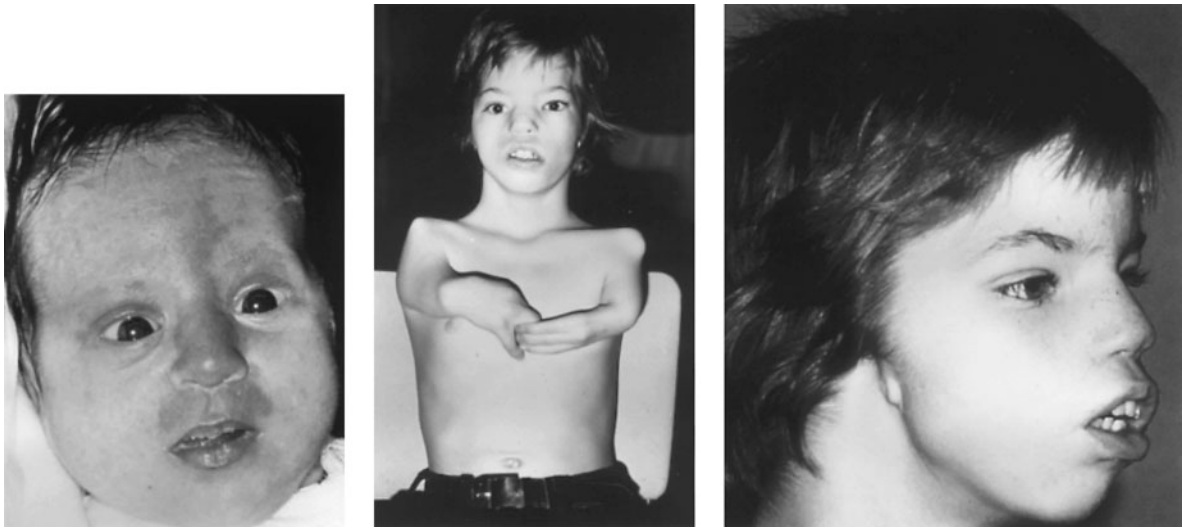
Thalidomide embryopathy

Thalidomide, used principally as a sedative for nausea during pregnancy, from 1958 to 1961 and mainly in Germany, The Netherlands, United Kingdom, Sweden, Brazil, and Japan, injured over 10,000 infants through prenatal exposure. In 1961, Wiedemann (15) noted an epidemic of limb malformations and Lenz (5) in Germany and McBride (9) in Australia attributed the cause of the malformations to thalidomide. The drug was not approved for use in the United States by the Food and Drug Administration. Frances Kelsey (4), who was in charge of the New Drug Branch, received reports that the drug caused peripheral neuritis, and had insufficient data to ensure safe use during pregnancy. The fascinating history of thalidomide embryopathy was further detailed in a series of papers published during the 25th year after recognition of the role of thalidomide in causing this epidemic (2,5,6,8). Because of its current use for leprosy, it is still a teratogenic threat in South America (3). Other recent uses are for aphthae, Behçet syndrome, lupus erythematosus, rheumatoid arthritis, diabetic retinopathy, and graft-versus-host disease (9a,14,16).

Clinical findings. The most findings have been limb defects, which range from triphalangeal thumb to phocomelia (principally of the upper limbs) (Fig. 2–9B). Aplasia of bones (thumb, radius, humerus, ulna, ulnar digits) is extremely variable, and preaxial polydactyly is not rare. The most critical period for occurrence of amelia is from days 39 to 44 following the last menstrual period or from the 27th to 30th day postconception. The peak period for occurrence of upper limb anomalies precedes that for lower limb abnormalities by a day or two. Triphalangeal thumb (digitalization) occurs most frequently if the drug is given during days 46 to 50 after the last menstrual period (2,6,7,10,11).

Facial anomalies include "stork bite" (forehead, nose, upper lip) hemangiomata, anotia, meatal microtia/atresia, stenosis, ear tags, facial palsy, external ophthalmoplegia, anophthalmia or microphthalmia, colobomata, cleft lip/palate, and choanal atresia (Fig. 2–9A,C). These anomalies are especially prominent when the thalidomide exposure is during days 20 to 29 postconception.

In addition to facial palsy, such unusual findings as jaw-winking and crocodile tear syndrome occur more frequently. Dental involvement



A B C

Fig. 2–9. *Thalidomide embryopathy.* (A) Midfacial hemangioma. (B,C) Phocomelia of both arms, absent ears. Patient also had ankylosis of temporomandibular joint, bifid uvula, and absence of one parotid gland. Mother had used thalidomide during the first three months of pregnancy. (A courtesy of H-R Wiedemann, Kiel, Germany. B,C courtesy of PJW Stoelinga, Arnhem, The Netherlands.)

consists of mild enamel dysplasia (50%) and agenesis of maxillary lateral incisors (8%), both deciduous and permanent (1).

Internal anomalies include esophageal and duodenal atresia, various cardiac defects, especially tetralogy of Fallot, PDA, ASD, VSD, pulmonary stenosis, and renal agenesis. Many of these anomalies contribute to the estimated 40% early mortality. Late involvement (46–50 days) is associated with anorectal stenosis.

The mechanism of action has never been firmly established; an excellent review of the various hypotheses is that of Stevens (12). Taken before or after the critical period, thalidomide apparently has no effect upon the embryo. In 2000, Stevens and Fillmore (13) suggested that thalidomide interfered with angiogenesis.

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Toluene embryopathy

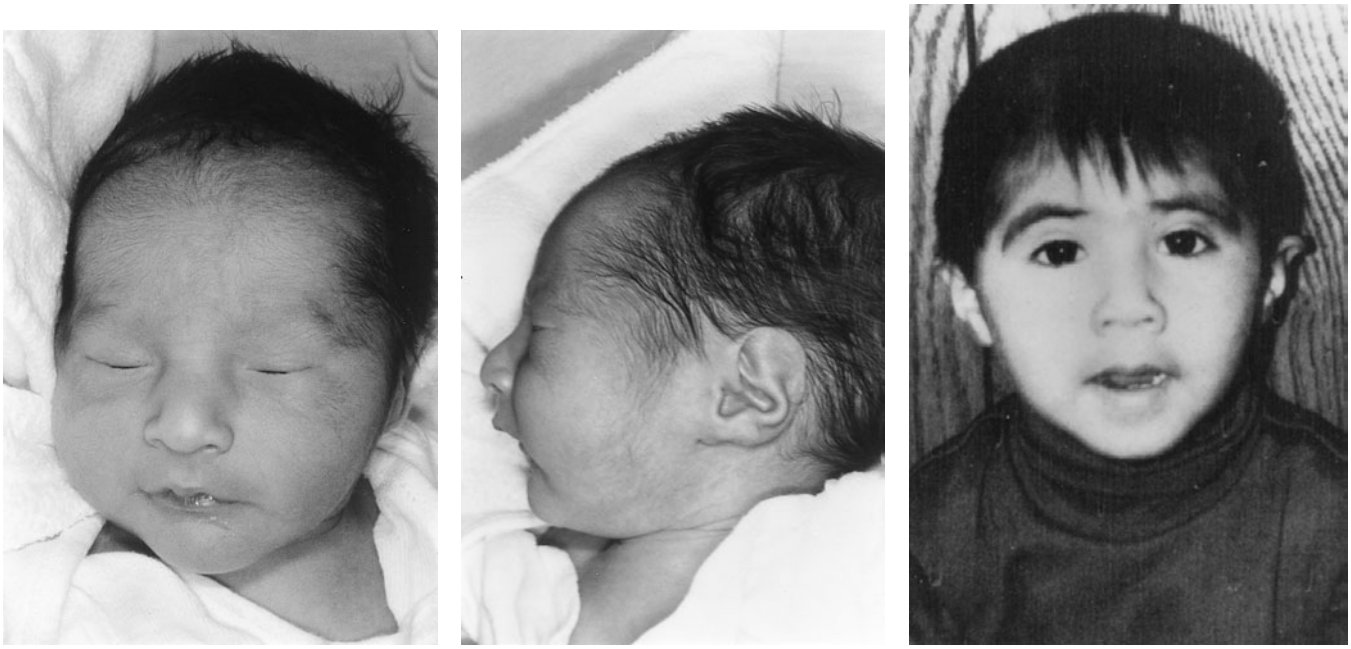
Toluene embryopathy, first described by Hudak and Ungvary (6) and Toutant and Lippman (9), is a consequence of solvent abuse (exposure to spray paint or lacquer, or glue sniffing). Paint or glue sniffing is especially common among teenagers, with some 3%–4% engaging in this activity on a regular basis. More than 50% are females in prime childbearing years (7). There is no evidence that exposure to organic solvents under normal laboratory conditions results in increased abortions or in malformed infants (2).

Toluene easily crosses the placenta, producing changes in infants that are very reminiscent of those seen in fetal alcohol embryopathy. Both toluene and alcohol probably effect a common insult to mesoderm ventral to the forebrain (7). At least 50 cases of toluene embryopathy have been reported (1–11).

Teratogenic timing and dosage have not been determined, but, as in the case of alcohol, it may be that there is no safe period. Neurogenesis is inhibited (3a).

Clinical findings. Prematurity (40%), pre- and postnatal growth deficiency (50%), prenatal microcephaly (33%), postnatal microcephaly (67%), and developmental delay (80%) occur. The facies is similar to that noted in *alcohol embryopathy*: micrognathia (65%), midfacial hypoplasia (65%), small palpebral fissures (65%), dysmorphic pinnae (60%), narrow bifrontal diameter (50%), abnormal scalp hair pattern (45%), thin upper lip and smooth philtrum (35%), small nose (35%), downturned corners of the mouth (33%), and large anterior fontanel (20%) (10) (Fig. 2–10). Nail hypoplasia (40%), altered palmar creases (35%), blunt fingertips (50%), clinodactyly (20%), hypotonia or hypertonia (35%), hemangiomata (30%), and hydronephrosis (25%) are additional findings (1,4,5,7,8,10,11). Similar findings have been noted in the offspring of mice and rats exposed to a variety of industrial solvents (3).

Findings more common in toluene embryopathy than in alcohol embryopathy include prematurity, micrognathia, ear abnormalities, narrow



A B C

Fig. 2–10. *Toluene embryopathy.* (A,B) Micrognathia, small palpebral fissures, ear anomalies, thin upper lip, and abnormal scalp hair patterning. (C) Microcephaly, short palpebral fissures, midfacial underdevelopment in 2-year-old boy. Note similarity to fetal alcohol embryopathy. (From MA Pearson et al, Pediatrics 93:211, 1994.)

bifrontal diameter, abnormal hair patterning, and large fontanel. The nose is less severely reduced than in alcohol embryopathy.

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Trimethadione embryopathy

As with other anti-epileptic drugs, it has been difficult to define distinct effects of trimethadione on growth and morphogenesis because so few epileptic women receive monotherapy. German et al (3) appear to be the first to have noted a teratogenic association with tridione in 1970. Spontaneous abortion or miscarriage occurs in about 25% of women taking trimethadione.

The most frequent features reported in association with taking paramethadione (Paradione) and trimethadione (Tridione), both oxazolidinediones, include a dysmorphic facies consisting of V-shaped eyebrows, low nasal bridge, anteverted nares, hypertelorism, occasional ptosis and/or epicanthic folds, mildly down-slanting palpebral fissures, and low-set, posteriorly rotated pinnae (Fig. 2–11). Cleft lip/palate was found in 25% of affected infants (6). About 5% had tracheoesophageal abnormalities (2). Mild mental delay was found in 50% with only intrauterine growth retardation and mild postnatal growth deficiency. About 50% of affected individuals have a mild reduction in head circumference. Speech is retarded in over 60% (1–8).

Congenital heart anomalies noted in 50% of affected infants have included PDA, pulmonic stenosis, tetralogy of Fallot, VSD, and coarctation of the aorta. Inguinal and/or umbilical hernia has been noted in 15%. Renal malformations and hypospadias were observed in 30% of cases.

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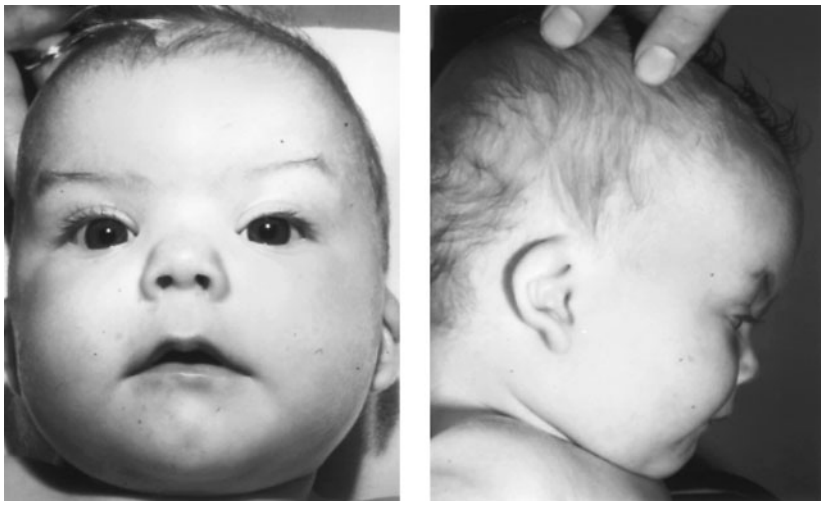
Valproate embryopathy

Valproic acid (Depakene) was first marketed in Europe in 1967 and in the United States in 1978 for treatment of seizure disorders. Although it may be used as the only agent, polytherapy with phenytoin, phenobarbitol, and carbamazepine is relatively common. Valproate use probably increases the risk of abnormalities in the developing fetus by 2–3 times that of the general population. The earliest reports of valproate embryopathy are



A B

Fig. 2–11. *Fetal trimethadione syndrome.* (A) V-shaped eyebrows and (B) dysplastic ears. (Courtesy of JW Hanson, Iowa City, Iowa.)

those of Dalens et al (10) in 1980, Gomez (12) in 1981, and Bjerkedal et al (3) in 1982. Over 100 cases have been reported.

We feel that the facies of valproate embryopathy is not significantly different from that produced by use of hydantoin (phenytoin, Dilantin) or carbamazepine (Tegretol). Facial changes include midface hypoplasia (60%), short, upturned nose with broad or flat nasal bridge (50%), epicanthic folds, mild dysmorphic changes in the pinnae, long flat philtrum, thin vermilion, and small mandible (4,5,8,15,21,23) (Fig. 2–12). Occurrence of cleft lip and/or palate is apparently not increased (17). Prominent metopic ridge, outer orbital ridge deficiency, and bifrontal narrowing are more often seen in valproate embryopathy. Developmental delay and hypotonia were found in up to 90% of affected patients (1,2,11,14). The variable effect on sib pairs has been discussed by Chitayat et al (6) and Christianson et al (7). Other findings include lumbosacral meningomyelocoele or meningocoele (1%–5%) (5,16,19,20), talipes equinovarus, and tracheomalacia or stridor.

Genital anomalies, seen in 30% of affected individuals, include hypospadias and cryptorchidism in males and incomplete fusion of müllerian duct structures in females. Cardiac abnormalities, seen in 20%, include VSD, coarctation of the aorta, and PDA (22). Anomalous right pulmonary artery has also been described (18).

Limb anomalies, noted in 65%, are usually mild ones: clinodactyly of fifth fingers and distal phalangeal hypoplasia (20a). However, radial ray reduction has also been described (13). Rodriguez-Pinilla et al (20a) noted that 36% of cases have congenital limb defects. Joint laxity has been noted (17a).

Postnatal growth is normal. Although there is global developmental delay, expressive speech delay is greater than receptive speech delay. Gross motor delay is less marked (6). Hyperactivity, learning difficulties, autistic features, and fine motor delay are frequent (17a).

Myopia has been described in 35% (17a).

Experimental teratogenesis has been reviewed by Cotariu and Zaidman (9).

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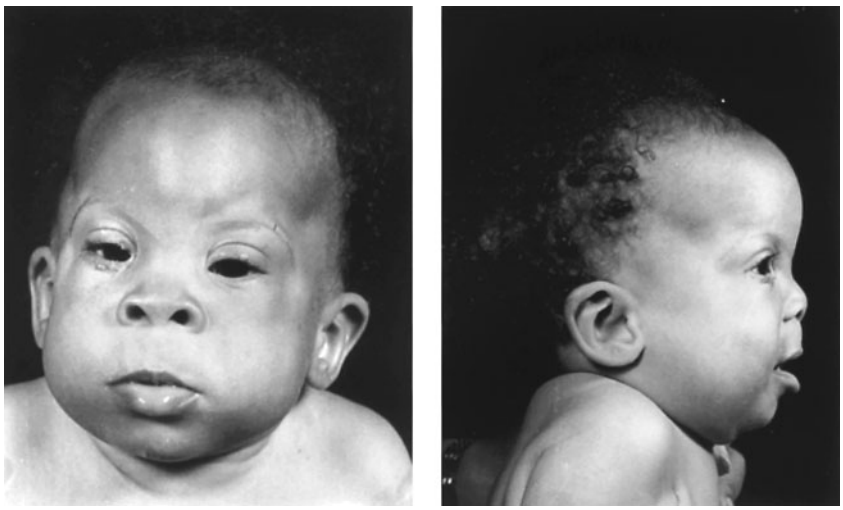

A B

Fig. 2–12. *Valproic acid embryopathy.* (A,B) Narrow bifrontal diameter, relative deficiency of outer orbital region, midface hypoplasia, short nose, broad flat nasal bridge, long flat philtrum, thin vermilion border of upper lip, and low-set posteriorly angulated ears. (From HH Ardinger et al, Am J Med Genet 29:171, 1988.)

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Varicella embryopathy

Infection with the varicella zoster virus during the first two trimesters of pregnancy causes fetal damage in 2.5% of the cases (4,9). Estimated incidence in the United Kingdom is 3/1000 (9), and in recent prospective studies, the rate of affected offspring has ranged from 0% to 9.1% (4,6,9,11). In 1947, Laforet and Lynch (8) first described multiple congenital defects following maternal varicella. A specific syndrome was postulated by Srabstein et al (13); at least 50 cases have been reported (4).

Findings in 10%–50% of reported cases include limb paralysis and various neurologic problems (hydrocephalus, microcephaly, cortical atrophy, mental retardation, weak cry, seizures, Horner syndrome, bulbar dysphagia, anal sphincter dysfunction, and phrenic nerve palsy) (5). Skeletal changes include talipes and hypoplastic scapulae, clavicles, ribs, fingers, or toes. Only rarely are gastrointestinal and genitourinary anomalies found (7). Cutaneous scars with dermatomal distribution are seen in over 50% of affected individuals. Eye anomalies include chorioretinitis, anisocoria, nystagmus, cataracts, and microphthalmia (1–3,8,10,12,14).

Asymptomatic fetal infection after maternal zoster infection is not uncommon but does give rise to varicella embryopathy.

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Warfarin and vitamin K deficiency embryopathy

Warfarin (coumadin), employed as a blood thinner for those having artificial heart valve replacement or because of thromboembolic disease, crosses the placental barrier. In 1966, DiSaia (4) may have been the first to report Warfarin embryopathy. In addition to an increased rate of spontaneous abortions and stillbirths, Hall et al (6) found that about 15% of such pregnancies resulted in abnormal liveborn infants, 15% in abortion or stillbirth, and about 70% in normal births. Wong et al (33) noted that 60% were spontaneously aborted or were stillborn. Iturbe-Alessio et al (11) and Wong et al (33) found that 15%–30% of pregnancies exposed to coumadin during the first trimester showed signs of the embryopathy. A rat model has been created using large doses of Warfarin and vitamin K1 (8).

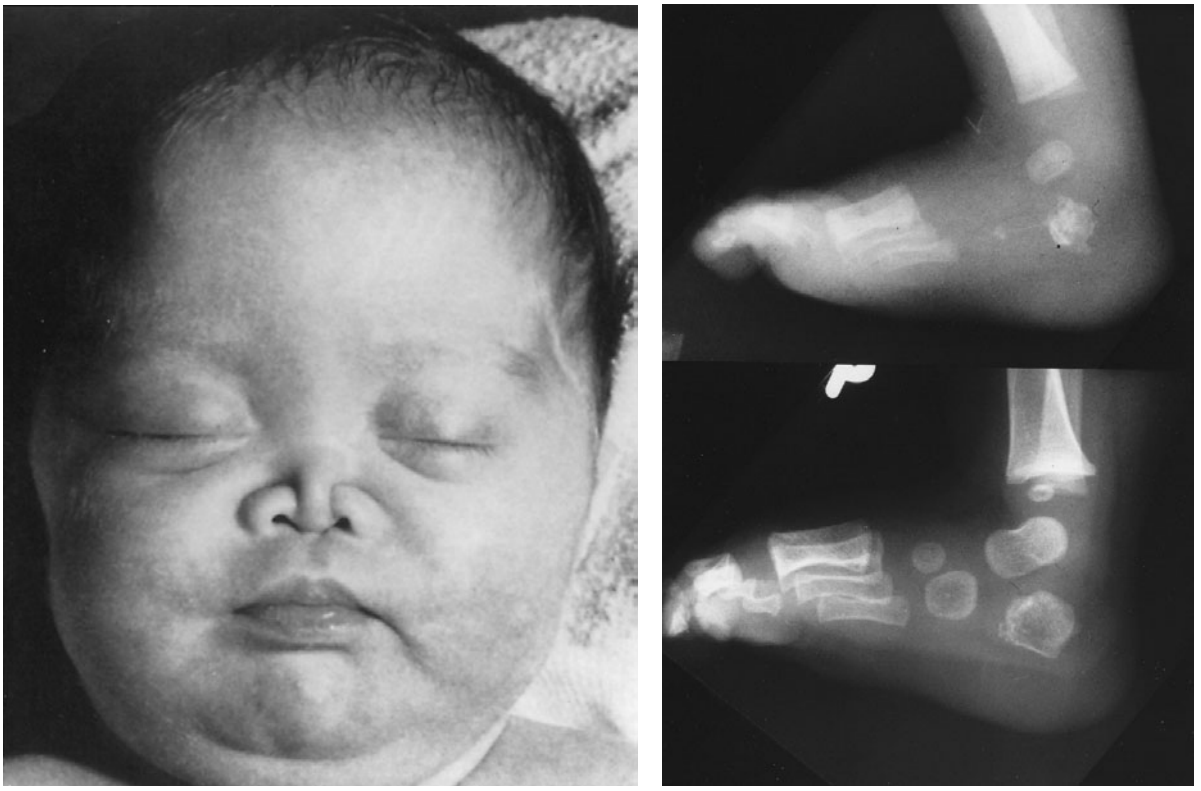
About 35% of infants exposed to coumadin anticoagulants during pregnancy die prenatally or suffer serious teratogenic consequences. Among those who survive, approximately 30% manifest prenatal growth deficiency. The most severe teratogenic damage occurs from 6 to 9 weeks postconception (3,12,19). After 9 weeks, ocular defects and central nervous system (CNS) malformations and hemorrhages are most characteristic. When taken after the first trimester, there is no effect on skeletal growth (30a).

Clinical findings. The most striking finding, although in itself rare (4%), is the hypoplastic nose (Fig. 2–13A). Exposure during the sixth-ninth week results in premature calcification of nasal cartilages (vide infra). The nose is small with upturned, narrowed nares. The nose often appears sunken into the face (1,2,5,7,20,24). Choanal narrowing or even choanal stenosis causes the breathing and/or feeding difficulties seen in about 70% during the first few months of life (15,29). In many cases, there is improvement both functionally and cosmetically with time.

When Warfarin is taken at any time during pregnancy, there is a 3% chance for CNS abnormalities (mental retardation, microcephaly, hydrocephaly, agenesis of the corpus callosum, Dandy-Walker malformation, seizures, and hearing loss) (12,13,22). Of those with Warfarin embryopathy, about 30% have mental retardation. Eye anomalies, which are also rare, include corneal opacities, cataract, optic atrophy, and microphthalmia (12,19,21,25).

Bone abnormalities of the axial and appendicular skeleton may be striking. The epiphyses of long bones (especially the femur), vertebrae, ribs, calcanei and cuboids, scapulae, terminal phalanges, and carpal and tarsal bones manifest a stippled radiographic appearance (10,26,28,32,34) (Fig. 2–13B). The paravertebral lumbosacral and cervical areas of the spine are especially affected. Brachydactyly is noted in 40%. The punctate features disappear with age by resorption or incorporation within bone. The laryngeal and nasal cartilages may appear calcified on X-ray. While short stature is seen in 35% (33), asymmetric growth is not observed.

Premature calcification occurs because Warfarin prevents the reduction in vitamin K, resulting in gamma carboxyglutamation of osteocalcins or



A B

Fig. 2–13. *Warfarin embryopathy.* (A) Hypoplastic nose with groove between alae and nasal tip. (B) Note stippling of calcaneus. (B courtesy of JG Hall, Vancouver, BC.)

other vitamin K–dependent bone proteins. Because osteocalcin binds less to calcium, it is deposited in the fetal cartilage (6,17,18). This mechanism of vitamin K deficiency also occurs in various forms of *chondrodysplasia punctata* and *Binder phenotype* (8,23). In the case of the former, there appears to be a mutation in arylsulfatase E (4a); in Warfarin embryopathy, it results from competitive inhibition by Warfarin (23). Thus, Warfarin embryopathy is a phenocopy for these disorders (30). Pauli et al (19) described the simultaneous occurrence of chondrodysplasia punctata and congenital deficiency of vitamin K–dependent coagulation factors in an infant and posited that there was a deficiency of vitamin K epoxide reductase.

If the mother is taken off Warfarin and given heparin, which does not cross the placenta, from the 6th to the 12th week of gestation, no signs of the embryopathy present. However, if she remains on Warfarin until the beginning of the eighth week, then about 25% of exposed infants have anomalies (12).

Differential diagnosis. Various forms of *chondrodysplasia punctata* and *Binder phenotype* must be excluded if, indeed, the latter is not a variant of the former or an expression of prenatal vitamin K deficiency (9,27). Various causes of stippled epiphyses include *Zellweger syndrome,* hypothyroidism, and genetic disorders of vitamin K metabolism (14,19). Malabsorption due to celiac disease, short bowel syndrome, and jejunalilial bypass will produce vitamin K deficiency and the associated syndrome in infants of pregnant mothers (16). Prenatal diagnosis of vitamin K deficiency embryopathy (31) has been made.

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Table 2–3A. Other drug and chemical hazards to the fetus

Agent	Congenital abnormalities
Environmental chemicals	
Organic mercurials	Microcephaly, cerebral palsy, mental retardation
Polychlorinated biphenyls (PCBs)	"Cola-colored" babies, growth deficiency, natal teeth, exophthalmos
Prescription drugs	
Anticancer agents	
Alkylating agents (e.g., chlorambucil, nitrogen mustards)	Fetal death, growth and mental deficiency, ocular, genitourinary, and limb malformations, cleft palate
Antibiotics	
Tetracyclines	Brownish yellow teeth, hypoplastic enamel
Streptomycin	Hearing loss
Kanamycin	Hearing loss[a]
Aminoglycosides (e.g., gentamicin)	Hearing loss[a]
Chloroquine	Ocular defects,[a] hearing loss[a]
Anticonvulsants	
Barbiturates (and primidone)	Possible syndrome, present evidence inconclusive[a]
Diazepam	Low risk for facial clefts[a]
Psychotropic agents	
Meprobamate[b]	Brain, heart, palate, and limb defects[a]
Benzodiazepines[b]	Cleft palate[a]
Thalidomide[c]	Facial asymmetry, cranial nerve palsies, cochlear hypoplasia with deafness, hypoplastic teeth, low nasal bridge with broad nasal tip, choanal atresia, colobomas, microphthalmia, cataracts, microtia, facial capillary hemangiomas, phocomelic limb defects
Lithium	Ebstein anomaly
Methimazole	Aplasia cutis, choanal atresia, absent nipples

[a]Proposed association; magnitude of risk uncertain; more information needed.

[b]These drugs have not been clearly associated with congenital defects, and available information is insufficient to ascribe specific risk estimates. In each case, if the risk is increased at all, it is estimated to be very low.

[c]Though thalidomide is of major historical interest, its clinical significance has waned somewhat, except for continuing legal problems and the health management issues among affected person. Nonetheless, it is important to note that this drug continues to be used in some parts of the world for the treatment of epilepsy and major aphthae. Accordingly, new cases still appear sporadically.

Table 2–3B. Hazardous maternal metabolic and genetic factors for the fetus

Factor	Effects
Diabetes mellitus (insulin dependent)	Cardiovascular, renal, and neural tube defects, facial clefts, holoprosencephaly, caudal regression syndrome
Phenylketonuria	Mental retardation, growth deficiency, microcephaly, heart defects,[a] vertebral defects,[a] fetal death[a]
Myotonic dystrophy	Severe early-onset myotonic dystrophy, arthrogryposis, heart defects,[a] hernia,[a] hydrocephaly,[a] hydronephrosis,[a] facial clefts[a]

[a]Proposed association; magnitude of risk uncertain; more information needed.

Table 2–3C. Infectious teratogenic agents

Agent	Congenital abnormalities
Viruses	
Rubella	Ocular and cardiovascular anomalies, deafness, microcephaly, immune and endocrine disturbances, delayed skeletal development, growth deficiency, mental deficiency
Cytomegalovirus	Ocular and cardiovascular anomalies, deafness, microcephaly, hydrocephaly, gastrointestinal tract anomalies,[a] growth deficiency,[a] mental deficiency
Herpes simplex	Ocular anomalies, microcephaly, patent ductus arteriosus, hypoplastic distal phalanges, growth deficiency,[a] mental deficiency
Varicella zoster	Ocular anomalies, microcephaly, hypoplastic limbs, neurogenic muscular atrophy, cutaneous defects, growth deficiency, mental deficiency
Bacteria	
Treponema pallidum	Ocular, dental, and skeletal anomalies, hydrocephaly, microcephaly, cutaneous lesions, nerve palsies, nephrosis, growth deficiency, mental deficiency
Mycoplasmas	Neural tube defects,[a] aneuploidy,[a] growth deficiency,[a] mental deficiency[a]
Parasites	
Toxoplasma gondii	Ocular anomalies, microcephaly, hydrocephaly, deafness, growth deficiency, mental deficiency
Possibly hazardous agents	
Influenza viruses	Neural tube defects,[a] hydrocephaly[a]
Lymphocytic choriomeningitis virus	Hydrocephaly[a]
HTLV-III(AIDS virus)[b]	Growth deficiency, microcephaly, hypertelorism, prominent forehead, short nose with low nasal bridge, long, slanting palpebral fissures, blue sclerae, triangular philtrum, patulous lips
Pestiviruses	Microcephaly

[a]Proposed association; magnitude of risk uncertain; more information needed.

[b]Present evidence clearly indicates that HTLV-III can be passed to the fetus from an infected mother. However, the dysmorphic features reported in some infants with documented prenatal infection are still of uncertain significance. No data have yet established whether these reported findings are the consequence of prenatal disturbances of growth, or may represent postnatal changes; nor have susceptible prenatal periods been defined.

Table 2–3D. Physical hazards to the fetus

Agent	Effects
Radiation	
High levels	Microcephaly, ocular defects,[a] mutations, malignancy
Heat or fever	Neural tube defects, other CNS anomalies,[a] mental retardation[a]
Mechanical factors	
Oligohydramnios, multiple gestation, uterine malformation	Positional deformities, limb reduction defects,[a] mandibular hypoplasia[a]
Amniotic bands	Syndactyly, prenatal limb amputations, atypical facial clefts, exencephaly, encephalocele, thoracogastroschisis, ocular defects

[a]Proposed association; magnitude of risk uncertain; more information needed.

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Other teratogenic agents

A number of other agents (1–29) have less dramatic or less well-characterized effects on craniofacial growth and development. These teratogens and their respective effects are summarized in Tables 2–3A–D. It can be anticipated that this list may be expanded substantially as further information becomes available.

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Chapter 3
Chromosomal Syndromes: Common and/or Well-Known Syndromes

Trisomy 21 syndrome (Down syndrome)

Trisomy 21 is the most common and best known of all malformation syndromes. More than 100 different signs have been reported (160). The reader is referred to the following sources: comprehensive coverage (10,136,160), biology (6,124), anatomic aspects (11,48,169), pediatric aspects (35,76,175), central nervous system manifestations (10,39,160,187), growth charts (41), craniofacial aspects (97), craniofacial pattern profiles (3), oral manifestations (34), contribution of S. Langdon Down and other history (76a,125,182), cytogenetic considerations and recurrence risk counseling (2,14,23,35,51,54,70,74,79,84–86,94,96, 111,115,118,122,123,126,130,145,160,164–168,178,183), prenatal screening (4,91,171), epidemiology (110), life tables (9), frequency of malformations (95,176), associated tumors (146), presentations for parents of an affected child (87,159).

In 1866, Langdon Down (107) described a condition that he named "mongolian idiocy." A description of the syndrome also appeared in the works of Séguin (150), who called the condition "furfuraceous cretinism" as early as 1846. Lejeune (109) demonstrated in 1959 that the condition was associated with an extra G group chromosome; in 1960, Polani et al (133) reported translocation-type Down syndrome; and Clarke et al (28) observed mosaicism for an extra G group chromosome in 1961.

Prevalence. The birth prevalence of trisomy 21 syndrome is generally stated to be 1/650 live births, but it is known to vary in different populations from 1/600 to 1/2000 live births. Fifteen percent of patients institutionalized for mental retardation have trisomy 21 (77,110,160). It has been estimated that from 65% to 80% of trisomy 21 conceptions result in spontaneous abortions (160). The prevalence in Japan has been discussed by Hoshi et al (88).

Cytogenetics and recurrence risks. Approximately 95% of all cases of Down syndrome result from nondisjunction. Although the syndrome occurs in offspring of mothers of all ages, the risk increases with increasing maternal age. The birth prevalence is 0.9/1000 when the mother is less than 33 years of age, 2.8/1000 when the mother is 35 to 38 years old, and 38/1000 when the mother is 44 years old or older (74). The association of advanced maternal age and nondisjunction has been discussed by several authors (86,94,178). Nondisjunction may occur during the first or the second meiotic division in either the female or male parent (94,115,118) (Table 3–1). The possibility of paternal age effect has been discussed by several investigators (145,167). The occurrence of a genetic predisposition or nondisjunction gene has been debated, and although the risk of trisomy 21 in second and third degree relatives of an individual with nondisjunction-type Down syndrome has been shown to be no greater than the risk to the general population (2,54), the recurrence risk for free trisomy 21 in couples with one affected child is generally accepted to be 1% (168). Rarely, unusual recurrences of free trisomy 21 are reported, such as three affected first cousins (23). Approximately 1 in 200 patients with trisomy 21 syndrome has a double primary nondisjunction, the most frequent type being 48,XXY,+21(78).

Approximately 4.8% of Down syndrome cases are caused by an unbalanced translocation, either arising de novo or being transmitted from one of the parents (70). Information available about translocation-type Down syndrome appears in the following references and tables: frequency of different types of translocations (74,111,160) (Table 3–2), ratio of de novo to inherited translocations (111) (Table 3–3), frequency of maternal and paternal origins of inherited translocations (77,94,111) (Table 3–1), and recurrence risks for translocation-type Down syndrome when one parent is a carrier (51,77,111,165,166) (Table 3–4).

Detectable mosaicism is found in approximately 3% of trisomy 21 cases (79); the Down syndrome phenotype may not be fully expressed. Although it is frequently assumed that the extra chromosome 21 in mosaic Down syndrome arises from nondisjunction in a chromosomally normal zygote, evidence based on maternal ages suggests that a large proportion of such cases arise from meiotic nondisjunction followed by a "normalizing" mitotic error (126,140). Mosaic normal/trisomy 21 patients show a significantly decreasing percentage of trisomy 21 cells with age (130,183). If gonadal mosaicism occurs in a parent, it is possible to have a child with Down syndrome (77).

Fertility in female Down syndrome patients has been well documented. Not uncommonly, a male relative is the parent. In about 50% of cases, the offspring has Down syndrome. Fertility in male Down syndrome patients is probably severely reduced but documented examples of fatherhood have been published (12,156).

Screening. Different types of prenatal screening, detection rates, and false-positive rates have been discussed by Johnson and Summers (91). Assessment of risk by combining maternal age, fetal nuchal translucency, and invasive testing in 5% of the pregnant population with the highest risk would identify about 80% of trisomy 21 pregnancies (4). The predictive value of triple screening [maternal serum α-fetoprotein, (AFP), human chorionic gonadotropin (hCG), and unconjugated estriol (uE3)] has been discussed by Tahski et al (171).

Mortality. In spite of advances in health care of the retarded and a gradual increase in the life span of those affected with Down syndrome, the average life expectancy is still 35 years (172). The periods of highest mortality risk are in infancy when congenital heart disease, leukemia, and respiratory diseases play a role and late adulthood when Alzheimer's disease and declining immunological function are significant. Estimates during the 1960s and 1970s vary from a 12-fold to a 124-fold increase in mortality from pneumonia and other infectious diseases. Death due to congenital heart disease is highest during the first 2 years of life and only 40%–60% of Down syndrome children with congenital heart

Table 3–1. Origin of nondisjunctions and inherited translocations

	Maternal (%)	Paternal (%)
Overall origin of nondisjunction	80	20
Ratio of first-to-second meiotic nondisjunction	80/20	60/40
Origin of inherited D/G translocations	93	7
Origin of inherited G/G translocations	50	50

(Based on TJ Lister and O Frota-Pessoa, Hum Genet 55:203, 1980; RC Juberg and PN Mowrey, Am J Med Genet 16:111, 1983; and JL Hamerton, Human Cytogenetics, Academic Press, New York, 1971.)

Table 3–2. Frequencies of different types of translocations

Type	Percent
t(Dq21q)	54
t(14q21q)	(58)
t(13q21q)	(22)
t(15q21q)	(20)
t(21qGq)	41
t(21q21q)	(83)
t(21q22q)	(17)
t(21qOther[a])	5

[a] For example, chromosomes 1, 2, 6, 7, 12, and 19 (160).

(Based on J de Grouchy and C Turleau, Autosomal disorders. In: Principles and Practice of Medical Genetics, Churchill Livingtstone, Edinburgh, 1983; and TJ Lister and O Frota-Pessoa, Hum Genet 55:203, 1980.)

disease live to age 10. Recent life expectancy figures have been provided by Baird and Sadovnick (9). Neoplastic disease accounts for approximately twice the expected number of deaths, which are mostly attributable to leukemia, but lymphomas and other neoplasms such as testicular carcinoma, retinoblastoma, and central nervous system tumors have also been reported with Down syndrome (124,160,172).

Common clinical diagnostic features. Hall (76) noted 10 common signs in the newborn period: hypotonia, poor Moro reflex, hyperextensibility of joints, loose skin on the nape, flat facial profile, up-slanting palpebral fissures, short ears with overhanging helices, dysplastic pelvis, clinodactyly of fifth fingers, and single palmar creases. At least four of these abnormalities were present in all of his cases, and six or more were present in 89% (Table 3–5). Other common signs include short stature, mental retardation, brachycephaly, flat occiput, epicanthic folds, Brushfield spots, fine lens opacities, open mouth with protruding tongue (Fig. 3–1A–D), short neck, short broad hands, distally placed axial triradii, wide gap between the first and second toes, and tibial arch pattern (160). Common physical findings in children and adults are listed together with their respective frequencies in Table 3–6, which is based on the combined data of Øster (129) and Domino and Newman (47).

A number of diagnostic indices have been developed. Rex and Preus (139) developed an index of eight phenotypic features capable of clinically diagnosing 95% of patients suspected of having Down syndrome. Various dermatoglyphic indices have also been developed (vide infra).

Growth and skeletal abnormalities. Both prenatal and postnatal growth deficiency are evident in Down syndrome. The average length is 2–3 cm less and average weight is 400 g less than for normal infants. There is also a tendency toward premature birth, although prematurely born Down syndrome infants are smaller than their premature counterparts for gestational age. Postnatally, both height and weight are usually 2–4 SD below those of the general population. Bone age is normal to advanced at birth and thereafter slows down so that by 3 years of age, osseous maturation is significantly delayed. For final height attainment, males average approximately 151 cm and females average approximately 141 cm. Among the most characteristic skeletal findings are flaring of the iliac wings and brachymesophalangy of the fifth fingers (160). Radiographic criteria for the diagnosis of Down syndrome in stillborn infants has been discussed by Dasgupta et al (44). Hand development in Down syndrome fetuses has been studied by Kjaer et al (99).

Table 3–3. Translocations

Characteristic	Type of translocation	
	D/21 (%)	G/21 (%)
De novo	53	91
Inherited	47	9

(Based on TJ Lister and O Frota-Pessoa, Hum Genet 55:203, 1980.)

Table 3–4. Recurrence risks for translocation-type trisomy 21 syndrome when one parent is a carrier[a]

Type of translocation	Risk (%)
D/G maternal	10
D/G paternal	2–5
G/G (21/22)	4
G/G (21/22)	100[b]

[a] The theoretical risk is that one-third of the offspring of a translocation carrier will have Down syndrome, but the actual risk is much lower, being related, in part, to in utero loss of Down syndrome fetuses.

[b] t(21q21q) results in monosomic or trisomic zygotes. Since monosomy for chromosome 21 does not produce a viable zygote, all viable zygotes will have translocation type Down syndrome.

(Based on TJ Lister and O Frota-Pessoa, Hum Genet 55:203, 1980; J Stene, Ann Hum Genet 34:93, 1970 and Hum Genet 20:465, 1970; B Dutrillaux and J Lejeune, Ann Genet 12:77, 1969; and JL Hamerton, Human Cytogenetics, Academic Press, New York, 1971.)

Central nervous system and performance. Fetal brain growth is clearly delayed, so that infants commonly are microcephalic at birth (10,50). A decrease in total brain weight has been observed (127,161). Neuropathologic examination has demonstrated that the cerebellum and certain nuclei in the brain stem appear to be smaller than normal. Specific deficits have been documented in certain areas, such as auditory sequencing (46,137), color retention (158), short-term memory (114,137), articulation (46,55,102), visual–motor tasks (114,137), ability to differentiate between symbols (114,137), and language development.

Various other lesions of the brain have been observed, including anomalous structure of the peduncles of the cerebellar flocculi and fibrous gliosis of the white matter (121). Many pathologic findings have been reported in the brain and spinal cord by Benda (10). Pi et al (132) and Urioste et al (180) reported holoprosencephaly in association with trisomy 21 syndrome. Moyamoya disease occurs with somewhat increased frequency (43a).

Pathologic observations of the brain in older patients demonstrate the atrophic changes characteristic of Alzheimer's disease. Senile plaques, neurofibrillary tangles, and granulovacuolar changes have been observed with both light and electron microscopy. In some patients, dementia follows slowly progressive intellectual and emotional deterioration; others seem less obviously affected (17,52,61,74,101,116,128,161). Heston (81) and Heston and Mastri (82) reported that relatives of probands with classic Alzheimer's disease had an excessive frequency of trisomy 21 syndrome and myeloproliferative disorders. The gene for amyloid beta-A4 precursor protein, which is found deposited in the brains of patients with Alzheimer's disease as well as in older individuals with Down syndrome, maps to chromosome 21. The overexpression of the gene appears to be responsible for the Alzheimer-like histopathologic features of Down syndrome (5).

Neoplasms of the brain and retinoblastoma have been reported occasionally with Down syndrome, but far less frequently than leukemia (124).

Table 3–5. Hall's ten cardinal features of trisomy 21 syndrome in the newborn[a]

Feature	Percent
Hypotonia	80
Poor Moro reflex	85
Hyperextensibility of joints	80
Excess skin on back of neck	80
Flat facial profile	90
Slanted palpebral fissures	80
Anomalous auricles	60
Dysplasia of pelvis	70
Brachymesophalangy of fifth finger	60
Single palmar crease	45

[a] 100% have at least four features and 89% have six or more features.

(Based on B Hall, Acta Paediatr Scand (Suppl) 154:1, 1964.)

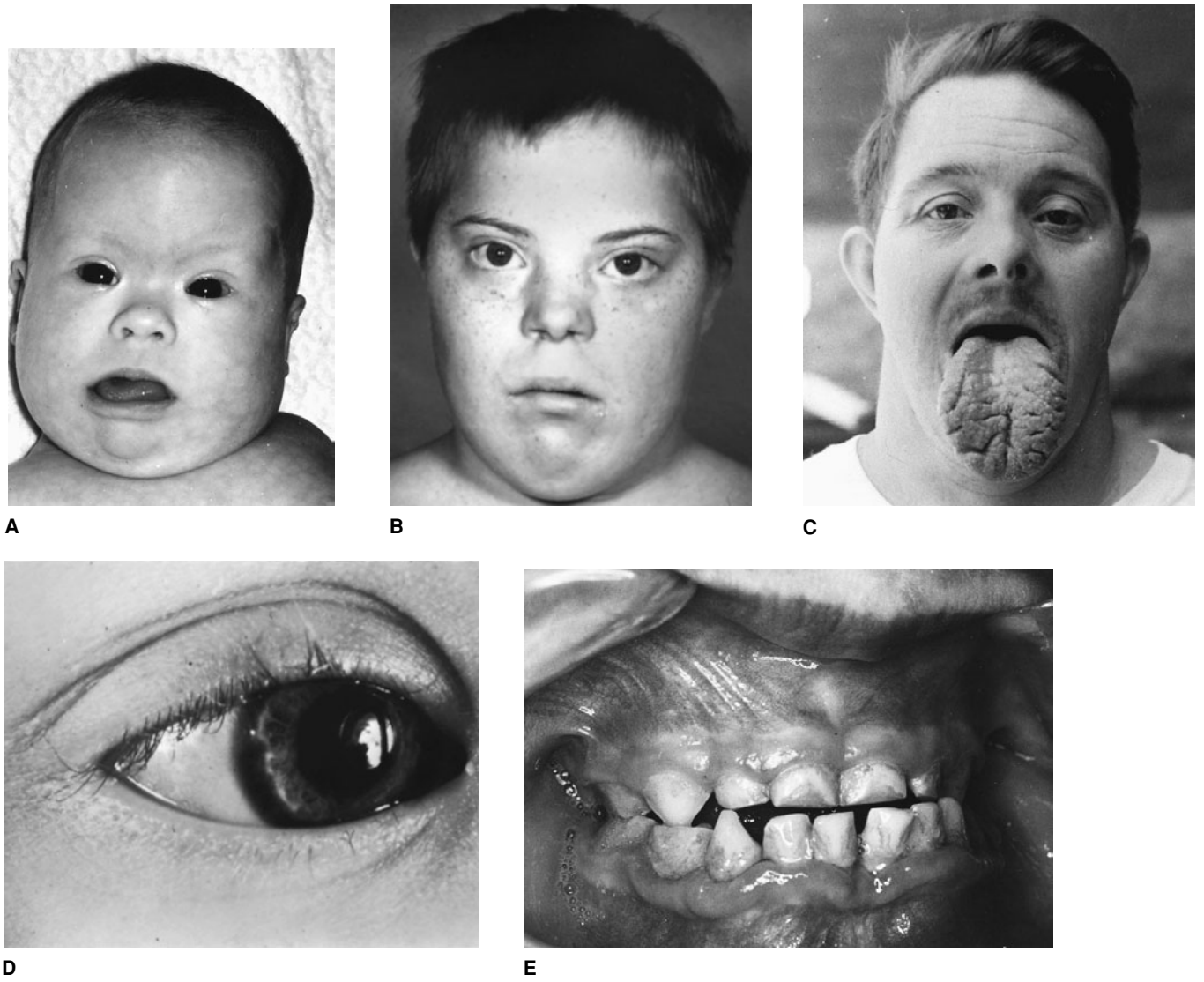

Fig. 3–1. *Trisomy 21 syndrome (Down syndrome).* (A) Typical facial appearance with up-slanting palpebral fissures, low nasal bridge, button-like nose, tendency of the mouth to be open with the tongue protruding. Note also overfolding of helix and cutis marmorata. (B) Compare facies to A and C. (C) Severe macroglossia. (D) Brushfield spots. (E) Primary dentition showing enamel hypoplasia, severe gingival and periodontal involvement with mobility and drifting of lower incisors. (A from MM Cohen Jr, The Child with Multiple Birth Defects, Raven Press, New York, 1982, p 20. B,D from B Russell, Gentofte, Denmark. C courtesy of J Cervenka, Minneapolis, Minnesota. E courtesy of MM Cohen Sr, Boston, Massachusetts.)

The most extensive EEG investigation was carried out by Ellingson et al (51a). They reported that 21% of Down syndrome cases had abnormalities including asymmetry and/or asynchrony, diffuse slow activity, and diffuse focal seizure activity. The frequency of epilepsy varies from $<1\%$ to nearly 10%. Epilepsy may be of the grand mal variety but other types, including myoclonic seizures and petit mal, may occur. In adults, epilepsy may sometimes be related to the cerebral changes of Alzheimer's disease (75,113,134,151,185).

Mental retardation is considered to be a hallmark of nonmosaic trisomy 21 syndrome. The degree of hypotonia is also important as it affects not only motor ability but language as well (38,64,113). In the study of Domino and Newman (47), no systematic relationship between IQ and various physical stigmata was found. Typically, the IQ is reported to vary between 30 and 50 (49,59). The IQ range for home-reared patients varies from 27.4 to 62.4 compared to a range of 17.4 to 37.4 for institutionalized patients (45). Furthermore, developmental milestones such as walking and talking are achieved at a much earlier age in affected children reared in the home (24,27,58,119,157,163,174). It is believed by some that the developmental potential of offspring with trisomy 21 syndrome is higher in families in which the parents have higher IQs (45,63). The study of Golden and Pashayan (71) showed that parental education is also a factor; the mean IQ of patients whose parents had graduated from high school was 50 (range 32–74), whereas the mean IQ was 35.6 (range 0–45) if the parents had completed grade school only.

The pattern of mental development usually demonstrates an early rise in IQ, which plateaus from ages 2 to 5 years, followed by a gradual decline (21,59,60,119). The social quotient tends to be substantially ahead of the mental age. The ability to make social adjustments sometimes makes Down syndrome individuals appear more intelligent than they are (37).

Investigation of the performance of individuals mosaic for trisomy 21 syndrome has shown that their mean performance level is above that of those with pure trisomy 21. Data suggest that the level of functioning tends to be higher in those with higher percentages of normal cells (59,60,62,140,144). Few mosaic individuals, however, test in the normal range. They often manifest milder physical stigmata than those with nonmosaic trisomy 21 (20,28,59,60,69). Kousseff (103) reported a Down syndrome patient with average intelligence. Chromosomal analysis of cultured peripheral lymphocytes showed trisomy 21 in all 62 mitoses counted.

Table 3–6. Physical findings in trisomy 21 children and adults but not newborns

Findings	Percent
Craniofacial	
Flat nasal bridge	61
Flat occiput	76
Eyes	
Up-slanting palpebral fissures	79
Epicanthic folds	48
Brushfield spots	53
Strabismus	22
Nystagmus	11
Ears	
Dysplastic	53
Absent lobules	70
Mouth	
Open mouth	61
Fissured lips	56
Protruding tongue	42
Macroglossia	43
Furrowing of tongue	61
Narrow palate[a]	67
Irregular alignment of teeth	71
Neck	
Broad, short	53
Chest	
Flat nipples	56
Pectus excavatum	10
Pectus carinatum	8
Dorsolumbar kyphosis	11
Abdomen	
Diastasis recti	82
Umbilical hernia	5
Genitalia	
Small penis	70
Cryptorchidism	21
Small scrotum	37
Hands	
Short broad hands	70
Brachydactyly	67
Single palmar crease	52
Clinodactyly	59
Short fifth finger	59
Single flexion crease on fifth finger	20
Feet	
Gap between hallux and second toe	50
Plantar furrow	31
Joints	
Hyperflexibility	62

[a]In trisomy 21 syndrome, the palate appears high because it is narrow. Palatal height, however, is no higher than that observed in the general population.

(Based on combined data of J Øster, Mongolism, Danish Science Press, Copenhagen; and G Domino and D Newman, Am J Ment Def 69:541, 1964.)

Although in older patients dementia may develop as a consequence of Alzheimer's disease, psychiatric problems are encountered in some children. In the study of Menolascino (120), 11 of 86 children were found to be emotionally disturbed, and absence of speech development was common.

Newborn infants are frequently described as being good babies because they are not easily disturbed and cause their mothers very little trouble. Such traits probably reflect reduced response to external stimuli and marked hypotonia. Later, children are often described as happy, cheerful, good tempered, and easily amused. They tend to mimic and may be mischievous. Langdon Down observed that they were humorous and had a lively sense of the ridiculous. Another common feature is obstinacy. Only a minority is judged to be aggressive or hostile or to display other varieties of maladaptive behavior (107,186).

The overwhelming majority have articulation defects; pronunciation is often slurred, making speech incomprehensible. Sibilants and affricates are more severely compromised than other consonants. More than one-third also have dysrhythmic or explosive speech, which is commonly identified with stuttering or inexact rapid speech leading to distortion of sound and phrasing. The voice is often hoarse, raucous, and low pitched.

Craniofacial manifestations. Brachycephaly and flat occiput result in a cephalic index that is usually >0.80 and may exceed 1.00 (normal, 0.75 to 0.80) (142). Head circumference in children has been studied by Palmer et al (131). Fontanels are large, and closure is late (160). In the study of Chemke and Robinson (25), a "third fontanel" was noted in all affected patients. Persistent metopic suture is found in 67% of males (normal, 8.8%) and in 42% of females (normal, 12.3%) (142). Frontal and sphenoidal sinuses are absent and maxillary sinuses are hypoplastic in over 90% of cases (90,142,143,162). Bony midface hypoplasia produces ocular hypotelorism, a small nose with flattening of the nasal bridge, and relative mandibular prognathism (15,68,73). The nasion-sella-basion angle is increased (18).

In an anthropometric study of craniofacial profile patterns, Allanson et al (3) showed a change in facial shape from rounded during infancy to oval in later life. Discriminant functional analysis identified three variables—ear length, maxillary arc, and upper facial depth—that would accurately classify more than 99% of a combined Down/non Down sample.

Upward slanting of palpebral fissures and epicanthic folds are common. Other ocular findings include Brushfield spots, fine lens opacities, convergent strabismus, nystagmus, keratoconus, and cataract (160).

The ears tend to be small (1). Overlapping of the superior rim of the helix and small or absent lobes are common (76,160).

Odontoid abnormalities are found in 16% of affected individuals, and atlantoaxial instability, a feature found in 10%–20% and sometimes found in association with occipitoatlantal instability, results from generalized congenital laxity of ligaments, which is especially noticeable at the craniocervical joint (40).

The lips are broad, irregular, fissured, and dry (19). An open mouth with a protruding tongue is observed. The tongue appears relatively large because of the small oral cavity. That the "large tongue" is relative was demonstrated by Ardran et al (7). Occasionally, true macroglossia may be present. A fissured tongue is common and geographic tongue has also been described (53) (Fig. 3–1C). Lingual papillae have been noted to be large even during infancy (34).

The palate is narrower and shorter but not higher than the mean (155). Radiographically, palatal length averages about 25 mm (normal, 31 ± 3 mm) in the newborn. Cleft of the lip and/or palate is present in 0.5% (72).

Parotid salivary flow rate is decreased. A significant rise in pH, sodium, calcium, bicarbonate, uric acid, and nonspecific esterase in pure parotid saliva has been reported (34,43,184).

Periodontal disease has been observed in over 90% of cases. Severe involvement even below the age of 6 years is particularly common in the mandibular anterior and maxillary molar regions (Fig. 3–1E). Exfoliation of the lower central incisors from periodontal bone loss occurs frequently. However, calculus formation is neither common nor severe. Necrotizing ulcerative gingivitis has been reported to occur in about 30% of patients (15,30,92,98,149,170). The prevalence of dental caries has been stated

to be low by several authors (15,34), although these findings have been challenged (105).

Eruption of both deciduous and permanent teeth is delayed in 75% of cases. An irregular sequence of eruption is common, deciduous first molars sometimes preceding incisors (90,106,108,141,170). Missing teeth have been reported in 23%–47% of patients. Third molars, second premolars, and lateral incisors are most frequently absent in the permanent dentition. In 12%–17% of patients, deciduous lateral incisors are absent. Peg-shaped maxillary lateral incisors have been observed in 10%. Extreme hypodontia and anodontia have been noted occasionally (34,146,153,173).

Crown-size asymmetry (66) and a gradient of reduction along a mesial-to-distal axis (31) have been reported. Fusion of a deciduous mandibular lateral incisor with a canine or, less commonly, with a central incisor is a low-frequency finding (19,34).

Morphologic crown alterations have been reported (16,33,34,67, 104,135,177). Almost 50% of patients have three or more dental irregularities (104). Enamel hypoplasia (Fig. 3–1E) and enamel hypocalcification have also been noted (29,34). Jaspers (89) indicated that taurodontism occurs with greater than expected frequency.

Irregular alignment of teeth is common. Posterior crossbite, mandibular overjet, mesiocclusion, anterior open bite, crowded teeth, and widely spaced teeth have been discussed by several authors (15,34,97).

Cardiovascular system. Cardiovascular anomalies occur in approximately 40% of cases and are a frequent cause (about 20%) of the recorded trisomy 21 syndrome deaths. Atrioventricular communis occurs in one-third of Down syndrome patients with congenital heart defects. In contrast, it is rare as an isolated defect in the general population. Another one-third of cardiac anomalies in Down syndrome are ventricular septal defects. Approximately one-fourth are either tetralogy of Fallot (7%), atrial septal defect (10%), or patent ductus arteriosus (3%). Transposition of the great vessels and coarctation of the aorta occur less frequently in Down syndrome patients than in the general population. Among patients with Eisenmenger complex, it has been noted that the proportion with trisomy 21 syndrome is higher than expected. It has also been reported that the highest mortality rate in Down syndrome patients with congenital heart defects occurred in those with right ventricular outflow tract obstruction or pulmonary vascular pressure at the systemic level, whereas the group with normal or slightly higher pulmonary vascular resistance did quite well (22,26,42,56,57,152,160).

Gastrointestinal system. Gastrointestinal malformations occur in 10%–18% of cases. Findings include tracheoesophageal fistula, pyloric stenosis, duodenal atresia, annular pancreas, Hirschsprung's disease, and imperforate anus (95,100). Knox and ten Bensel (100) reported that approximately 8% die from their gastrointestinal anomalies. Celiac disease is increased (187).

Skin. Dermatologic features include palmoplantar hyperkeratosis (40.8%), xerosis (9.8%), and seborrheic dermatitis (30.9%) (53). Cutis marmorata is common during infancy.

Dermatoglyphics. Many dermatoglyphic studies of trisomy 21 syndrome have been carried out, and several dermatoglyphic indices have been developed (13,83,112,138,160). Such indices have been particularly useful as a diagnostic aid in trisomy 21 syndrome. The Walker index allows discrimination of approximately 70% of affected individuals from controls. Borgaonkar et al (13) developed a method by which 88% of trisomy 21 syndrome patients could be discriminated from the control population. This method was simplified by Reed et al (138) as a nomogram that discriminated 81% of patients with trisomy 21 syndrome. Lu (112) devised a discriminant analysis that permits the identification of 89% of those with trisomy 21 syndrome.

Significant findings in Down syndrome include a hallucal tibial arch or small distal loop, distally placed axial triradius on the palm, single palmar creases, single flexion crease on the fifth finger, and an increased number of ulnar loops on the fingertips. An unusual finding of a radial loop on the fourth and fifth fingers is also increased in trisomy 21 syndrome. In Table 3–7, significant dermatoglyphic features are summarized as percentages in the Down syndrome population compared with percentages of such findings in the general population.

Table 3–7. Dermatoglyphic features of trisomy 21 syndrome

Dermatoglyphic pattern	Trisomy 21 syndrome (%)	Controls (%)
Hallucal tibial arch	72	$\simeq 0.5$
Hallucal small distal loop	32	11
Bilateral t″	82	3
Single crease, digit 5	17	<1
Bilateral single palmar crease	31	2
10 ulnar loops on fingers	31	7
Radial loop, digit 4 or 5	13	4
Bilateral I_3 pattern	46	26
Thenar pattern	4	11

(From M Preus and FC Fraser: Am J Dis Child 124:933, 1972.)

Other anomalies. A variety of low-frequency anomalies have been reported and these are extensively reviewed by several authors (57,160). It has been noted that there may be a greater association with anomalies such as polydactyly and omphalocele than that observed in the general population (95,117).

Hematologic system. Congenital hematologic disorders are common in Down syndrome and a benign natural history is common. Newborns frequently have polycythemia. A number of Down syndrome patients, usually newborns, have had transient, severe disorders of hematopoiesis simulating leukemia but with full recovery (vide infra). Down syndrome studies have also shown a preponderance of younger forms of polymorphonuclear leukocytes that may be explained by an increased turnover of granulocytes.

Tumors. Acute lymphoblastic leukemia occurs with increased frequency in Down syndrome and the peak in the leukemia mortality rate occurs at an earlier age than in childhood leukemia without Down syndrome (124,160).

A tumor profile of Down syndrome (148) shows a 20-fold excess of leukemias and some excess in lymphomas, gonadal and extragonadal germ cell tumors, and possibly retinoblastomas and pancreatic and bone tumors. Other solid tumors appear to be underrepresented when compared to the frequency in the general population.

Immune system. Immunodeficiency in Down syndrome is related to an increased susceptibility to infection, an increased risk for developing neoplasia, particularly leukemia, an increased frequency of autoantibodies, and early aging. Autoantibodies against thyroid antigen are frequently found during early life (175). An increased prevalence of hypothyroidism and, less commonly, hyperthyroidism has been reported (147). The disturbed immunoglobulin (Ig) balance increases with age; IgG and IgA rise after 5 years of age whereas IgM stays within normal limits. T-cell deficiency is observed from birth onward (175).

Differential diagnosis. The Down syndrome phenotype is distinctive. Conditions that are sometimes clinically confused with it include hypothyroidism, *XXXXY syndrome, penta-X syndrome* (65), and *Zellweger syndrome.*

Laboratory aids. Chromosome study is necessary to confirm all cases. Amniocentesis or chorionic villus biopsy can be offered to all mothers with a previous history of having a child with Down syndrome, to older mothers, and to translocation carriers. Pelvic radiograph is sometimes diagnostically useful in suspected cases. There are low levels of AFP in maternal serum and amniotic fluid in trisomy 21 and in other trisomies (8,180).

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Trisomy 13 (Patau) syndrome

In 1960, Patau et al (22) first identified trisomy 13 in the laboratory, although the clinical description of the syndrome may date back as early as 1657 in the writings of Bartholin. Trisomy 13 syndrome is characterized by microcephaly, scalp defects, frequent holoprosencephaly, microphthalmia, orofacial clefting, congenital heart defects, polydactyly, severe developmental retardation, and early demise (Fig. 3–2). The reader is referred to the following sources for extensive coverage: general review (9,14,30,33), epidemiology (1,7,10,15,18,33), cytogenetic aspects (4,9,12,15,16), partial trisomy (26,27), anatomic studies (6,17,23), pathologic studies (19,20,30), holoprosencephaly (3,5,29), neoplasia (8,13), and long-term survival (25,28,33,35).

Birth prevalence for free trisomy 13 is approximately 1/12,000, that of Robertsonian translocations, 1/56,000 to 1/80,000, and that of familial cases, 1/33,000 to 1/42,000 (10,33). The rate of trisomy 13 spontaneous abortions is about 100-fold greater than the rate of live births. Trisomy 13 is seen in approximately 1% of all recognized spontaneous abortions (15). A slightly greater number of females than males are affected.

Free trisomy 13 occurs in approximately 75% of all cases and is associated with a maternal age effect (mean age, 31.6 years) (29). Free trisomy originates in nondisjunction. Ishikiriyama and Niikawa (16) have shown that in trisomy 13, the ratio of nondisjunction in maternal and paternal meiosis was 14:3. For maternal meiosis, nondisjunction occurred more frequently during the first than during the second meiotic division (9:4) (12). Approximately 20% result from translocations, mostly t(13q14q). The overwhelming majority arise de novo. Approximately 5% of the translocation type are transmitted by one of the parents, with the recurrence risk being 5% and the risk of spontaneous abortion being approximately 20%. In the unusual translocation t(13q13q), the risk of recurrence or abortion is 100%. About 5% of all cases are mosaic for trisomy 13 (27) with areas of hypomelanosis (11a). In such instances, the phenotype tends to be less severe (2). Distinct clinical syndromes involving a partial proximal or partial distal trisomy segment of chromosome 13 have been phenotypically defined (26,27). Different features of trisomy 13 syndrome are associated with these partial trisomic segments.

Mean life expectancy is 130 days. Approximately 45% die during the first month, 70% during the first 6 months, and 86% during the first year (27). Survival beyond 3 years is exceptional (25,28,33,34). Recurrent chronic cellulitis, affecting the parotid region, axilla, groin, and abdominal wall, with sinus formation and resistance to antibiotic treatment have been found as well as wasting of the distal limb muscles (28). Survival appears to be better with translocation cases than with free trisomy (15). Females appear to live longer than males, but this difference has not been statistically significant (15).

Trisomy 13 syndrome and trisomy 18 syndrome share a number of features in common; these are listed in Table 3–8. Features more common to trisomy 13 syndrome and features more common to trisomy 18 syndrome are also listed. Extensive clinical and pathological findings of

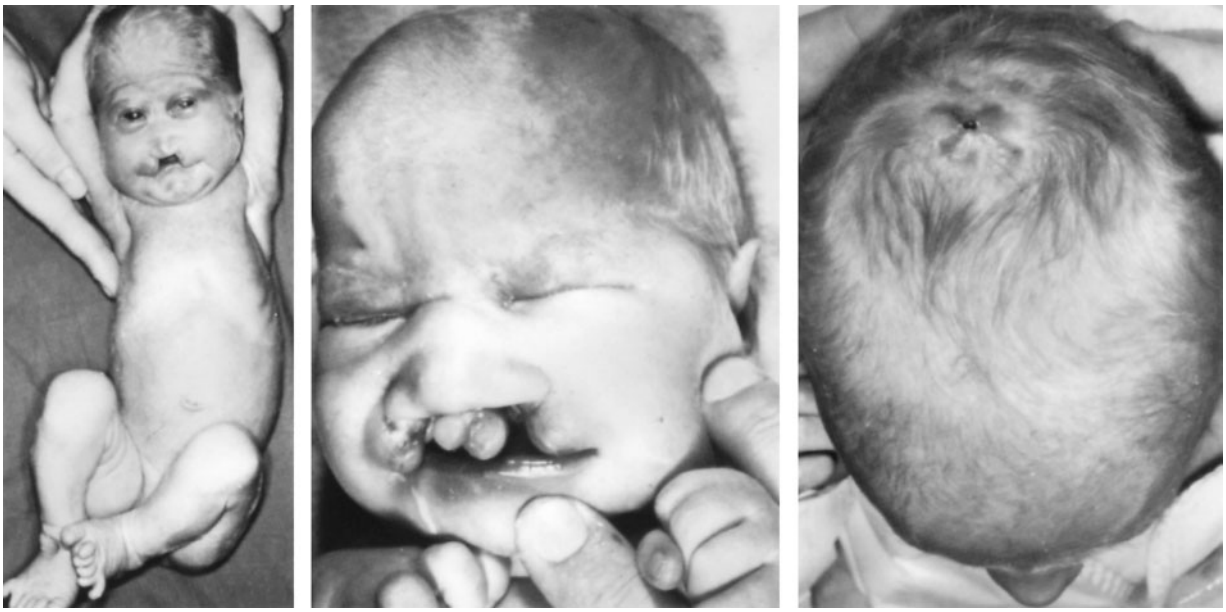

Fig. 3–2. *Trisomy 13 syndrome.* (A) Premaxillary agenesis type of holoprosencephaly with trisomy 13. Note hypotelorism, lack of nasal bones, and extra digits. (B) Bilateral cleft lip/palate, microphthalmia, ulnar hexadactyly, and superficial angioma over brow. (C) Skin defect at vertex of skull. (A from PE Conan, Am J Dis Child 111:236, 1966.)

trisomy 13 syndrome are noted in Table 3–9 together with approximate percentages.

Growth. Mean birth weight is 2600 g. Feeding difficulties and failure to thrive are characteristic (27). Crown-rump length is significantly decreased (29).

Central nervous system. Moderate microcephaly with sloping forehead and wide sagittal suture and fontanels are characteristic. Some degree of holoprosencephaly is common and is accompanied by apneic episodes and seizures. Severe developmental retardation is the rule and presumptive deafness is common. Hypotonia, hypertonia, and hydrocephaly have been encountered in some instances. Cerebellar hypoplasia and meningomyelocele are less commonly observed (3,14,30). Lipoma of corpus callosum has been noted (32).

Craniofacial features. Scalp ulceration is commonly observed at the vertex and may be variable in size. Sloping forehead and capillary hemangiomas, particularly in the glabellar region, are commonly observed. Accompanying variable degrees of holoprosencephaly are ocular hypotelorism and various associated features including, most commonly, lateral cleft lip, median cleft lip, and cebocephaly. Cyclopia occurs infrequently and ethmocephaly is rare. Ocular findings include microphthalmia, iris coloboma, and retinal dysplasia characterized by intraocular cartilage extending from the retrolental region to the sclera at the site of the iris coloboma. Cleft palate, micrognathia, and malformed ears, which may be low set in some instances, are also observed (Fig. 3–2). Inner ear anomalies are of the Mondini or Scheibe types (3,5,11,14,30).

Neck. The neck is short and loose skin on the nape may be seen (29,30). This nuchal translucency may be used in diagnosis (29). Fetal cystic hygroma has been reported (21).

Cardiovascular system. Cardiovascular anomalies are common and autopsy studies have shown that more than one type may be present in the same individual. Those most commonly observed are patent ductus arteriosus, infundibular ventricular septal defect, and atrial septal defect. Also reported are left superior vena cava, dextrocardia, aorta arising from the left ventricle, bicuspid aortic valve, bicuspid pulmonary valve, coarctation of the aorta, atretic pulmonary valve, hypoplastic pulmonary trunk, hypoplastic left atrium, hypoplastic left ventricle, and abnormal semilunar valves (19). Renal abnormalities are common and may include cystic dysplasia, renal hyperlobulation, hydronephrosis, hydroureters, double ureters, horseshoe kidney, and persistent nodular renal blastema (19).

Genitalia. Cryptorchidism and scrotal anomalies are present in males. Bicornuate uterus is found in females. Other findings have been reported including hypertrophy of the clitoris, double vagina, hypoplastic ovaries, gonadal dysgenesis, and hypospadias (9,30).

Limb anomalies. Postaxial polydactyly, flexion of the fingers, sometimes with overlapping, and hyperconvex nails are common (18a). Prominent calcaneus may be observed in some instances. Dermatoglyphic alterations include single palmar creases, distal palmar axial triradius, and fibular S-shaped hallucal pattern or hallucal loop tibial. Also frequent are thenar exit of the A mainline (80%) and radial loops on fingers other than the index finger (50%) (9,14,30).

Other findings. Other reported findings are single umbilical artery, inguinal hernia, umbilical hernia, thin posterior ribs with or without a missing rib, hypoplastic pelvis with shallow acetabular angle, retroflexible thumb, ulnar deviation at the wrist, talipes equinovarus, ectrodactyly, various malformations of the spine, as well as other abnormalities (9,14,30,31). Pancreatic dysplasia is a characteristic feature (19). An odd pigmentary disorder has been noted (24).

Hematologic findings. Polymorphonuclear leukocytes often have nuclear projections (25%–80%). Persistence in the newborn period of embryonic hemoglobin Gower-2 has been observed (9). Those with myelofibrosis do not do well (34).

Neoplasia. Leukemia has been noted in patients with trisomy 13 (13). The association of trisomy 13 syndrome and neuroblastoma in the same family has been reported (8). Wilms tumor has been documented on a few occasions (21a,29a).

Anatomic features. Autosomal trisomies are known to have rather specific constellations of muscle, peripheral nerve, and vascular variations that are not usually examined by either clinicians or pathologists. Trisomy 13 syndrome has the following characteristics: absence of

Table 3–8. Comparison of trisomy 13 and 18 syndromes

Features	Trisomy 13 syndrome (%) ($n = 19$)	Trisomy 18 syndrome (%) ($n = 29$)
Common to both syndromes		
Ear anomalies	87	100
Cardiac defects	94	93
Micrognathia	66	96
Overlapping fingers	73	100
Microcephaly	86	70
Prominent heels	62	87
Highly arched palate	72	87
Microphthalmia	88	82
Hypertonia	67	60
Umbilical hernia	83	67
Cryptorchidism	100	43
More common to trisomy 13		
Cleft palate	63	
Polydactyly	78	
Scalp defects	75	
Cleft lip	50	
Apneic episodes	100	
Capillary hemangiomas	88	
Dextrocardia	100	
Hypotelorism/hypertelorism	83	
Iris coloboma	67	
Sloping forehead	100	
Flat head	75	
Hypoplastic nipples	100	
Prominent nasal bridge	100	
Short neck	100	
More common to trisomy 18		
Prominent occiput		91
Hip dislocation		82
Hypoplastic nails		100
Clubfoot		89
Widely spaced nipples		90
Hypertrophic clitoris[a]		89
Hammertoes		89
Narrow palpebral fissures		80
Short sternum		100
Small mouth		86
Excess skin, neck		86
Seizures		62
Abnormal head		83
Hypoplastic labia		100

[a] Sex-adjusted percentage.
(Adapted from ME Hodes et al, J Med Genet 15:48, 1978.)

the palmaris longus, palmaris brevis, plantaris and peroneus tertius, presence of a pectorodorsalis muscle and unusual muscles from the central tendon of the diaphragm to the pericardium, and variations in extensor indicis, extensors carpi radialis longus and brevus, biceps brachii, and suprahyoid muscles (6,23).

Differential diagnosis. Many syndromes have *holoprosencephaly* as one feature. Pseudotrisomy 13, *Meckel syndrome,* and even *Pallister-Hall syndrome* can have holoprosencephaly and polydactyly concurrently (3). *Smith-Lemli-Opitz syndrome* and *hydrolethalus syndrome* have some individual features in common with trisomy 13, but the overall pattern of anomalies in each of these syndromes is distinctive.

Laboratory aids. Diagnosis is established by banded chromosome study.

Table 3–9. Features of trisomy 13 syndrome

Feature	Percent
Growth	
Failure to thrive	87
Central nervous system	
Microcephaly	86
Holoprosencephaly	70
Apneic episodes	58
Seizures	25
Hypotonia	48
Hypertonia	26
Severe developmental retardation	100
Presumptive deafness	50
Craniofacial features	
Scalp defects	75
Sloping forehead	100
Capillary hemangiomas	72
Ocular hypotelorism	83
Epicanthic folds	56
Microphthalmia	76
Iris coloboma	33
Other eye defects	88
Cleft lip	58
Cleft palate	69
Micrognathia	84
Malformed ears	80
Neck	
Short neck	79
Loose skin, nape	59
Cardiovascular anomalies	
Patent ductus arteriosus	(82)[a]
Ventricular septal defect	(73)
Atrial septal defect	(91)
Left superior vena cava	(14)
Dextrocardia	(24)
Aorta from right ventricle	(11)
Bicuspid aortic valve	(8)
Bicuspid pulmonary valve	(8)
Coarctation of aorta	(9)
Renal anomalies	30–60
Polycystic kidneys	(70)[b]
Renal hyperlobulation	(22)
Hydronephrosis	(25)
Hydroureters	(10)
Double ureters	(12)
Horseshoe kidney	(9)
Genitalia	
Cryptorchidism	(100)
Bicornuate uterus	(50)
Limb anomalies	
Polydactyly	76
Flexion of fingers, sometimes with overlapping	68
Hyperconvex nails	68
Single palmar crease	64
Distal axial triradius	74
Prominent calcaneus	28
Fibular S-shaped hallucal pattern	39
Other findings	
Inguinal/umbilical hernia	40

[a] Percentages in parentheses are from necropsy series that biases findings.
[b] Sex-adjusted percentage.
(Adapted from AI Taylor, J Med Genet 5:227, 1968; ME Hales et al, J Med Genet 15: 48, 1978; C Addor et al, J Genet Hum 23:83, 1975; and MM Cohen Jr, Teratology 40:211, 1989.)

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Trisomy 18 (Edwards) syndrome

In 1960, Edwards et al (14) described a new syndrome associated with the presence of an extra chromosome 18. Features included growth deficiency, developmental retardation, prominent occiput, low-set malformed ears, micrognathia, short sternum, congenital heart defects, overlapped flexed fingers, dorsiflexed halluces, and prominent calcaneus (13,43) (Fig. 3–3A–C). The reader is referred to the following sources for extensive coverage: general aspects (4,13,23,27,33), epidemiology (3,11,22,24,50), growth curves (4), cytogenetics (18,32,34,38,47), anatomic aspects (6,46), pathology (23,27,32,45), central nervous system anomalies (30), ophthalmological aspects (7), cardiovascular defects (9,32,36), renal anomalies (32,36), long-term survival (4,8,20,26,33), prenatal diagnosis and counseling (1,35), and neoplasia (2,12,20,26,40). A diagnostic scoring system has been developed (31).

Large surveys have indicated a prevalence of approximately 1/5000 to 1/7000 (8,20,41). Sex ratio shows an excess of affected females (4 F:1 M) (4,13). Trisomy 18 is associated with a maternal age effect, with the mean maternal age being 32.5 years (44).

The overwhelming majority of cases of trisomy 18 syndrome are due to de novo meiotic nondisjunction (13). About 85% of the examples come from the mother from either the first or second meiosis (15,37,49). Translocations may arise de novo or may be transmitted in a family. Mosaicism occurs in approximately 10% of cases (13). Classic trisomy 18 in two sibs was reported by Pauli et al (38). Translocation, isochromosome formation, partial trisomy 18, and mosaicism have been discussed by several authors (19,29,34,38,47). Double trisomies have been discussed. Sibling recurrence risk for trisomy 18 is about 0.5% (4).

Tetrasomy for 18p produces a distinct phenotype (16,39): moderate mental retardation, spasticity, lowset malformed pinnae, strabismus, upslanting palpebral fissures, flat nasal bridge, small pinched nose, long philtrum, small mouth, simian creases, and scoliosis.

Partial duplication 18q21.1–qter results in the phenotype of trisomy 18 (35).

The median life expectancy for liveborn infants with trisomy 18 is 4 days with a range of 1 hour to 18 months. Mean age at death is 48 days. In patients without accompanying cardiac defects or life-threatening gastrointestinal anomalies, median life expectancy is 40 days with a range of 4 hours to 18 months. Although females survive longer than males, the difference is trivial (8). About 45% survive 1 week, 3%–9% survive 6 months, and 0%–5% live more than 1 year (8,13,20,41,50). There are several reports of children surviving into the second decade (33).

Average duration of pregnancy is 42 weeks with low fetal activity, polyhydramnios, and small placenta. A single umbilical artery is common. Altered gestational timing may occur with premature delivery in some instances (13,43). About 50% are delivered by cesarean section because of fetal distress (4).

Clinical findings are summarized in Table 3–10 and internal malformations are listed in Table 3–11. The features of trisomy 18 and trisomy 13 are compared in Table 3–8.

Growth. Mean birth weight is 2240 g. Postnatally, there is failure to thrive. Characteristically, hypoplasia of skeletal muscle, subcutaneous tissue, and adipose tissue is encountered. Some examples of trisomy 18 mosaicism have been associated with asymmetry of the body and/or face, and anomalies that lateralize, such as limb defects, may occur on one side but not on the other (43).

Central nervous system. Mental deficiency is severe. Hypotonia during the neonatal period is followed by hypertonia. The cry is weak and there is diminished response to sound (43). Variable degrees of holoprosencephaly associated with apneic episodes, seizures, and poikilothermia

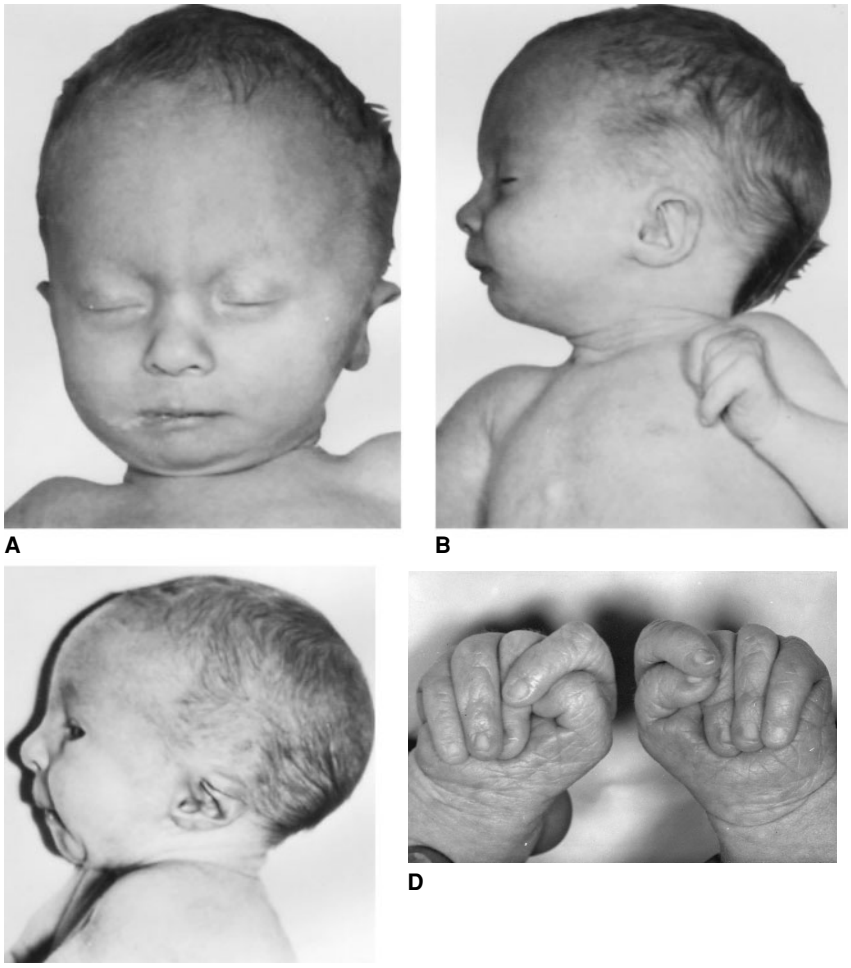

Fig. 3–3. *Trisomy 18 syndrome.* (A) Narrow bifrontal diameter and small lower jaw. (B) Prominent occiput, ptosis of the eyelid, low-set ears, and micrognathia. (C) Compare facies with patient in B. (D) Overlapping fingers. (A,B,C from P Paerregård, Acta Pathol Microbiol Scand 67:479, 1966.)

can be found on occasion (9,30). Psychomotor development has been discussed at length by Baty et al (5). With apparently somewhat higher frequency, simple absence of the corpus callosum has been noted. Rarely, hydrocephaly, anencephaly, meningomyelocele, and facial palsy may be observed (35,43). Paucity of myelinization, microgyria, cerebellar hypoplasia, absent geniculate body, absent occipital lobes, and occipital lobe hemorrhage have been recorded.

Heterotopias of well-formed neurons either with or without undifferentiated neuroblastic cells have been found in the periventricular areas of the brain, located most commonly above or lateral to the head of the caudate nucleus and/or in the roof and lateral wall of the inferior and posterior horns, within fibers converging on the internal capsule and around the optic radiation. Heterotopias appear to result from excessive formation of embryonic neuroblasts with focally arrested migration in the periventricular white matter without resulting in deficient neuronal composition of the cerebral cortex (7,45).

Craniofacial features. The head is dolichocephalic in shape. The bifrontal diameter is narrow and the occiput is prominent. The ears are malformed and low set. The mouth is small, the palate is narrow, and micrognathia is evident (43) (Fig. 3–3). Cleft lip is found in about 5%, cleft palate in another 5% (4).

Less frequently occurring craniofacial abnormalities include microcephaly, wide fontanels, hypoplasia of orbital ridges, Wormian bones, shallow elongated sella turcica (43), and various eye anomalies: globe (corneal opacities, corneal clouding, microphthalmia, iris colobomas, cataracts, persistent hyaloid artery, glaucoma, blue sclera, absent retinal pigment, persistent iridopupillary membrane), adnexa (slanted or narrow palpebral fissures, epicanthic folds, ptosis of the eyelids, congenital filiform ankyloblepharon, abnormally thick eyelids, abnormally long or sparse eyelashes, inability to close the eyelids, blepharophimosis), orbit (hypertelorism, hypotelorism), and neuroophthalmology (strabismus, lateral gaze, asynergy of extraocular movement, decreased response to visual stimuli, nystagmus, anisocoria) (17). Ocular histopathology has been reviewed extensively by Calderone et al (7).

Inner ear defects may include complete or partial absence of the auditory nerve, defects of the osseous spiral laminae and interscalar septa, abnormalities of the utriculoendolymphatic valve, atresia or absence of the semicircular ducts, and deformities of the organ of Corti (21,48).

Limbs. The hands are clenched with a tendency toward overlapping of the second finger over the third finger and the fifth finger over the fourth. The distal crease on the fifth finger may be absent with less frequently occurring absence of the distal creases on the third and fourth fingers (Fig. 3–3D). The nails are hypoplastic, particularly on the fifth finger and the toes (43).

Dermatoglyphic analysis shows an increased frequency of arched fingertip patterns on six or more fingers. Abnormalities of the feet include dorsiflexed halluces, prominent calcaneus, talipes equinovarus, rocker-bottom feet, and syndactyly of the second and third toes. Low-frequency anomalies include syndactyly of the third and fourth fingers, polydactyly, short fifth metacarpals, and limb reduction malformations (10,43).

Cardiovascular system. Cardiovascular anomalies occur in about 85% of cases and include polyvalvular disease, ventricular septal defect (VSD), high takeoff of the right coronary ostium, patent ductus arteriosus (PDA), and various other abnormalities (23,32,44). Cardiopulmonary abnormalities are the chief cause of death (4). These are listed in Table 3–11.

Table 3–10. Features of trisomy 18 syndrome

Feature	Percent
Growth	
Growth deficiency	96
Central nervous system	
Severe developmental retardation	96
Hypertonia	60
Craniofacial	
Microcephaly	70
Dolichocephaly	93
Prominent occiput	91
Narrow palpebral fissures	80
Small mouth	86
Micrognathia	96
Low-set, malformed ears	88
Neck	
Loose skin, nape	56
Thorax	
Short sternum	68
Widely spaced nipples	90
Cardiovascular anomalies	85
Abdominal wall	
Inguinal or umbilical hernia	67
Urogenital system	
Renal anomalies	30
Cryptorchidism	100
Prominent clitoris[a]	89
Pelvis and hips	
Small pelvis, limited hip abduction	68
Limbs	
Overlapped, flexible fingers	89
Hypoplastic nails	100
Arch fingertip patterns	96
Clubfoot	89
Prominent calcaneus	77
Rockerbottom feet	10–50
Dorsiflexed hallux	75
Syndactyly, second and third toes	10–50

[a] Sex-adjusted percentage.

(Adapted from ME Hodes et al, J Med Genet 15:48, 1978; and AI Taylor, J Med Genet 5:227, 1968.)

Urogenital system. Urogenital anomalies are common (Table 3–10) and may include cryptorchidism, prominent clitoris, cystic kidneys, horseshoe kidneys, gonadal dysgenesis, and other abnormalities (23,32,44) (Table 3–11).

Other anomalies. A variety of other abnormalities have been reported, including tracheoesophageal fistula, Meckel's diverticulum, incomplete fixation of the colon, ectopic pancreas, anal atresia, thyroglossal duct cyst, eventration of the diaphragm, diaphragmatic hernia, and skeletal anomalies (32) (Table 3–11).

Anatomical studies. Bersu and Ramirez-Castro (6) dissected eight infants and found hypoplastic occipitofrontalis, auricular, and nasal muscles. Extensive fusion of muscles occurred around the corners of the mouth, a supernumerary muscle band extending from the corner of the mouth to the occipital attachment of the trapezius muscle. The otomandibular region showed a variable spectrum of muscular, skeletal, arterial, and salivary gland variations. Absence of muscles, supernumerary muscles, and variations in musculature of the upper and lower limbs have been described by Urban and Bersu (46). Kjaer et al (28) described the following axial changes in the skeleton of trisomy 18 fetuses: notched basilar occiput, hypoplastic nasal bones, and malformations of thoracic or thoracolumbar vertebrae.

Table 3–11. Internal malformations in trisomy 18 syndrome

Finding	Frequency
Central nervous system	
Hypoplasia or absence of corpus callosum	3/15
Absent septum pellucidum	2/15
Short frontal lobe	2/15
Abnormal gyri	2/15
Persistent paraventricular nerve cells	3/15
Cardiovascular system	
Polyvalvular disease	15/15
Ventricular septal defect	13/15
High takeoff of the right coronary ostium	12/15
Patent ductus arteriosus	11/15
Common brachiocephalic trunk	7/15
Coarctation of aorta	3/15
Mitral atresia with hypoplastic left ventricle	1/15
Patent foramen ovale	14/15
Urogenital system	
Cystic kidneys	5/15
Horseshoe kidney	7/15
Ovarian cyst	1/15
Double ureter	2/15
Alimentary tract	
Esophageal atresia (TEF)	1/15
Meckel's diverticulum	8/15
Incomplete fixation of the colon	7/15
Ectopic pancreas	10/15
Anal atresia	2/15
Other	
Thyroglossal duct cyst	2/15
Eventration of diaphragm	2/15
Skeletal anomalies	5/15
Single umbilical artery	2/15
Diaphragmatic hernia	1/15

(Adapted from R Matsuoka et al, Am J Med Genet 14:657, 1983, autopsy cases.)

Neoplasia. Various neoplasms have been reported on occasion, including Wilms tumor (20,26), hepatoblastoma (12), neurogenic tumor (40), and benign congenital papillary tumor of the bicuspid valve (2).

Differential diagnosis. Differential diagnosis includes *Pena-Shokeir syndrome I* and *trisomy 13 syndrome.*

Laboratory aids. Diagnosis is established by banded chromosome study. Cases may be referred for ultrasonographic evaluation of polyhydramnios around the 30th week of gestation. Fluorescent in situ hybridization (FISH) studies may be used if the tissues are formalin-fixed or paraffin-embedded (24a).

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del(4p) syndrome (Wolf-Hirschhorn syndrome)

Although the defect is due to deletion of the 4p16.3 band (5,8,16), the deletion may be submicroscopic. Milder expression has been called "Pitt-Rogers-Danks syndrome" (13,34). In most cases one-third to two-thirds of the short arm is deleted. The critical region is 4p16.3 (20a). The facial phenotype is not deletion size dependent (22). Translocation is responsible for 10%–15% of the cases (3,11,18,25,30); the rest are largely de novo, nearly always from the paternal chromosome (23,27,28). Polymerase chain reaction (PCR)-based screening (1) or fluorescence in situ hybridization (FISH) (33) can be used to detect this syndrome. Frequency appears to be about 1/50,000 births with a 2:1 female predilection. At least 35% of affected infants die during the first year of life due to heart defects, but some survive to adulthood (20). The phenotype is quite striking. In spite of normal gestation time, birth weight is usually reduced. Fetal activity is diminished and the child is characteristically hypotonic. In addition to very severe psychomotor and growth retardation (75%), mild microcephaly (90%), craniofacial asymmetry, high forehead, wide nasal bridge with prominent glabella (50%) and nasal beaking (65%), hypertelorism (75%), and epicanthal folds are seen (Fig. 3–4). About 10% have a midline scalp defect. The eyebrows are highly arched and somewhat sparse medially. About 50% exhibit ptosis, downward slanting palpebral fissures, facial angiomas, and divergent strabismus. The facies has been likened to that of a Greek helmet (6) (Fig. 3–4). About 25% have coloboma of the iris and corectopia (31). The ears are deep seated, poorly differentiated, and have lobeless pinnae (26) and narrow external canals. Most have a preauricular dimple or skin tag. Sensorineural hearing loss has been documented in 25%(15). The philtrum is short and deep and the mouth usually has downturned corners. Cleft lip with cleft palate (Fig. 3–4A) (10%), cleft palate (25%), and micrognathia (50%) have been documented (19). Hypodontia has been reported (4). The neck is long and thin. There are some changes with age (2a,2b).

Congenital heart malformations, most often ASD or VSD, are noted in about 45%. Seizures occur in about 50%. Cryptorchidism (40%) and, particularly, hypospadias (70%) are found in affected males; and absent uterus and streak gonads have been described along with disproportionately small kidneys including bilateral small kidneys with large glomeruli that are reduced in number and dilation of proximal renal tubules (oligomeganephronia) (9,16,21). Sacral dimple is an almost constant feature (32). The trunk is long and the limbs are thin. Talipes

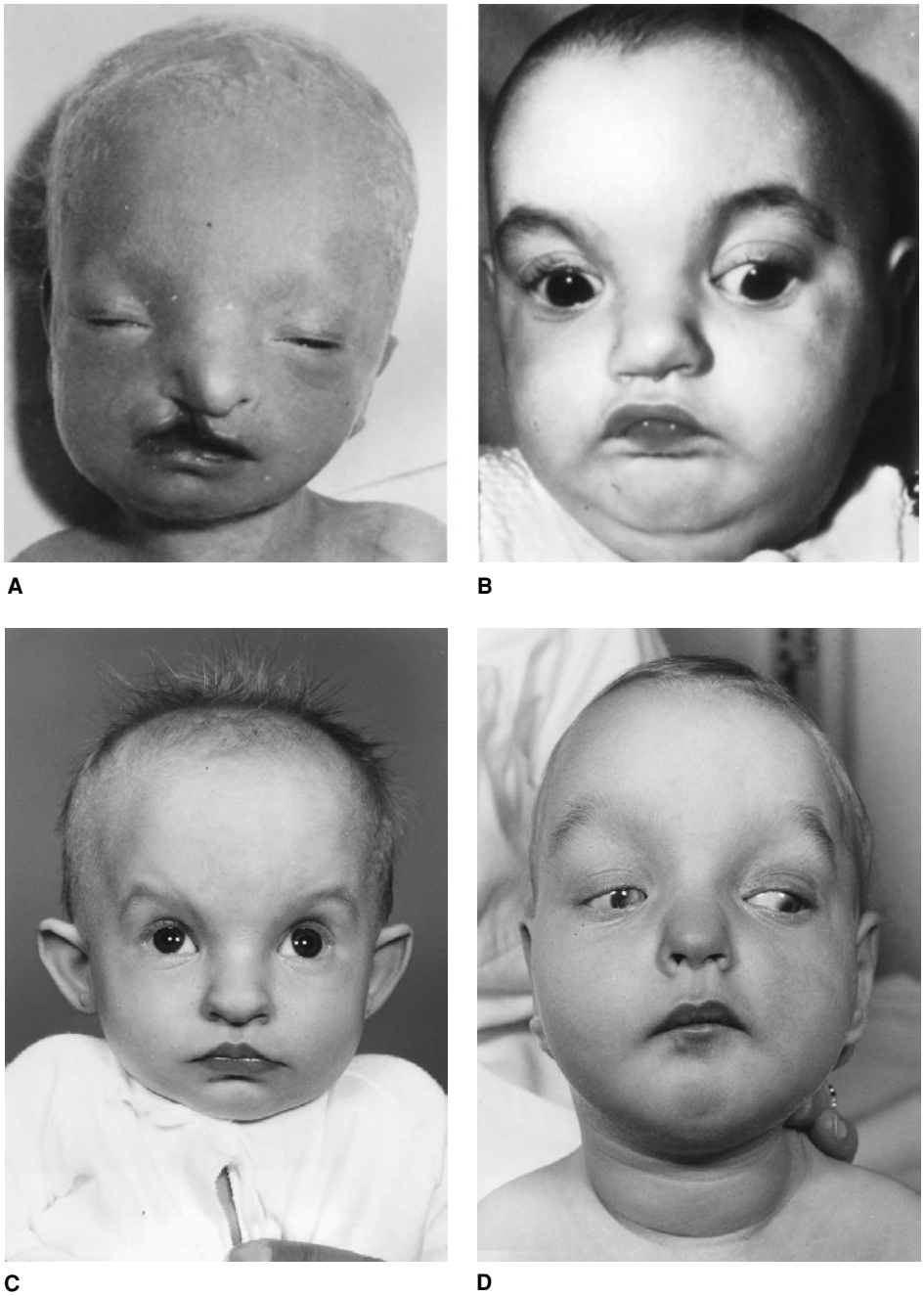

Fig. 3–4. *del(4p) syndrome (Wolf-Hirschhorn syndrome).* (A) Small head, hypertelorism, flat nose, cleft lip, short philtrum, down-turned mouth. (B) Microcephaly, cranial asymmetry, hypertelorism, strabismus, broad-based nose with asymmetric nares, short philtrum, and down-turned mouth. (C,D) Compare facies with patients A and B. (A from AI Taylor, J Med Genet 5:227, 1968. B from D Arias et al, J Pediatr 76:82, 1970. C,D from A Schinzel and W Schmid, Arch Genet 45:88, 1972.)

equinovarus is relatively common. Radiographically, proximal radioulnar synostosis, anterior fusion of vertebrae, fused ribs, dislocated hips, and talipes have been reported (17). The clavicle may look like a bottle opener (14). The pelvis and carpal bones are late in ossification and pseudoepiphyses are seen at the base of each metacarpal. The fingers may be long and tapering with ulnar deviation. Preaxial polydactyly, split hand, and other digital anomalies have been noted (2,10,24).

Proximal deletion of 4p produces a nonspecific phenotype (7,29). FISH detection is used for demonstration of the deletion (12,20a).

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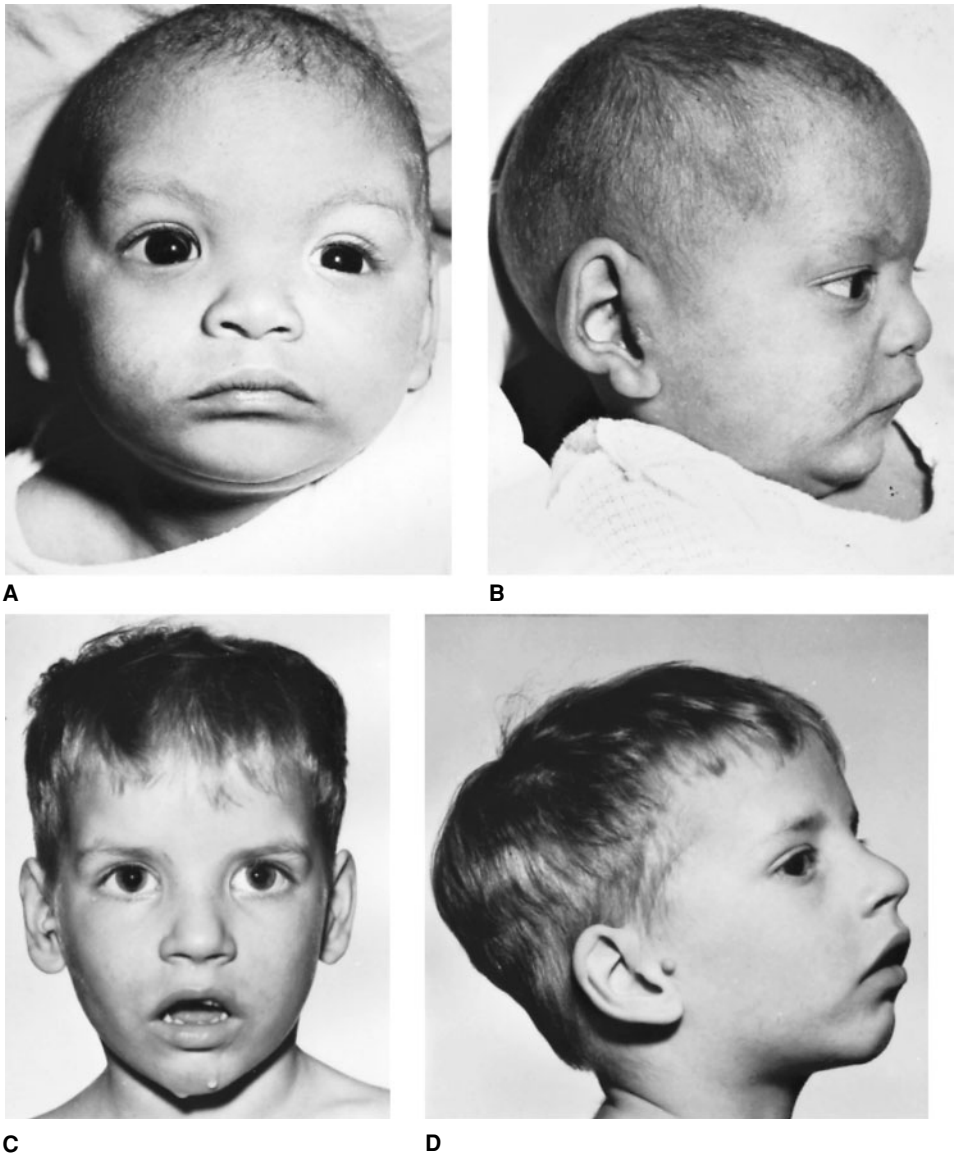

Fig. 3–5. *del(5p) syndrome (cri-du-chat syndrome).* (A,B) Microcephaly, round face, hypertelorism with broad nasal bridge, and malformed ears. (C,D) As the child ages, the round face disappears. Note preauricular tag. (A,B from C Weinkove and R McDonald, S Afr Med J 43:218, 1969. C,D from HB Dyggve and M Mikkelsen Arch Dis Child 40:82, 1965.)

del(5p) syndrome (cri-du-chat syndrome)

The basic defect is due to a partial deletion, either terminal or interstitial, of 5p15.2–p15.3 (8,11). This may result from either a de novo deletion of the short arm (about 85%) or unbalanced translocation inherited from a carrier parent (about 15%) (1,4,6), the latter being more severely affected (16). In a large series of deletions of varying size, the high-pitched cry seemed to map to 5p15.3 whereas the rest of the phenotype mapped to 5p15.2 (11). The δ-catenin gene is deleted. More proximal deletions do not produce the phenotype (5,14). The greater the deletion, the lower the intelligence, height, and weight and the more severe the microcephaly (15). Growth charts are available (7a). The frequency has been estimated at about 1/50,000 births. There is usually reduced life span. The syndrome is seen in approximately 1% of institutionalized mentally retarded patients. A good study of cognitive function is that of Cornish et al (2a). The syndrome is characterized by a high, shrill cry during infancy. However, the cry is neither pathognomonic nor present in all patients. It appears to be central, not laryngeal (7). In addition to severe somatic and mental retardation (7b), the child exhibits microcephaly, increased inner canthal distance, and round face (3). Other features include downward-slanting palpebral fissures (60%), hypertelorism (75%), epicanthal folds, posteriorly rotated pinnae, preauricular tags (20%), and broad nasal bridge with prominent nasal root and micrognathia (Fig. 3–5). With time, the face becomes asymmetric and the plumpness disappears (1). Malocclusion is common, particularly overjet. The hair becomes prematurely gray. Cleft lip/palate occurs in 8%–15% (9,16). The hands are smaller than normal with clinodactyly (10). Various congenital defects of the heart (30%–50%) and frequent upper respiratory infections, otitis media, and feeding problems are common (15).

Musculoskeletal anomalies include talipes, dislocated hips, and inguinal hernia (16). Hypotonia, very marked in infancy, disappears and reflexes become hyperactive. The gait becomes shuffling. Malrotation of the bowel or megacolon is found in about 25% of the cases resulting from parental translocation (15). The reader is referred to the study by Van Buggenhout et al for the changing phenotype in older patients (13).

Prenatal diagnosis has been accomplished on uncultured amniocytes using a FISH probe in a case of balanced carrier mother (2,13).

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Trisomy 8 (Warkany) syndrome

Trisomy 8 (15%), or far more frequently trisomy 8 mosaicism (85%) syndrome, is a relatively common autosomal chromosomal disorder. The estimated frequency is about 1/25,000 to 50,000 children, accounting for about 10% of autosomal trisomies. There is at least a 5:1 male predilection. Full trisomy 8 is rare postnatally but has been seen in 10% of spontaneous abortions (8). There is no significant difference in phenotype between so-called pure trisomy 8 and trisomy 8 mosaicism. Over 100 cases have been reported (1–19).

Life expectancy is essentially normal. Most infants have normal birth weight for gestational age. Mental retardation, usually of moderate degree (IQ 40–75), is a virtually constant feature, but occasionally near normal intelligence is noted (8). Agenesis of the corpus callosum is somewhat increased (13).

The forehead is usually high and prominent. The skull is often scaphocephalic. The face is elongated and the pinnae dysplastic. Mild hypertelorism and strabismus are evident in over 50% of the patients. Corneal opacities are frequent. The nose is broad based with an upturned tip in 60%. The mandible is small and retruded and the lower lip is commonly everted in about 40% of cases (Fig. 3–6A,B). Cleft palate has been reported (1). Beemer et al (2) reported a cephalometric study of three cases.

About 70% of affected individuals manifest contractures of fingers and toes, and generalized progressive joint restriction is common (Fig. 3–6C,D). About 35% of the patients have a long slender trunk with narrow chest and slender pelvis and about 65% have a spinal deformity, most often scoliosis. Broad ribs, extra ribs, first rib gap, spina bifida occulta, and butterfly vertebrae are common (1,10). Absent or hypoplastic patellae are frequent. Cardiac anomalies, found in 25% of patients, include VSD, PDA, pulmonary stenosis, coarctation of the aorta, total anomalous pulmonary venous connection, and truncus arteriosus. Hydronephrosis and/or hydroureter are relatively common. Cryptorchidism has been noted in about 50%, and hydronephrosis, hydroureter, or ureteral obstruction in 40% of patients (1,13). Wilms tumor and various types of leukemia have been described (12). Deep palmar and/or particularly plantar furrows are seen in about 75%. Other dermatoglyphic changes have been found (15). Recombinant 8 syndrome is associated with similar findings (19).

The abnormal cell line tends to disappear from the lymphocytes with age (11).

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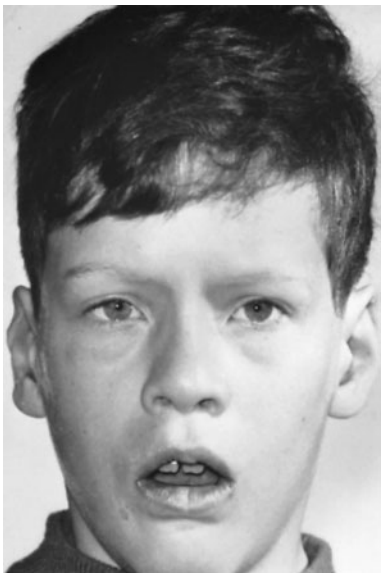

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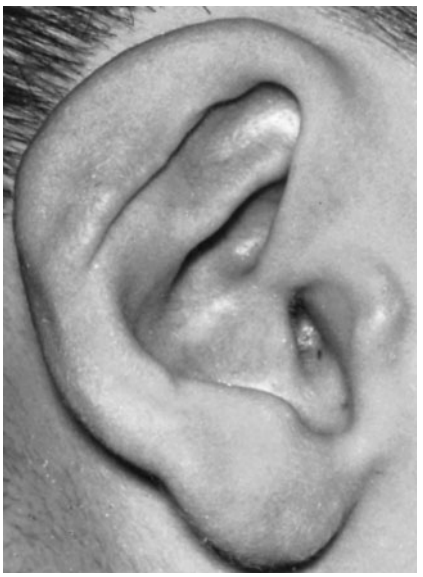

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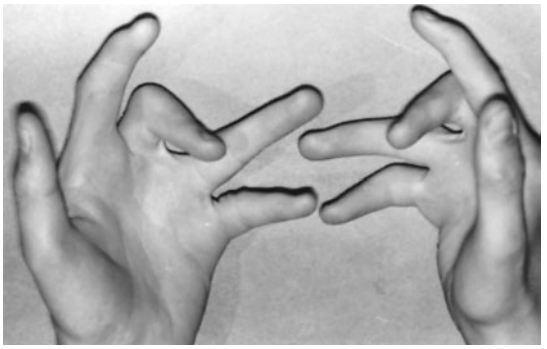

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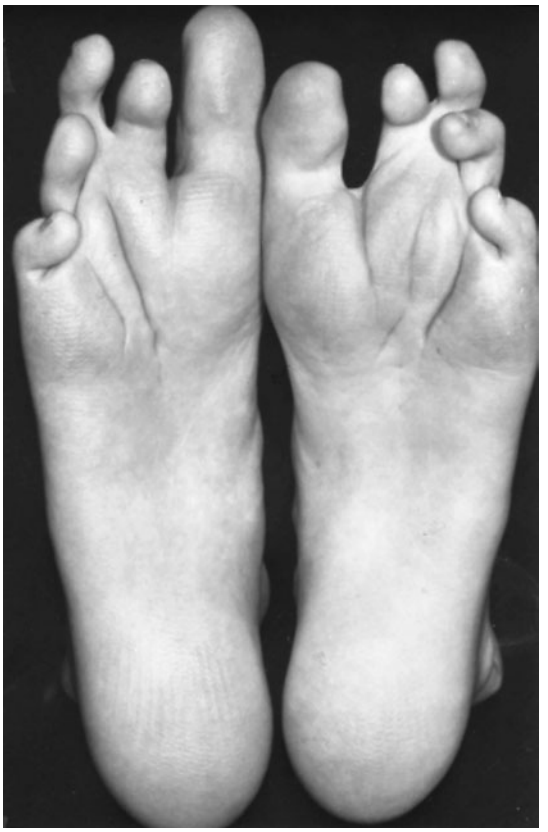

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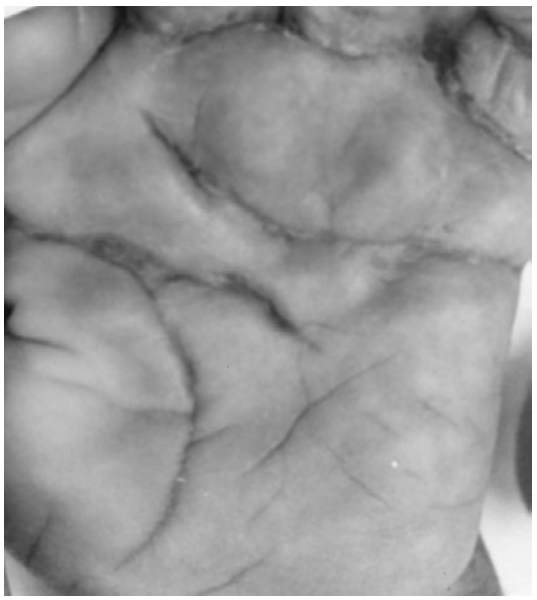

E

Fig. 3–6. *Trisomy 8 syndrome.* (A–D) Mentally retarded boy with joint contractures of fingers and toes, absent patellae, malformed ears, and vertical grooves on soles. (E) Deep palmar grooves. (E from MA Jordan et al, Genet Couns 9:136, 1998.)

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dup(9p) syndrome

Although less striking than 13 or 21 trisomy, the phenotype of dup(9p) nevertheless has classic craniofacial stigmata. There is a 2:1 female predilection. Over 125 cases have been reported (11).

The classic features involve short stature, characteristic facies, variable mental retardation, and hypoplasia and/or dysplasia of the terminal phalanges, particularly those of the second and fifth fingers (Fig. 3–7). The facies is characterized by microcephaly/brachycephaly, high, broad forehead, large fontanel and open metopic suture in childhood, mild microbrachycephaly, flat occiput, enophthalmus, mild hypertelorism, and divergent strabismus. The eyes appear relatively small and deeply set with mildly downward-slanting palpebral fissures. The nose has a large globular tip, broad nasal root, and short philtrum. The mouth is large with the angles turned down and the lower lip everted. The pinnae are large, low set, and outstanding with abnormal anthelix. The auditory canals are narrow. Cleft lip and/or palate has been found in 5% of patients. The neck is short and webbed with a low hairline (1,3–6,8,9,11,12).

Intelligence quotients have varied between 30 and 65. There may be mild finger contractures, brachydactyly, and mild syndactyly of the third and fourth fingers. The clinodactylous fifth fingers often have a single flexion crease. The nails are frequently hypoplastic and most have transverse palmar creases. Congenital heart disease is found in 15%–20%. Skeletal anomalies include hallux valgus, limited extension at the elbow, genua valga, kyphosis, and/or lumbar hyperlordosis.

Radiographically there is delayed bone age and retarded closure of anterior fontanel, thoracolumbar scoliosis, hypoplastic terminal and middle phalanges of fingers and toes, and proximal ossification centers of the metacarpals.

Among the several examples of tetrasomy for 9p, about one-third have cleft lip/palate, congenital heart disease, and hydrocephalus (2,7,10,11).

References [dup(9p) syndrome]

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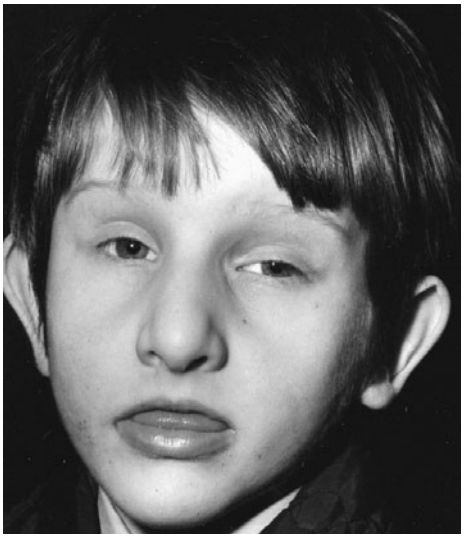
del(11)(p13) syndrome (aniridia-Wilms tumor syndrome, WAGR)

The syndrome of aniridia, mental retardation, and Wilms tumor (Fig. 3–8) is associated with deletion of the distal half of band 13 of the short arm of chromosome 11 (9,11). Maternal age appears to be advanced (10). The syndrome is generally sporadic. However, familial occurrence has been reported (7,13).

Fig. 3–7. *dup(9p) syndrome.* (A–C) Globular nasal tip, divergent strabismus, down-turned mouth, clinodactyly of fifth fingers, and small nails. (A from CE Blank et al, Clin Genet 7:261, 1975. B,C from P Balicek, Hum Genet 27:253, 1975.)



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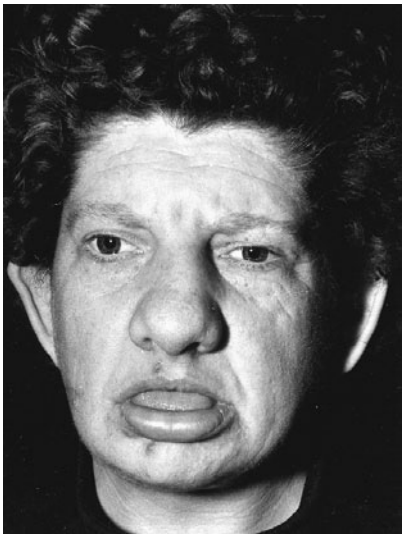

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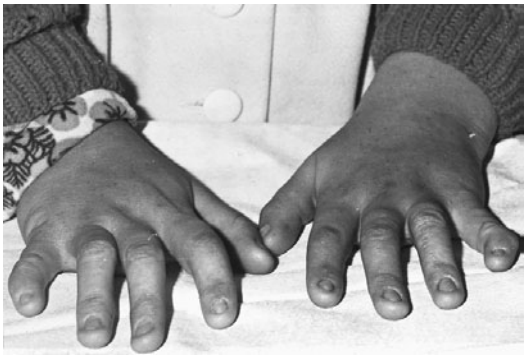

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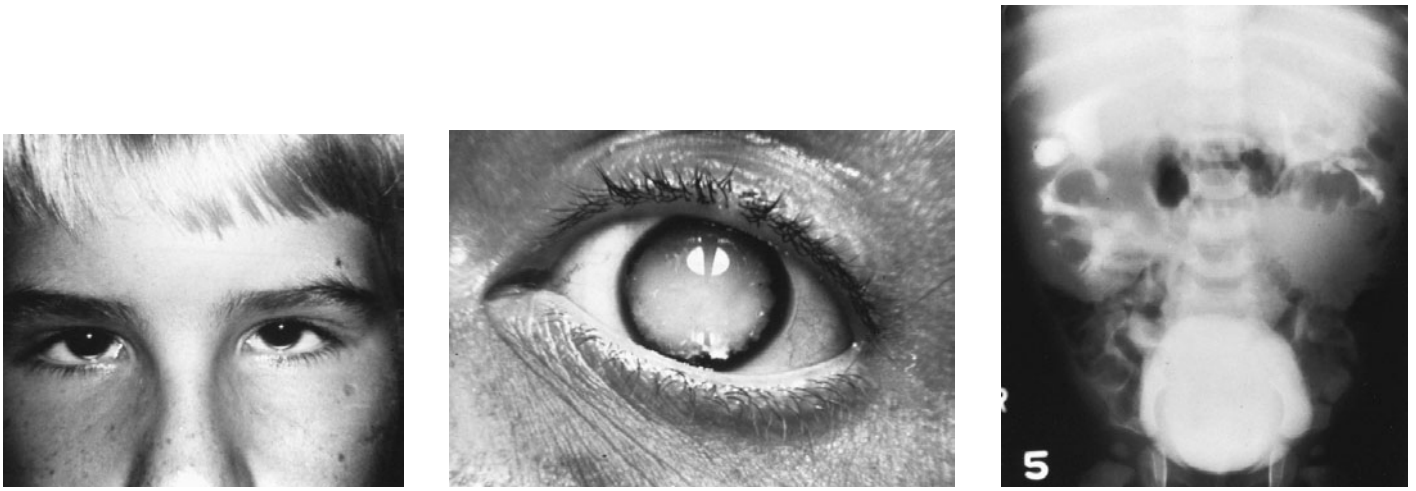

Fig. 3–8. *del(11)(p13) syndrome (aniridia-Wilms tumor syndrome).* (A) Bilateral aniridia. (B) Cataract developing in patient with aniridia. (C) Radiograph of bilateral Wilms tumor.

Craniofacial alterations include microcephaly with a prominent forehead, cranial asymmetry, long, narrow face, high nasal root, ptosis of eyelids, and low-set poorly lobulated pinnae.

Mental retardation is nearly always a constant feature as well as hypospadias and cryptorchidism in males. Hyperkinesis is common. About one-half of the children exhibit growth retardation.

Among children with Wilms tumor, the syndrome is seen in about 1%–2%. There is a definite male predilection, possibly as great as 3:1. In about 35% of the cases the Wilms tumor is bilateral, contrasting sharply with bilateral Wilms tumor not associated with the syndrome (2%–4%). In the syndrome, the tumor appears at a somewhat younger age (2–3 years) than in those with isolated Wilms tumor (4–5 years).

Rarely gonadoblastoma is found instead of Wilms tumor (1,11). The syndrome has been concordant in monozygotic twins with a variable degree of expression (e.g., Wilms tumor in only one twin), indicating that the event is postzygotic and that the deletion is not predisposing to the Wilms tumor (3,5). Although the interstitial deletion of 11p has varied from case to case, all have in common del(11)(p13). The gene for catalase is located in the same band. This has been demonstrated by its dosage effect in normal individuals, compared to the effect in those who are trisomic and monosomic for this region. Thus, catalase levels allow for differentiation of either isolated aniridia or isolated Wilms tumor from the syndrome, particularly since the syndrome is variably expressed (4,6). The genetic aspects of aniridia are discussed by Churchill and Booth (2).

Wilms tumor may also be found in association with *hemihyperplasia, Beckwith-Wiedemann syndrome, Simpson-Golabi-Behmel syndrome,* Perlman syndrome, Denys-Drash syndrome, *Sotos syndrome, Weaver syndrome,* and crossed renal ectopia (8).

References [del(11)(p13) syndrome (aniridia-Wilms tumor syndrome, WAGR)]

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del(13q) syndrome

Virtually constant features are reduced birth weight, psychomotor retardation, hypotonia, and microcephaly. Neural tube defects (NTDs), holoprosencephaly, and agenesis of the corpus callosum have also been noted (5). About one-half of the patients exhibit trigonocephaly. A critical region for producing this phenotype is 13q32 (2,10). The facies is characterized by frontal bossing, broad prominent nasal root, protruding maxilla and incisors, and large, prominent, malrotated ears with deep helical sulcus. Eye anomalies consist of ptosis, epicanthal folds, microphthalmia, and colobomas. Retinoblastoma occurs in approximately 15% of patients (3,4,6,7,13,14). Osteosarcoma and synovial sarcoma are found with increased frequency. The neck is short with redundant skin folds. Various congenital heart anomalies have been noted in approximately 35%. About 60% of the males have genital malformations including hypospadias, small or bifid scrotum, cryptorchidism, micropenis, and perineal fistula (Fig. 3–9). Anal atresia or ectopic anus has been noted in about 20% of all patients. Microcrania, hip dislocation, talipes equinovarus, delayed skeletal maturation, and metaphyseal undulations have increased frequency and thumbs are hypoplastic or absent in about 30% (4).

Most of the reported cases have involved loss of the distal two-thirds of the long arm. In some, this has resulted from deletion, in others, from translocation, and, in still others, from deletion and fusion, producing a ring chromosome (8). Deletion of bands 13q33–qter results in severe mental retardation, microcephaly, ocular hypertelorism, frontal bossing, protruding maxilla, large ears, and more NTDs. Those with additional deletion of bands 13q31–q32 exhibit mental retardation, microcephaly, trigonocephaly, hypoplastic or absent thumbs and metacarpals, and male

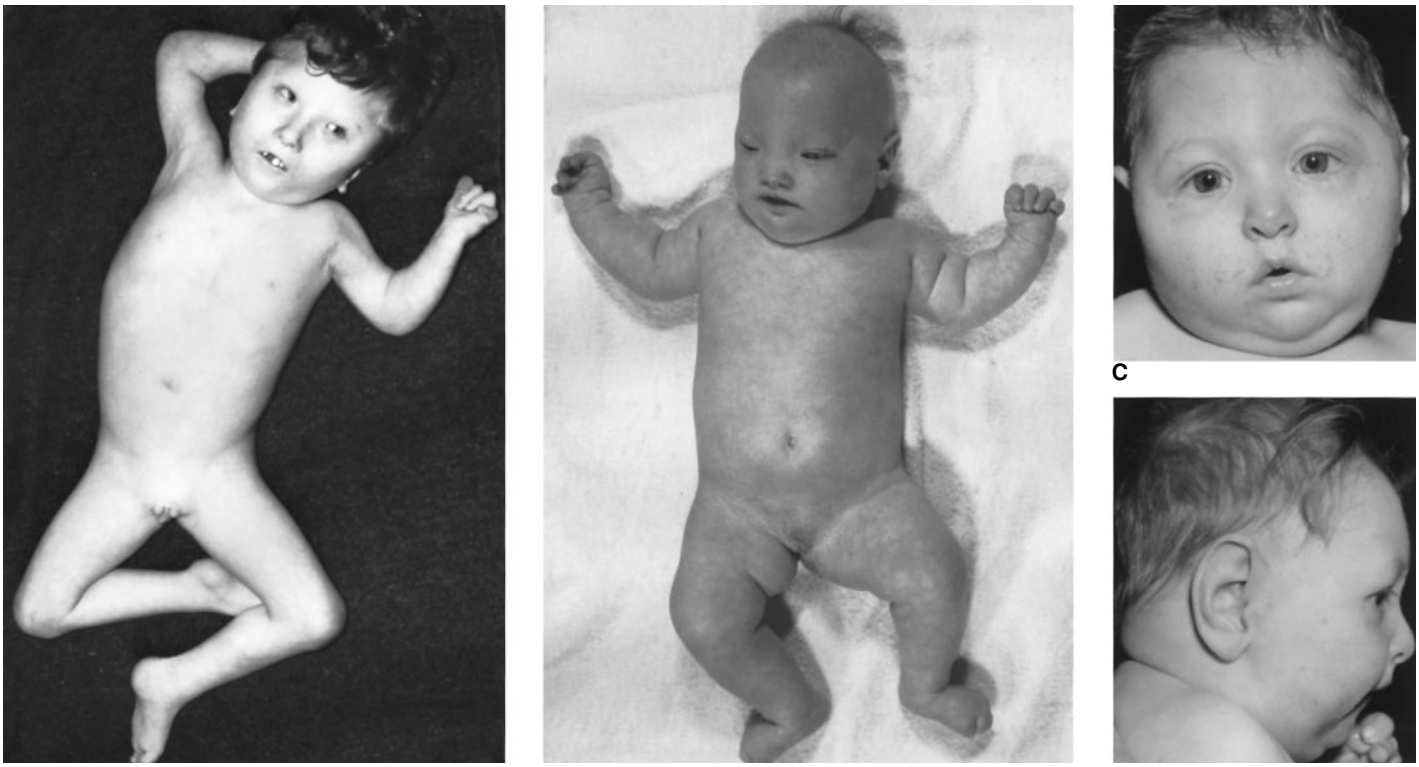

Fig. 3–9. *del(13q) syndrome.* (A) Absence of thumbs, micropenis, cleft scrotum in severely retarded child. (B) Broad-based nose, ptosis of eyelids, and absent thumbs. (C,D) Microcephaly, trigonocephaly, apparent hypertelorism, prominent nasal bridge, and short neck. (A from RS Sparkes et al, Am J Hum Genet 19:644, 1967. B from RC Juberg et al, J Med Genet 6:314, 1969. C,D from E Grace et al, J Med Genet 8:351, 1971.)

genital abnormalities. Retinoblastoma is associated with deletion of band 13q14, but only about 20% of those with that deletion have the tumor. With large deletions, holoprosencephaly may be found. Chromosome 13 deletion has also been seen with Waardenburg syndrome, type 2 (11). In a related way, Weigel et al (12) and Sparkes et al (9) described the combination of retinoblastoma and Hirschsprung disease in a patient with deletion of 13q13–q22. A child with von Voss-Cherstvoy syndrome (occipital encephalocele, radial ray defects, urogenital anomalies) had deletion of 13q (1). The gene for esterase D is proximate; thus it can be used for prenatal diagnosis and prediction for occurrence of retinoblastoma (3). J Fenyk (Minneapolis, 2000) has noted multiple areas of linear aplasia of the scalp in a newborn with ring 13.

References [del(13q) syndrome]

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del(18p) syndrome

At least 120 cases of del(18p) syndrome have been reported (1–12). There is a 3F:2M predilection. Mean parental age is increased (9). At least 85% arise de novo from translocation in 10% and rarely is familial (11). The extent of deletion of the short arm of chromosome 18 does not correlate with the clinical picture (4). In addition to the mental (100%) and somatic (75%) retardation, the phenotype is not striking unless associated with holoprosencephaly. Growth hormone deficiency has been reported (1,3). Microcephaly (50%), round face (40%), ocular hypertelorism (50%), ptosis (50%), strabismus (40%), epicanthus (40%), broad flat nose (80%), large outstanding ears (60%), carp mouth (65%), microretrognathia (45%), and short neck (45%) characterize the facies (Fig. 3–10) (7). Perhaps 25% exhibit pterygium colli. About 5% have cleft lip and 10% have cleft palate (10,11). As noted, about 10% exhibit semilobar or alobar holoprosencephaly (6,11). Single central incisor has been reported (2,3,5). No more than 5% have congenital heart anomalies. These are heterogeneous (VSD, coarctation of the aorta, AV canal, PDA, and transposition of large vessels) (10,11). About 50% of the males have micropenis and/or cryptorchidism. Dystonia has been noted in several patients (8).

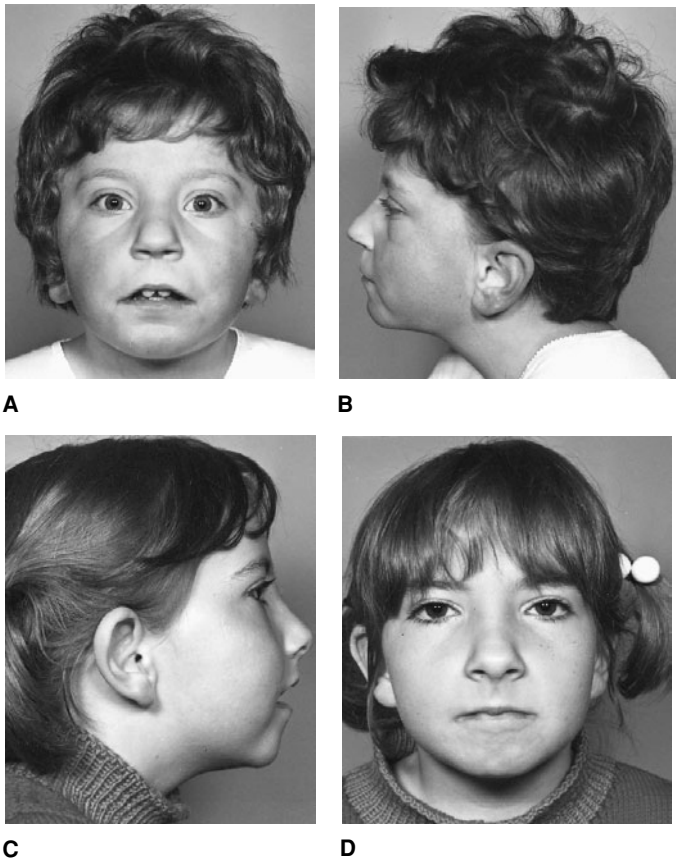

Fig. 3–10. *del(18p) syndrome.* Essentially normal facies but mild hypertelorism and wide mouth. (From A Schinzel et al, Arch Genet 47:1, 1974.)

References [del(18p) syndrome]

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del(18q) (de Grouchy) syndrome

In 1964, de Grouchy et al (4) reported partial deletion of the long arm of chromosome 18. The phenotype is distinctive, consisting of hypotonia, mental retardation, characteristic facial dysmorphism (Fig. 3–11), abnormal genitalia, and tapered fingers. More than 100 cases have been reported (1,5,6) and several extensive reviews are available (2,3,18). Wilson et al (22) and others (13) indicated that the typical syndrome with rare exception (20,21) had deletion in band 18q21 and identified a different clinical syndrome in association with a more proximal deletion within band 18q12. Most observers have found poor correlation between phenotype and size of deletion (17,20). However, Kline et al (12) found that low limb anomalies mapped to the most distal part of 18q with microcephaly and mental retardation to the more proximal part. In 80% of cases, the deletion occurs de novo; in 10%, the deletion results from parental pericentric inversion or translocation (15); and in 10%, the deletion is in the mosaic state, resulting in a less severe phenotype (3). There is a predilection for females, with a 2:3 male-to-female sex ratio. Mean birth weight is below 2700 g and, with growth and development, short stature below the fifth centile is observed in 78% (18,19). Growth hormone deficiency has been noted (8). Approximately 10% of affected infants die within the first few months of life (3) but, in general, most have a normal life expectancy (17). Hypotonia is a nearly constant feature but seizures are noted in only 10%. Mental retardation (100%) is profound, with few patients having an IQ over 30. The voice is often low pitched (18,19,22).

Microcephaly with head circumference below the second centile is observed in 68%. In some instances, fontanel closure is delayed. The midface is retruded (85%) and relative mandibular prognathism becomes evident with age. The eyes are deeply set. Other features may include epicanthic folds (42%), strabismus (34%), nystagmus (80%), coloboma of the iris (7%), pale optic discs (84%), prominent anthelix or antitragus (84%), stenotic ear canals (50%), impaired hearing (61%), broad nasal bridge (81%), carp-like mouth (87%), cleft lip (9%), and cleft palate (29%) (3,7,10,11,18,19,22). A small subcutaneous nodule may be evident at the site of cheek dimples (18).

The nipples are widely spaced (79%) and bilateral subacromial dimples are observed. Umbilical hernia is a feature in 16% of cases. Congenital heart defects occur in 35% (3,19,22), with atrial septal defect, pulmonary

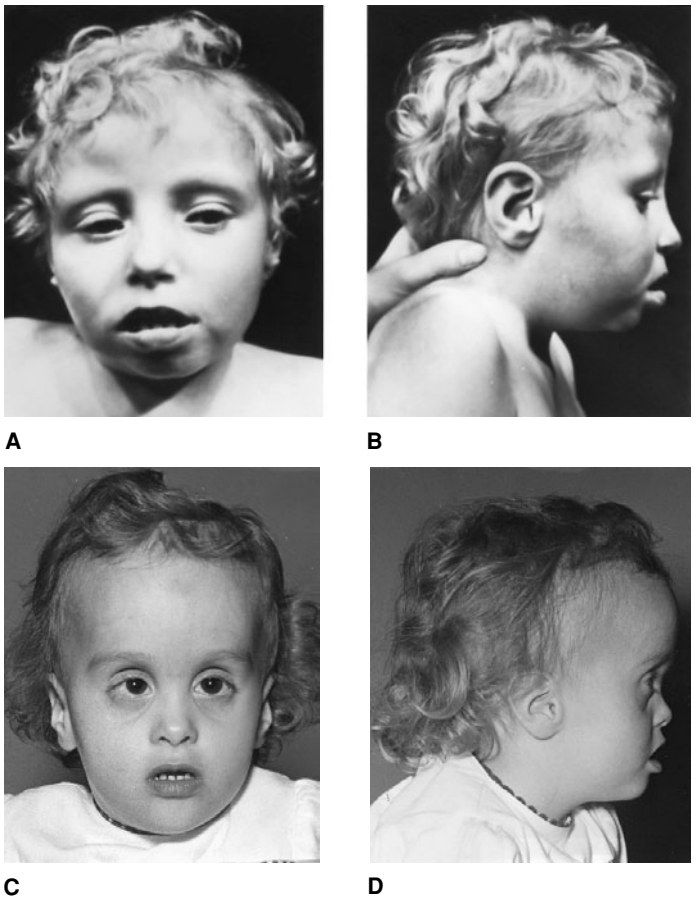

Fig. 3–11. *del(18q) syndrome.* (A,B) Midface hypoplasia, deeply set eyes, and prominent anthelix and antitragus in patient with 18r karyotype. (C,D) Compare facies of patient with that of patient in A,B. (A,B from JD Mürken et al, Z Kinderheilkd 109:1, 1970.)

stenosis, patent ductus arteriosus, and ventricular septal defect occurring in decreasing order of frequency.

The genitalia are abnormal in both sexes. Findings include cryptorchidism (52%), hypospadias, micropenis, and hypoplasia of the labia minora (47%) (3,18,19). Inguinal hernia occurs in 13% (19).

Dimples are present on the epitrochleal regions, over the knuckles, and on the lateral surfaces of the knees. The hands are long, thin, and tapered (90%). The thumbs are proximally placed in 90% and transverse palmar creases occur in 92% of cases. An excess number of fingertip whorl patterns and a high total finger ridge count are characteristic. Other findings include abnormal implantation of the second toes (84%) and talipes equinovarus (21%) (3,19).

Approximately half the cases are associated with osteoarticular anomalies, including supernumerary or hypoplastic ribs, costal synostoses, spina bifida occulta, and coxa valga (4).

IgA deficiency is found in approximately 30% (3,16,22). Diagnosis is based on banded chromosome study and FISH technique. Similar findings are noted in 18r syndrome (9,14).

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Turner syndrome

In 1938, Turner (58) recognized the combination of sexual infantilism, webbed neck, and cubitus valgus as a distinct entity. In 1959, Ford et al (13) showed that patients with Turner syndrome were missing one sex chromosome (45,X). The syndrome consists of short stature, streak gonads, webbed neck, shield chest, peripheral lymphedema at birth, coarctation of the aorta, hypoplastic nails, short metacarpals, and multiple pigmented nevi (Fig. 3–12) (11). The reader is referred to the following sources for extensive coverage: general aspects (8,9,14), cytogenetics (5,6,10,11,19,26,27,38,39,52), growth and development (29,44), cognitive and psychosocial aspects (33,46,48,49), cardiovascular anomalies (24,32,35–37), craniofacial and oral aspects (12,15,16,34,55), renal anomalies (43), and neoplasia (2,42,54,61). The prevalence is 1/2500 female births (11,17).

Cytogenetics. Approximately 98%–99% of Turner syndrome fetuses are spontaneously aborted (19); maternal origin of the single X chromosome occurs much more commonly than an X chromosome of paternal origin (5). The clinical phenotype is identical (57a). About 20% of all spontaneously aborted fetuses have Turner syndrome (8,9,17). About one-third of patients are diagnosed in the newborn period, one-third during childhood, and one-third during the teenage years when failure to go through puberty becomes evident. Maternal origin of the single X chromosome is also more common in 45,X survivors than in those with an X chromosome of paternal origin (27). Minimal diagnostic criterion is an abnormal karyotype in which all or part of one of the X chromosomes is absent. The overwhelming majority of patients have gonadal dysgenesis and short stature.

Approximately one-half of patients with Turner syndrome have 45,X karyotypes. The frequencies of different karyotypes are listed in Table 3–12 and the most common nonmosaic and mosaic karyotypes are listed in Table 3–13. Unusual mosaic karyotypes are also known to occur (41). Cryptic Y mosaicism has been discussed by several authors (26,40). Magee et al (30) noted seven pregnancies in a 45,X woman who, following hysterectomy and oophorectomy, was found to have two alleles in ovarian tissue. Clinical diagnosis is based on the overall pattern of anomalies; there are no obligatory malformations and even phenotypic features such as amenorrhea and short stature may be absent (54). Patients mosaic for Turner syndrome tend to have fewer phenotypic features than patients with isochromosome of the long arm of the X chromosome or with pure 45,X Turner syndrome (Table 3–14). The clinical severity of Turner syndrome mosaics increases with the relative increase in the abnormal cell line population (50). Patients with isochromosome formation of the short arm of the X chromosome are frequently normal phenotypically (54). Mosaicism of the 45,X/46,XY type exhibits variable findings. Approximately 15% have features of Turner syndrome, about 80% have ambiguous genitalia, and about 5% have a male phenotype with bilateral cryptorchidism (8). Phenotypic features of pure 45,X Turner syndrome are listed together with percentages in Table 3–15.

Candidate genes. Zinn (63) and Zinn and Ross (64) have discussed candidate genes such as *SHOX, ZFX,* and *RPS4X.* Accumulating evidence indicates that the latter two genes with haploinsufficiency are not the causes of Turner syndrome. *SHOX,* in the pseudoautosomal region, may be responsible for short stature, but haploinsufficient mutations have been shown to cause Leri-Weill dyschondrosteosis and Langer mesomelic dwarfism.

Growth. Average birth length is 47 cm (8) and birth weight is lower than normal, 2933 ± 467 g. Ranke et al (44) studied growth in 150 patients from three German-American centers, observing that growth could be divided into four phases: (*a*) intrauterine growth retardation; (*b*) height development, which is normal up to a bone age of 2 year; (*c*) bone age of 2 to 11 years, when growth is markedly stunted; and (*d*) bone age after 11 years when the growth phase is prolonged but total height gain is below normal. Ranke et al (44) observed no difference in height between 45,X patients and other chromosomal variants. Lyon et al (29) provided growth data for four published series of European patients. Their results enable reasonable prediction of adult height in any patient with Turner syndrome. Lyon et al (29) also noted that estrogen treatment, although resulting in initial accelerated growth, had no significant effect on final height attainment. Lemli and Smith (23) and Brook et al (3) observed that familial height played a role in determining final height attainment in patients with Turner syndrome, with taller parents having taller daughters. Final height attainment is usually between

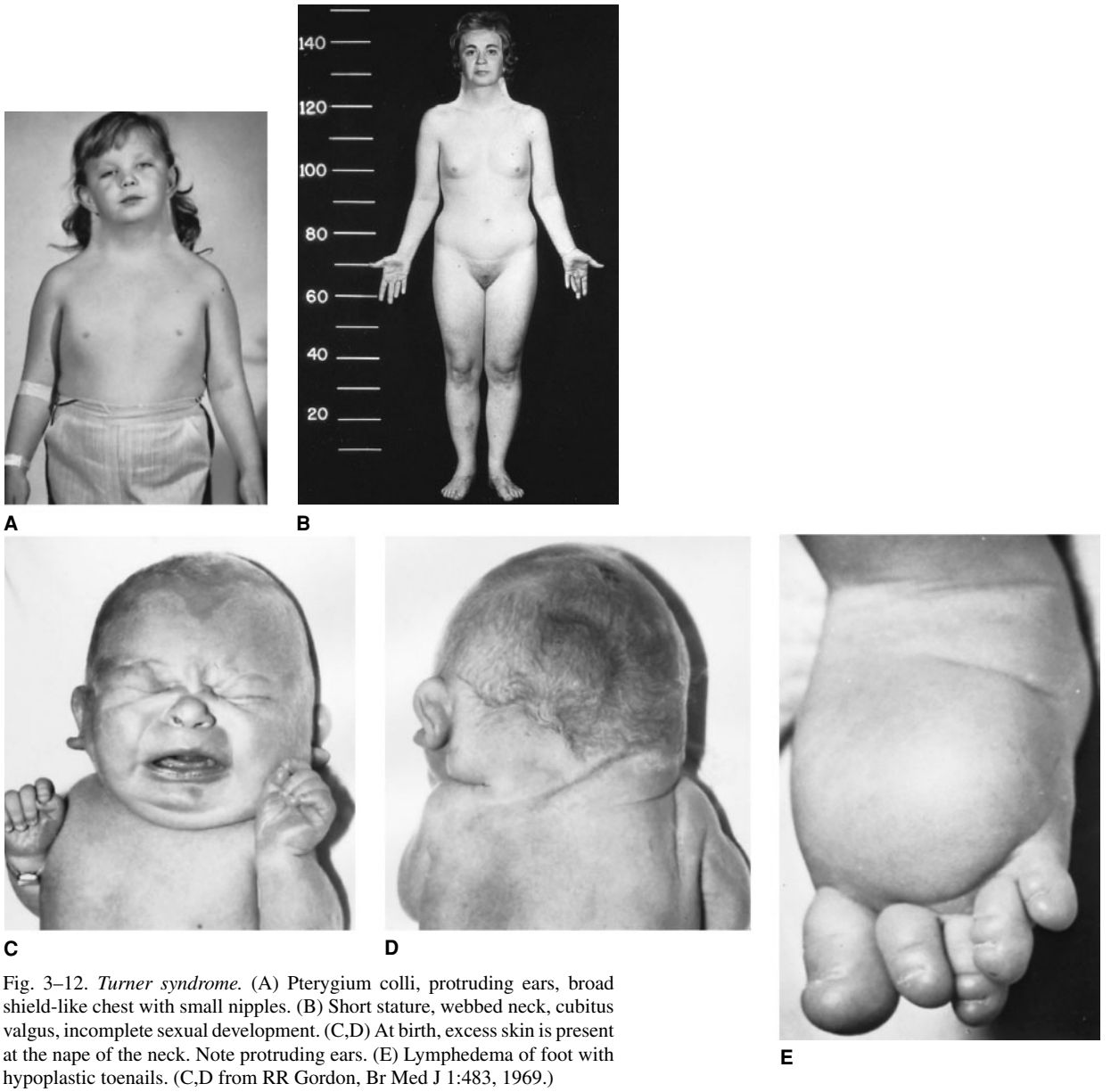

Fig. 3–12. *Turner syndrome.* (A) Pterygium colli, protruding ears, broad shield-like chest with small nipples. (B) Short stature, webbed neck, cubitus valgus, incomplete sexual development. (C,D) At birth, excess skin is present at the nape of the neck. Note protruding ears. (E) Lymphedema of foot with hypoplastic toenails. (C,D from RR Gordon, Br Med J 1:483, 1969.)

122 and 152 cm (11). Ranke et al (44) found a mean adult height attainment of 146.8 cm. Short legs make for the disproportionate short height (47).

Central nervous system. Studies of performance in Turner syndrome have been subject to methodological shortcomings, including (*a*) faulty reporting of mental retardation in some patients when, in fact, reduced performance IQ in the presence of a normal verbal IQ results from specific deficit in spatial ability rather than global reduction in

Table 3–12. Frequency of chromosomal constitutions seen in Turner syndrome

Chromosomal constitution	Approximate percent
45,X	50
Isochromosome X	12–20
Mosaicism	30–40
45,X/46,XX	(10–15)
45,X/46,XY	(2–5)

(Adapted from JG Hall et al, West J Med 137:32, 1982.)

Table 3–13. Most common karyotypes associated with Turner syndrome

Most common nonmosaic karyotypes

45,X
46,X,i(Xq)
46,X,del(Xp) or 46,XXp–
46,X,del(Xq) or 46,XXq–
46,X,r(X)
46,X,i(Xp)
46,X,i(Yq)
46,X,t(X;X) or 46,X,ter rea (X;X)
46,X,t(X;any autosome) or 46,X,t(X;Y)

Most common mosaic karyotypes

45,X/46,XX
45,X/47,XXX
45,X/46,XX/47,XXX
45,X/46,XY
45,X/any karyotype with a structurally abnormal X or Y

(Adapted from A de la Chapelle, Sex chromosome abnormalities. In: Principles and Practice of Medical Genetics, Emery EH, Rimoin DL (eds), Churchill Livingstone, Edinburgh, 1983, p 193.)

Table 3–14. Comparison of findings in pure Turner syndrome and Turner mosaicism

Finding	45,X (%) ($n = 59$)	Mosaic Turner (%) ($n = 41$)
Head and neck		
Epicanthic folds	37	12
Ptosis of the eyelids	14	7
Myopia	14	15
Abnormal ears	56	37
Low hairline	66	37
Webbed neck	51	27
Thorax		
Shield chest	66	39
Coarctation of aorta	12	5
Heart murmur	46	39
Limbs		
Lymphedema	53	12
Abnormal nails	53	20
Cubitus valgus	56	54
Renal abnormalities	32	20

(Modified from JG Hall et al, West J Med 137:32, 1982.)

intelligence; (*b*) ascertainment bias of patients by severe phenotypic stigmata instead of independently by karyotype; and (*c*) samples composed of pooled karyotypic subgroups instead of independent examination of each subgroup (1). Visual–spatial deficit has been related to reduced functioning in the right cerebral hemisphere, specifically the right parietal lobe (1). This has been shown to be due to deletion of the most distal area of the short arm of the X chromosome (49a). Bender et al (1b) found that 45,X Turner syndrome subjects were slightly delayed in walking, had a moderately decreased full-scale and performance IQ, and demonstrated striking deficit in perceptual organization and fine motor skills, but had average language skills. Linden et al (25) noted that features such as slow speech development, hyperactivity, learning disabilities, neuromotor deficits, and short stature could contribute to poor self-image and lowered self-esteem during adolescence. In a study of 99 Turner syndrome subjects, Romans et al (46) and Ross et al (49) found problems in spatial/perceptual skills, visual–motor integration, affect recognition, visual memory, attentional abilities, and executive function. Motor problems are not related to cognitive defects (36a).

Several psychiatric disturbances have been reported. A slight increase in the risk for anorexia nervosa has been noted (21). McCauley et al (33), studying 30 adult subjects, reported a significant subgroup with major psychiatric problems, especially depression with markedly low self-esteem.

Head and neck abnormalities. Epicanthic folds, ptosis of the eyelids, prominent ears, and micrognathia are common facial features. Visual abnormalities, particularly strabismus, are found in approximately 20% of patients. Chronic suppurative otitis with resultant hearing loss occurs in some cases (22,56). In infants, excess skin on the nape of the neck is common. During embryonic life, neck blebs or cystic hygromas are common (4). With age, the excess skin on the neck metamorphoses into pterygium colli. The ears are prominent and the posterior hairline is low (Fig. 3–12). The palate is highly arched in approximately 35% and cleft palate may occur with a somewhat higher than normal frequency. The teeth may erupt prematurely, the first permanent molars appearing between 1.5 and 4 years of age (12,15,16,34,55). There is increased molarization of premolars (60). Cusp height is reduced (31) as is crown size (55a).

The cranial base is short, so the face is retrognathic. The mandible is short, the maxilla being of normal length (1).

Chest. The chest is broad with seemingly wide-spaced, hypoplastic, and, at times, inverted nipples. Breast development is poor.

Table 3–15. Features of 45,X Turner syndrome

Feature	Percent or Finding
Growth	
Birth length	$\overline{X} = 47$ cm
Birth weight	$\overline{X} = 2933 \pm 467$ g
Final height attainment	122–152 cm
Performance	
Cognitive	Deficits[a]
Intelligence	Normal
Psychiatric	Slightly increased risk for anorexia nervosa[b]
Head and neck	
Epicanthic folds	25
Highly arched palate	36
Visual abnormalities, usually strabismus	22
Auditory problems	50
Webbed neck	46
Short, broad neck, low hairline	74
Chest	
Shield chest	53
Cardiovascular	
Coarctation of the aorta, ventricular septal defect	10–16
Renal	38
Horseshoe kidney	—
Duplicated or otherwise anomalous ureters	—
Unilateral renal aplasia or hypoplasia	—
Gastrointestinal	
Telangiectases	—
Skin and lymphatics	
Pigmented nevi	63
Lymphedema of hands and feet	38
Nails	
Hypoplasia	66
Skeletal	
Cubitus valgus	54
Short metacarpals, metatarsals (usually 4)	48
Deformed medial tibial condyle	65
Osteoporosis	50

[a] For specific deficits, see text and B Bender et al, Pediatrics 73:175, 1984.
[b] For other psychiatric abnormalities, see text and JG Hall et al, West J Med 137:32, 1982. For psychosocial adjustment, see E McCauley et al, Clin Genet 29:284, 1986.
(Adapted in part from JL Simpson, Disorders of Sexual Differentiation, Academic Press, New York, 1976; and A de la Chapelle, Sex Chromosome abnormalities. In: Principles and Practice of Medical Genetics, EH Emery, DL Rimoin (eds), Churchill Livingstone, Edinburgh, 1983, pp 193–215.)

Genitalia. Gonadal dysgenesis or streak gonads are characteristic. The histologic pattern consists of long streaks of white wavy connective tissue stroma without follicles. However, follicles are present in fetal and infantile ovaries of patients with Turner syndrome. Patients have primary amenorrhea and sterility. Exogenous hormone replacement is essential for establishing secondary sexual characteristics. Fertility is a rare possibility and has been recorded in a number of instances.

Cardiovascular abnormalities. In a study of 594 Turner syndrome patients, Mazzanti et al (32) found a prevalence of cardiac malformations of 23%; bicuspid aortic valve (12.5%), aortic coarctation 6.9%), and aortic valve disease (3.2%) were most common. Bastianon et al (1a) found 26% of patients with mitral valve prolapse and 15% with bicuspid aortic valve. Only 4% had aortic root dilatation. Coarctation of the aorta occurs with higher frequency with pure 45,X karyotype. Dissecting aortic aneurysm has also been reported (24). Coarctation of the aorta is the most common cause of hypertension and blood pressure often returns to normal following surgical repair. Adults have an increased frequency of hypertension (30%) even when coarctation of the aorta, renal parenchymal, and renal vascular disease have been eliminated as causes. Less common anomalies include ventricular septal defect, atrial septal defect, dextrocardia, bicuspid aortic valves, and hypoplastic left heart (37).

A variety of other vascular anomalies may be observed infrequently, including intestinal telangiectasias, vascular malformations, and lymphangiectasia. Gastrointestinal bleeding may indicate vascular malformations of the intestinal tract. Since the frequency of ulcerative colitis and Crohn's disease is higher in Turner syndrome than in the general population, gastrointestinal bleeding may also indicate primary bowel disease. Protein-losing enteropathy from gastrointestinal lymphatic malformations has also been recorded. Patients with Turner syndrome also have a higher frequency (90%) of increased numbers of renal arteries. Lymphedema occurs in approximately 80% of newborns. The hands and feet may appear puffy but lymphedema is usually transient, resolving in childhood. Recurrent lymphedema of the extremities may be observed in some patients and, rarely, severe lymphedema may be found in adulthood with chylous ascites (57). Lymphedema is almost always secondary to congenital hypoplasia of the lymphatic channels. Shepard et al (53) documented hypoalbuminemia in 45,X fetuses and suggested that lowered plasma albumin concentration could contribute to the edema by lowering osmotic pressure in the blood vessels.

Renal anomalies. Renal findings include horseshoe kidneys (20%), duplication of the collecting ducts (20%), and malrotation of the kidney (15%) (43). Potter sequence has been observed with Turner syndrome (28,62) and may result from cystic dysplasia, small kidneys, or obstructive uropathy (43). When the latter occurs, prune belly may be present (51). The various renal anomalies depend upon the karyotype (1c).

Skeletal abnormalities. Bone age remains within normal limits until 12–14 years of age when the adolescent growth spurt fails to take place. Bone age is generally 2–3 years behind (34). The homeobox *SHOX* is involved in skeletal abnormalities (4a). Without hormone therapy, epiphyses usually fail to fuse until patients reach their 20's. Common skeletal abnormalities include cubitus valgus (approximately 75%), short fourth metacarpals (about 65%), deformity of the medial tibial condyle (about 65%), cervical ribs (100%) (20), hypoplasia of the cervical vertebrae (about 80%), small carpal angle (45) and *relatively* longer hands (59). Some degree of osteoporosis is found in about 50%. However, bone radiolucency and coarse trabeculations can be observed in childhood. Common radiographic findings are listed in Table 3–16. Cohen (7) reviewed five cases with craniosynostosis.

Table 3–16. Common radiographic features of Turner syndrome

Hand

- Drumstick distal phalanges
- Short fourth metacarpals
- Carpal sign: change in angulation of carpal bones
- Shortening of all hand bones
- Madelung's deformity

Feet

- Similar to hands
- Pes cavus

Knees

- Lateral dislocation of patellae
- Hypoplastic patellae
- Irregularity of tibial metaphysis and epiphysis
- "Mushroom" projections, medial surface of proximal tibial metaphysis (medial tibial condyle)

Spine

- Scoliosis
- Lack of lumbar lordosis
- Schmorl's nodes (abnormalities of cartilaginous endplates)
- Hypoplasia of arch of atlas
- Shortening of anteroposterior diameter of vertebral bodies

Ribs

- Thin
- Developmental abnormalities

Pelvis

- Android configuration (50%)
- Occasional widening of symphysis pubis

Skull

- Midfacial hypoplasia
- Deepening of posterior cranial fossa
- Widely spaced mandibular rami

(Adapted from CG Brook et al, Ann Hum Biol 4:17, 1977; WD Risch et al, Am J Roentgenol 126:1302, 1976; and JG Hall et al, West J Med 137:32, 1982.)

Dermatologic features. Hypoplastic, deeply set nails, and multiple pigmented nevi are common. Kato (18) noted a patient with a combined nevus of the compound and Spitz types. Seborrhea, xerosis, hirsutism, and keloid formation occur with increased frequency. Dermatoglyphic findings include an increased total finger ridge count. Redundant folds of skin resulting in pterygium colli and low nuchal hairline have already been discussed.

Neoplasia. Patients who are mosaic for 45,X/46,XY have an increased risk of gonadoblastoma. Such neoplasia develops in a high percentage during early childhood, but there is also an increase around puberty (54). Wertelecki et al (61) studied 289 patients with Turner syndrome and found nongonadal neoplasia in 2.8%. Three tumors were of neural origin, three were gastrointestinal, and one case of leukemia and one of carcinoma of the thyroid were noted. Wertelecki et al (61) listed all other cases of nongonadal neoplasia, including, among others, two pituitary tumors, two adrenal tumors, and four brain tumors. Neuroblastoma and ganglioneuroblastoma have been reported (2). Simultaneous neuroblastoma and adrenocortical carcinoma were noted in a patient with a germline *p53* mutation (42).

Autoimmune disease. Hypothyroidism, diabetes mellitus, and inflammatory bowel disease occur more frequently in the Turner syndrome population than in the general population. Acute Hashimoto's thyroiditis occurs infrequently, but hypothyroidism on an autoimmune basis occurs in approximately 20% of adult women with Turner syndrome. Papendieck et al (39) reported that 55% of patients had thyroid disturbances (n = 49).

Differential diagnosis. Short stature can be observed with *Noonan syndrome,* familial short stature, dyschondrosteosis, type E brachydactyly, growth hormone deficiency, hypothyroidism, glucocorticoid excess, *multiple pterygium syndrome, Klippel-Feil anomaly,* and short stature due to chronic disease. Amenorrhea or failure to begin puberty occurs in pure gonadal dysgenesis, Stein-Leventhal syndrome, and primary or secondary amenorrhea. Lymphedema occurs as Milroy disease, lymphedema with distichiasis, *Hennekam syndrome,* lymphedema with recurrent cholestasis, and lymphedema with intestinal angiectasia. Fetal lymphaticovenous malformations may be seen in *fetal alcohol syndrome, trisomy 21, trisomy 18, del(13q), del(18p), trisomy 22 mosaicism,* and *Noonan syndrome.*

Laboratory aids. Banded chromosome studies should be carried out when a clinical diagnosis of Turner syndrome is suspected. Fifty cells should be counted to rule out mosaicism. If leukocyte studies are normal but clinical suspicion of Turner syndrome is strong, fibroblast cultures should be carried out. Buccal smears should no longer be used because patients with isochromosome X often show Barr body material, resulting in misdiagnosis.

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Klinefelter syndrome and its variants

Klinefelter et al (28) reported postpubertal males with small testes and tubular hyalinization, normal numbers of Leydig cells, azospermia, gynecomastia, elevated urinary gonadotropins, and decreased urinary 17-ketosteroids. By 1956, such patients were shown to have Barr bodies (37). In 1959, Jacobs and Strong (25) described an XXY sex chromosome complement in chromatin-positive Klinefelter syndrome. The birth prevalence of chromatin-positive males is approximately 2/1000 and is composed of several X-aneuploidy variants: 47,XXY, 48,XXYY, 46,XY/47,XXY, 48,XXXY, and 49,XXXXY. Approximately 80% are 47,XXY, about 10% represent mosaics, and the remainder have more unusual karyotypes. The prevalence of "classic" Klinefelter syndrome (47,XXY) is approximately 1.18/1000 births. XXY Klinefelter syndrome is at least 20 times as common as other types of X-chromosome polysomy (27). At conception, mean maternal age has been advanced—31.3 years; mean paternal age is 35.5 years (12). Klinefelter syndrome occurs with a frequency of about 0.5%–1.0% in males institutionalized for mental retardation, seizures, or mental illness and in about 10% of males who have sterility. Double aneuploidy of Klinefelter syndrome and Down syndrome occurs with greater frequency than expected by chance (6). Mosaicism has been discussed by several authors (12,26,27,39). Except during screening, it is unusual for clinical diagnosis to be made during infancy or childhood, except for severe conditions such as 49,XXXXY. Classic Klinefelter syndrome is diagnosed most commonly at puberty, although rarely clinical clues may be evident in childhood (9). With increasing X-aneuploidy (47,XXY to 49,XXXXY) several clinical trends become evident: decrease in stature, increase in mental retardation, decrease in total finger ridge count, increase in varicosities, increase in hypostatic leg ulcerations, increased frequency of radioulnar synostosis, increased frequency of mandibular prognathism, and increased frequency of taurodontism (10,29). It should be emphasized that these are statistical trends and need not apply to individual cases (47,XXY).

Growth. Mean birth weight is 3048 g, which tends to be lower than in normal brothers of Klinefelter infants (39). Until 3 years of age, height distribution in a large series of Klinefelter children is unremarkable, but after 3 years of age, the distribution is skewed, with significantly fewer boys below the 25th centile than expected. Head circumference distribution during infancy is similar to that found in the general population. However, at about 4 years of age, head circumference distribution tends to be skewed to the lower half of the normal curve (39). In adulthood, typical Klinefelter individuals are of average or somewhat above-average height; in most populations, Klinefelter individuals are 2–5 cm taller than average normal males. Mean height of such individuals in northern Europe is 177.4 cm. Tall stature is primarily the result of increase in leg length, which is present before puberty but not particularly obvious. In approximately 60% of cases, arm span exceeds height by 3 cm or more (12,39).

Central nervous system and performance. Delayed speech is found in 50% of patients. Delays in emotional development are common (30%), and school maladjustment has been reported in 45%. Poor gross motor coordination is a feature in approximately 25%. During childhood, psychiatric problems do not occur more frequently than in normal individuals. Average IQ is approximately 90 with about 30% below 90. In general, Klinefelter individuals are usually neither highly intelligent nor severely retarded (12,16,39,40).

In adults, there may be disturbances of behavior, deviations in personality, as well as neurotic and psychotic reactions. Antisocial behavior, alcoholism, aggressiveness, depression, and periods of mania have been reported to occur commonly (12,39). Feelings of inadequacy and poor body image often accompany gynecomastia and testicular atrophy (30) (Fig. 3–13A). However, most Klinefelter individuals tend to lead a quiet, passive type of existence (12,39).

Psychosexual orientation is male. Erection, coitus, and ejaculation occur but libido is often subnormal. Many Klinefelter individuals lead normal married lives (12,39).

Genitalia. Penile size is normal or slightly reduced. Small testes are a constant feature, with adult size measuring 1–2 cm compared with 3.5–4.5 cm in normal males. In nearly all cases, the testes are descended. The scrotum is normal in size and in pigmentation. Approximately 50% have a female pubic escutcheon. The prostate is smaller than normal (39,45).

Prepubertal testes are of normal size and microscopic appearance, but during adolescence they fail to enlarge. The testes are small, soft, and often insensitive to pressure. The seminiferous tubules are usually shrunken, hyalinized, and irregularly arranged. Tubules that are not sclerotic are immature and lined exclusively with Sertoli cells. Elastic fibers are absent around the tunica propria of the tubules. Leydig cells are clumped. Rarely, spermatogenesis can be demonstrated. Generally, Klinefelter syndrome is associated with sterility, but in a number of instances, indisputable evidence of paternity has been found (12,39,45).

Secondary sexual characteristics. Typically, Klinefelter syndrome patients do not have female fat distribution, a high-pitched voice, or notably scanty body hair (Fig. 3–13A). However, these features may be present. Facial hair is sparse in 60%–90% and untreated Klinefelter individuals shave only once or twice per week. Gynecomastia develops after puberty in approximately 50% (12,39) (Fig. 3–13A).

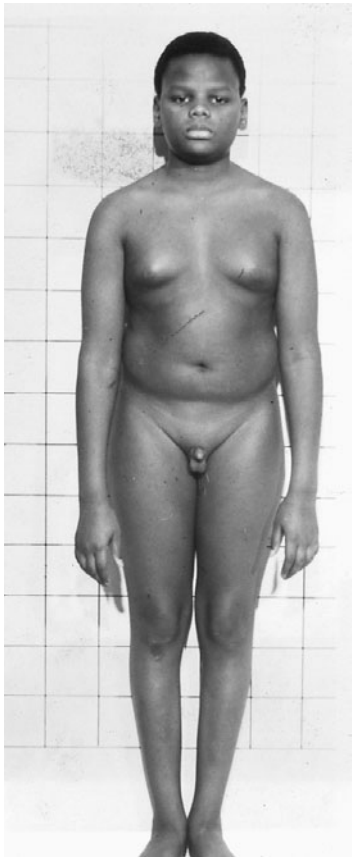
Hormones. Leydig cells are defective; plasma testosterone is low in the presence of normal or high follicle-stimulating hormone (FSH) and leutinizing hormone (LH). Typically, patients have 50% or less of normal levels of plasma testosterone and a four-fold increase in urinary excretion of pituitary gonadotropin (12,39) (Fig. 3–13A).

Dermatologic findings. Varicose veins and hypostatic leg ulceration have been reported (10). There are no suggestive dermatoglyphic findings, although the total finger ridge count tends to be lower than average because of an increased number of arches (12).

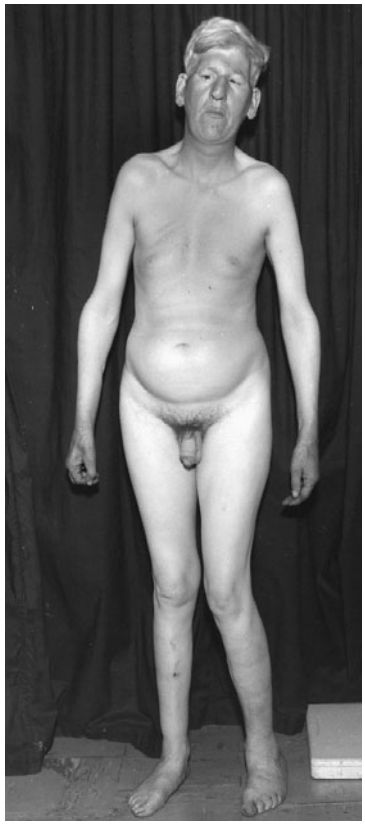
Craniofacial features. Cephalometric investigation shows smaller calvarial size, smaller cranial base angle, and larger gonial angle than normal (5). Both maxillary and mandibular prognathism tend to occur (22). Alvesalo and Portin (2) found permanent tooth crowns to be larger in 47,XXY males than in control males. Taurodontism has been reported in some instances (14,29).

Congenital malformations. Major malformations are found in approximately 20%, but no clear patterns have emerged. Findings may include cleft palate, inguinal hernia, cryptorchidism, unilateral renal aplasia, microcephaly, corneal opacity, aortic stenosis, mitral valve prolapse, omphalocele, nerve deafness, hypospadias, pectus excavatum, or scoliosis. Minor anomalies are observed in 25% of patients, with clinodactyly being the most common (20%). Other findings may include ear anomalies, single palmar creases, strabismus, external rotation of legs, "third" fontanel, micropenis, down-slanting palpebral fissures, or genu recurvatum (12,39).

Other findings. Some evidence indicates an increase in pulmonary disorders (39) and, perhaps, lupus erythematosus (46). Autoimmune disorders, in general, are increased (2a). Diabetes mellitus is present in 8% of adult XXY patients.



A



B

Fig. 3–13. *Klinefelter syndrome.* (A) Note gynecomastia, female fat distribution, paucity of pubic hair; small testes in XXY male. (B) Male with XXYY karyotype. Note mild gynecomastia, knock-knees, female pubic escutcheon, stasis dermatitis of lower legs.

Neoplasia. An increased frequency of carcinoma of the breast has been noted, the risk being 66 times that in normal men and approaching the risk in normal women (24). Conversely, Klinefelter syndrome is found in 3.3% of men with breast cancer (19). Isurugi et al (23) reported seminoma of the testis.

48,XXYY. Birth prevalence is 0.04/1000 male births. At least 120 cases have been analyzed (13). The frequency is 50 to 100 times greater among males in mental institutions and prisons (12). Most likely, the disorder is caused by nondisjunction in both the first and second meiotic divisions during spermatogenesis, with the production of an XYY sperm. The less likely possibility of nondisjunction at the second meiotic division in both parents must be rare. Advanced parental age has not been observed (12,39).

In general, individuals with 48,XXYY karyotype tend to be approximately 4 cm taller, more aggressive with more truncal obesity, and more mentally retarded than those with 47,XXY karyotype. Characteristic features include small testes, eunuchoid habitus, sparse body hair, gynecomastia, varicose ulceration, and elevated gonadotropins (8,13,17) (Fig. 3–13B). Dermatoglyphic studies have shown that fingertip arch patterns are more common in 48,XXYY individuals. Thus, the total finger ridge count is low (12).

48,XXXY. This condition is rare and arises from successive nondisjunction in either maternal or paternal meiotic divisions (12,39).

Mental retardation is a constant finding. The penis is hypoplastic in 50% of cases and gynecomastia is observed in approximately 35%. Other findings include facial asymmetry, epicanthic folds (25%), ocular hypertelorism, protruding lips, mandibular prognathism, short neck, radioulnar synostosis (10%), clinodactyly of fifth finger (30%), coxa valga, and other abnormalities (12,39).

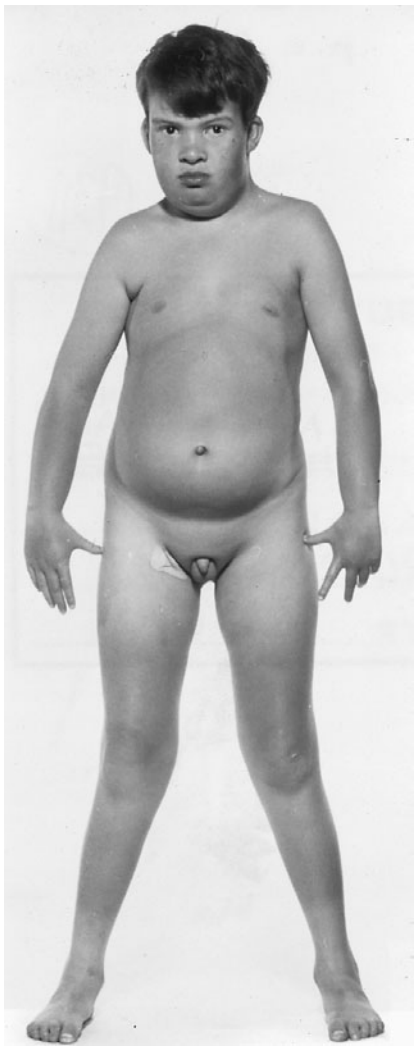
49,XXXXY. Over 100 cases of 49,XXXXY syndrome have been reported (7,31,49). A frequency of 1 in 85,000 births has been noted (36). Postzygotic nondisjunction during both meiosis I and meiosis II appears to cause the XXXXY state, all the X chromosomes being of maternal origin (21,48). Maternal age does not appear to be advanced (12,39). Sarto et al (41) suggested two hypotheses to best explain the abnormal phenotype that accompanies 49,XXXXY karyotype: (1) increased dosage of active genes that escape X inactivation and (2) asynchronous replication of the extra X chromosomes.

Average birth weight is approximately 2500 g. Height is often below the third centile and bone age is delayed in 90%. However, Borghgraef et al (7) reported infants small for their age who had significant catch-up growth, being at the 50th to 75th centiles after age 4 years. Variable mental retardation is found, with IQs ranging from 20 to 70. There is some evidence of decline in intellectual performance with age. Affected individuals may be extremely shy and timid (7,11,32,43). Language development is especially retarded (11,32). Hypotonia, joint laxity, or both are found in approximately 33% (12,39). Hypoplasia of the corpus callosum and growth hormone deficiency have been noted (18).

The phenotype is distinctive (Fig. 3–14). Hypogonadism is severe, with pea-sized testes, micropenis, and pronounced infantilism of secondary sex characteristics. The scrotum is usually hypoplastic (80%) and the testes may be cryptorchid (25%). Histologically, Leydig cells are hypoplastic and germ cells are absent (3,12,38).

Clinical features (Table 3–17) include mild microbrachycephaly, ocular hypertelorism (30%), up-slanting palpebral fissures (70%), epicanthic folds (85%), strabismus (60%), myopia (25%), low broad nasal bridge, sometimes with upturned nasal tip (95%), poorly modeled ears (80%), and short neck, sometimes with webbing (12,20,39).

During infancy, the face is rounded (36). With growth, the midface appears retruded with relative mandibular prognathism (50%).



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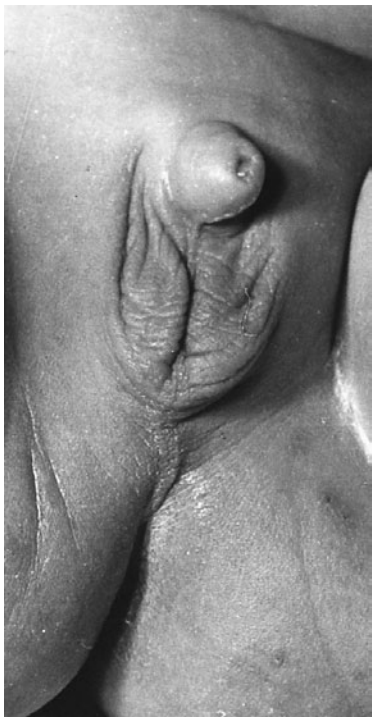

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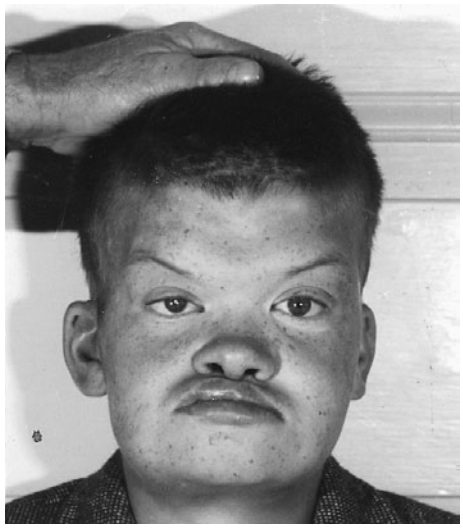

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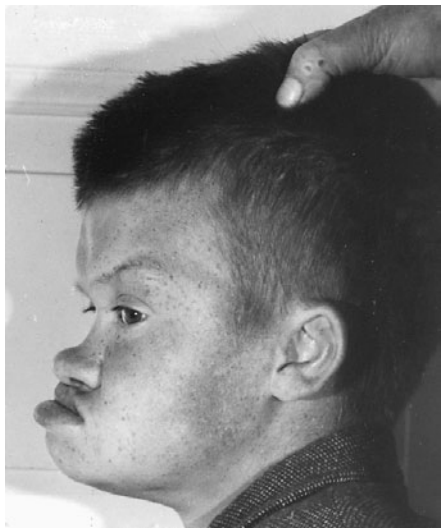

D

Fig. 3–14. *49,XXXXY Klinefelter syndrome.* (A) Up-slanting palpebral fissures, small ears, hypogenitalism, and cubitus valgus. (B) Hypogenitalism. (C,D) Marked mandibular prognathism. (A from MC Joseph et al, J Med Genet 1:95, 1964. B from RA Pfeiffer, Z Kinderheilkd 87:356, 1962. C,D courtesy of H Schade, Münster, Germany.)

Taurodontism is a common finding (29). Cleft palate has been documented (47).

Skeletal anomalies (Table 3–17) occur in over half of the cases and include sclerotic cranial sutures (60%), thick sternum, radioulnar synostosis, cubitus valgus, elongation of distal ulna and proximal radius, wide proximal ulna, pseudoepiphyses of metacarpals and metatarsals, hypoplasia of middle phalanx of fifth digit with clinodactyly (95%), coxa valga (85%), genua valga (15%), and pes planus (55%). Other findings may include malformed cervical vertebrae, narrow chest, thoracic kyphosis, retarded bone age, and scoliosis (11,35,42,44).

Congenital heart defects, particularly patent ductus arteriosus, are present in approximately 20% of cases (11,27). Gynecomastia is not a feature of 49,XXXXY individuals, but the nipples may be widely spaced. Gonadotropins are not elevated (12,39). A low total finger ridge count with an increased number of fingertip arch patterns may be observed (12).

46,XX males. Suggested birth prevalence is 1/25,000 newborn males. Phenotypic features are very similar to those of 47,XXY Klinefelter syndrome, with two major differences. First, mean height attainment (168.2 cm) is below that of 47,XXY subjects (177.4 cm) (15). Second, disproportion between trunk and limbs found in 47,XXY is not found in 46,XX males. About 10%–15% of 46,XX males have some degree of hypospadias (33,34). Other differences are less striking; intelligence is normal (15). Gynecomastia occurs slightly less frequently than in classic Klinefelter syndrome (12). Measurements of permanent tooth size indicate that teeth in 46,XX males are smaller than those of normal males and are similar in size to those of normal females (1).

At present, no single hypothesis explains the 46,XX male condition, which may be etiologically heterogeneous. One possibility is undetected mosaicism involving a Y chromosome–containing cell line, although this has not been shown (33). A second possibility involves translocation of the testis-determining factor (*TDF*) gene from the short arm of the Y chromosome to the X chromosome or to an autosome during paternal meiosis. Most cases are due to Y-X interchange. This hypothesis is supported by observing an increased length in the short arm of one X chromosome in some 46,XX males, although short arm length of X chromosomes is normal in others. Finally, testes and maleness in 46,XX individuals might result from an X-linked *TDF* gene mutation, suggested by the small number of families with more than one 46,XX male (15,33,39).

Differential diagnosis. Differential diagnosis includes eunuchoidism, *homocystinuria*, and *47,XYY* syndrome. Patients with

Table 3–17. Clinical and radiological features of 49,XXXXY syndrome

Feature	Percent
Craniofacial	
Ocular hypertelorism	30
Upslanting palpebral fissures	71
Epicanthic folds	85
Strabismus	57
Broad flat nose	96
Mandibular prognathism	47
Malformed ears	78
Central nervous system	
Mental retardation	100
Cardiac abnormalities	18
Genitalia	
Hypogonadism	91
Small penis	79
Abnormal scrotum	79
Cryptorchidism	24
Limb anomalies	
Limitation of elbow movement	89
Radioulnar synostosis	32
Clinodactyly, fifth finger	93
Coxa valga	84
Genua valga	13
Gap between hallux and second toe	55
Pes planus	54
Other skeletal findings	
Retarded bone age	89
Sclerotic cranial sutures	57
Capitate defect	83
Thoracic kyphosis	53
Scoliosis	35

(Modified from CL Levy et al, J Med Gent 15:301, 1978.)

49,XXXXY syndrome are distinctive clinically, but sometimes their features suggest *trisomy 21 syndrome* in fetuses (38) and newborns, although the overall pattern of anomalies is at variance with the latter.

Clinical clues leading to the detection of classic 47,XXY Klinefelter syndrome during childhood include dull mentality, school or behavioral problems, altered body habitus with relatively long legs and slim build, small testes, and inadequately developed phallus (9).

Laboratory aids. Banded chromosome study is essential when a clinical diagnosis of Klinefelter syndrome is suspected. Fifty cells should be counted to rule out mosaicism.

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47,XYY males and other poly-Y conditions

The 47,XYY chromosomal constitution was first observed by Sandberg et al (27) in 1961; the subject was a man of normal intelligence who had, with two different women, numerous progeny, including an amenorrheic female, twins (one with trisomy 21, the other a "blue baby"), and two spontaneous abortions (13). The 47,XYY karyotype aroused considerable public attention because of the many reports of criminal behavior, most of which had a known ascertainment bias favoring behavioral disability (3,5,8,14,16,21). Birth prevalence is approximately 1/1000 male births (26,29). Sumner et al (32), using a fluorescent technique, showed that over 1% of sperm from normal males contained two Y chromosomes, implying marked selection against such sperm.

Growth. Tall stature in adult life is characteristic. Mean final height attainment varies from 180 to 186 cm (26). Leg length and trunk length are increased, but the leg/trunk ratio is normal (17). Birth weight and length are normal (26). In a study of 43 affected boys (26), overall distribution of growth centiles was not significantly different from normal, although one subset from Edinburgh (25) suggested a growth spurt between ages 2 and 6 years in approximately one-third of the cases. By 5 years, all boys were above the 50th centile for height and approximately 38% were above the 90th centile.

Central nervous system and performance. Approximately one-third of affected individuals have delayed speech or language development and there is some evidence of fine motor problems (26). Muscle weakness and poor coordination are commonly noted (9). In a study of 43 affected subjects (26), IQ scores ranged from 78 to 145. Approximately 38% showed IQs from 70 to 89. Thus, average IQ is lower than in normal males and verbal IQs tend to be more affected than performance IQs.

Males with 47,XYY chromosomal constitution probably blend into the general population as normal individuals. The most frequently observed stigmatizing features are excessive height for age, excessively impulsive behavior, and excessive temper tantrums in childhood. Stigmatization does not correlate with socioeconomic class (21). Psychological studies have shown that infantilism, lack of emotional control, increased impulsiveness after emotional stimulation, and weak sense of self are so characteristic of 47,XYY men that they can be recognized by psychological tests alone.

Even correcting for earlier biased ascertainment from mental institutions and prisons, it is now well established that among 47,XYY males, an excess degree of criminal behavior exists compared to 46,XY males. For example, Daly and Harley (8) karyotyped 3011 males from five Wisconsin state correctional institutions and found a 47,XYY frequency of 1%, which is five times greater than the newborn prevalence for 47,XYY males. Crimes are similar to those committed by 46,XY men. The preponderance of serious aggressive behavior against people has not been substantiated. Rather, theft, arson, and burglary are the crimes most often cited. The cause of antisocial behavior leading to conflict with the law is not entirely resolved and still much debated. None of the suggested causes, which include impaired intellectual function, abnormal electroencephalographic findings in a few instances, low socioeconomic status, or very tall stature, either separately or together, explains the increased risk of antisocial behavior (26).

Gonadal status and fertility. Gonadal development, testicular size, and testicular histology are normal (7,11,26). Many 47,XYY males have fathered offspring who are chromosomally normal. Pregnancies resulting from XYY individuals have ended in miscarriage or perinatal deaths, or have produced offspring with various chromosomal abnormalities (12). In rare instances, subjects have procreated 47,XYY sons (33). In a few instances, however, small testes, decreased spermatogenesis, subfertility, and sterility have been noted. Cryptorchidism, micropenis, or hypospadias are rarely observed (11).

Congenital malformations. In a study of 43 affected infants, Robinson and de la Chapelle (26) found the overwhelming majority to be completely normal in appearance. Major malformations were not increased, although approximately 20% had minor anomalies. Although no clear pattern of minor anomalies emerged, clinodactyly with single fifth finger crease, inguinal hernia, and abnormal ears were observed in two instances each. Other minor anomalies and subtle phenotypic alterations have been noted, including mild facial asymmetry, mild pectus carinatum or excavatum, mild winging of the scapula, glabellar mounding, long ears, highly arched palate, and bony chin point (4,9,26). A number of major abnormalities have also been noted, including urinary tract malformations (20) and radioulnar synostosis (6).

Dermatologic findings. Nodulocystic acne involving the face, chest, and back has been reported in association with 47,XYY subjects (36).

Dentition. Careful measurement of teeth has indicated that tooth size in 47,XYY males is larger than normal in both the deciduous and permanent dentitions (1,2). In a study of shovel-shaped maxillary incisors, affected central incisors were similar to those of normal controls, but lateral incisors were more shoveled and showed deeper lingual fossae in 47,XYY subjects than in control subjects (18).

Differential diagnosis. Differential diagnosis includes *Klinefelter syndrome* and *Marfan syndrome*. Males with 48,XXYY karyotype have features that combine Klinefelter syndrome with above-normal stature and frequent mental deficiency. Several poly-Y karyotypes have been reported, including 48,XYY (15,28,34) and 49,XYYYY (23,24,29–31,35). Townes et al (34) described a 48,XYYY patient with mild mental deficiency, inguinal hernia, cryptorchidism, valvular pulmonic stenosis, and single palmar creases. Das et al (10) reported a 49,XXYYY male with mild microcephaly, limited supination of elbows, delayed bone age, and mild mental retardation. Schoepflin and Centerwall (28) described a 48,XYY patient with mental retardation, impulsive aggressive behavior, single palmar creases, clinodactyly, delayed bone age, pseudoepiphyses at the bases of the metacarpals and metatarsals, and lack of patellar epiphyseal calcification. Hunter and Quaife (15) noted a 48,XYYY individual with no stigmata other than sterility. Sirota et al (30,31) reported a 49,XYYYY patient with trigonocephaly, up-slanting palpebral fissures, epicanthic folds, highly arched palate, micrognathia, low-set ears, limitation of motion at the elbows and knees, and an IQ of 50. Mosaic 45,X/49,XYYYY was documented by van den Berghe et al (35). Findings included mental retardation, facial asymmetry, cataracts, and clinodactyly.

Laboratory findings. Karyotypic findings are usually unrelated to the reason for testing. Whether discovery occurs prenatally, during childhood, or later, it is a formidable challenge to counselors and patients alike. The ethical controversies of XYY screening are discussed elsewhere (19).

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47,XXX, 48,XXXX and 49,XXXXX syndromes

47,XXX. No specific phenotype is characteristic and no increase in major malformations has been observed. This syndrome has been found in about 1 in 1200 female newborns. The condition arises from maternal nondysjunction in meiosis I. The mothers of the probands tend to be older. In a study of 43 females with 47,XXX (15), the overwhelming majority of infants appeared normal at birth and no unusual karyotype would be suspected. Minor anomalies have been noted in some instances, and an increased frequency of epicanthic folds, minor ear anomalies, and clinodactyly was reported by Robinson and de la Chapelle (15). Judisch and Patil (10) described a case with bilateral retinoblastoma and pinealoma.

In general, birth weights tend to be low but within normal limits. Height percentiles increase with age (15,17), most being above the 50th percentile by age 6 years. The greater height affects the legs rather than the trunk. In contrast, head circumference tends to be between the 25th and 35th centiles. Frank microcephaly has been noted in an occasional instance (15).

Delay in both receptive and expressive language is common (7,9,11,15). Full-scale IQs tend to be significantly lower than normal (15). Fryns et al (4) found mental deficiency as the presenting symptom in over 25% of cases, but noted that his sample was biased. Deficit in gross motor skills and poor coordination have been reported (7). Also encountered have been emotional immaturity, social problems, passivity, learning disorders, and psychosis (4,7,9,11).

As a rule, sexual development is normal. However, there may be late-onset menarche, oligomenorrhea, or early-onset menopause. Fertility may range from normal to complete infertility with streak gonads (4). Some triple-X patients suffer from recurrent urinary tract infections (5). Most of their children have been chromosomally normal.

48,XXXX. More than 40 cases have been recorded to date (6,15,18). No specific phenotype is associated with tetra-X females, although mental deficiency appears to be an essentially constant feature, IQs averaging 55 with a range of 30–75. Speech and behavioral problems are frequently encountered. No increased frequency in congenital heart defects has been observed. Facial anomalies have included midface hypoplasia, mild hypertelorism, epicanthic folds, and mild micrognathia (6,18). On occasion, the face has been suggestive of trisomy 21 syndrome. A patient reported by Fryns et al (4) had features of Turner syndrome, although final height attainment was normal. Occasionally, clinodactyly of the fifth finger and radioulnar synostosis have been observed. The shoulder girdle may be narrow. Development of secondary sexual characteristics is incomplete with small breasts, scanty axillary and pubic hair, and frequently hypoplastic external genitalia. Menarche may occur spontaneously, but disturbances in the menstrual cycle have been noted in about 50% of cases. Ovarian tissue may be normal in some instances, although bilateral gonadal agenesis has also been reported (5).

49,XXXXX. Approximately 30 cases (at least 3 mosaic) of the penta-X syndrome have been described to date (1–5,12–14,16,19,20). Some patients are initially thought to have Down syndrome. Several reviews of clinical findings are available (5,19). Features of the penta-X syndrome appear in Table 3–18.

Growth deficiency of prenatal onset with failure to thrive and short stature are common (5). Delayed bone age has been reported. The head circumference is small in about 55% of cases, and moderate to severe mental or psychomotor retardation occurs in approximately 80% (5,13). Hypotonia has been reported (4,14).

The craniofacial appearance can be striking, with up-slanting palpebral fissures, flat nasal bridge, abnormal ears, and short neck (5). The hairline may be low. Ocular findings have included hypertelorism, epicanthic folds, ptosis of eyelids, and iris coloboma (4,5,13,16). Small ears and ear tags have been mentioned (5,13), as has hearing loss (13). Other features have occasionally been noted: everted, furrowed, or thick lips, cleft palate, and micrognathia. Dental abnormalities include malocclusion, hypodontia, and taurodontism (1,5,20).

The phenotypic appearance may be striking, with narrow shoulders and genua valga (Fig. 3–15) (1,2,16). Radioulnar synostosis occurs in about 45% of cases with joint hyperflexion or dislocations in approximately 35%. The patient reported by Dryer et al (3) had multiple dislocations suggestive of Larsen syndrome. Camptodactyly and/or clinodactyly are common, occurring in about 75%. Other reported findings have included micromelia, low total finger ridge count, clubfoot, metatarsus varus, and malposed toes (4,5).

Congenital heart defects occur in about 40% of patients, with PDA and VSD being particularly common (13,20). Small uterus and ovarian agenesis have been recorded in some cases. Delayed puberty has been noted (5,13,19). The kidneys are hypoplastic in some instances (5,19). In one

Table 3–18. Features of the penta-X syndrome

Feature	Percent ($n = 20$)[a]
Growth	
Low birth weight	55
Failure to thrive	35
Short stature	65
Delayed bone age	30
Small head circumference	55
Performance	
Mental or psychomotor retardation	80
Craniofacial	
Up-slanting palpebral fissures	60
Flat nasal bridge	55
Ears abnormal in position or structure	65
Lips everted and furrowed/thick	15
Dental abnormalities	50
Cleft palate	10
Micrognathia	25
Short neck	45
Low hairline	20
Limbs	
Radioulnar synostosis/abnormal elbows	45
Joint hyperflexion or dislocations	35
Micromelia	30
Camptodactyly/clinodactyly	75
Finger dermal ridge hypoplasia	40
Genua valga	20
Talipes	25
Metatarsus varus	5
Cardiac	
Congenital heart defect	40
Genitourinary	
Small uterus/abnormal ovaries	25
Renal hypoplasia	10

[a]Features considered present only when specifically mentioned by authors.
(Adapted from SJ Funderburk et al, Am J Med Genet 8:27, 1981.)

patient, pyelonephritis and renal failure were described (5). Moedjono et al (12) reported ketotic hypoglycemia.

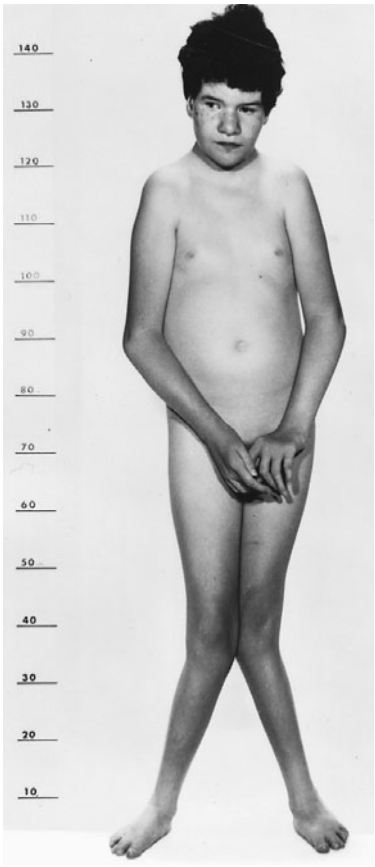

Fig. 3–15. *49,XXXXX syndrome.* Narrow shoulders and genua valga.

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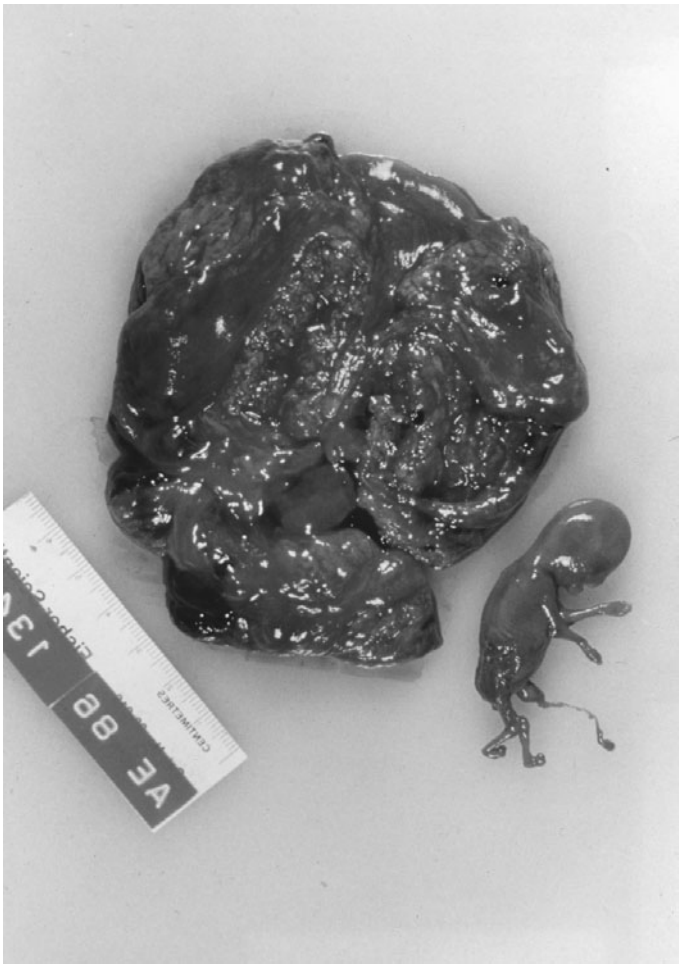
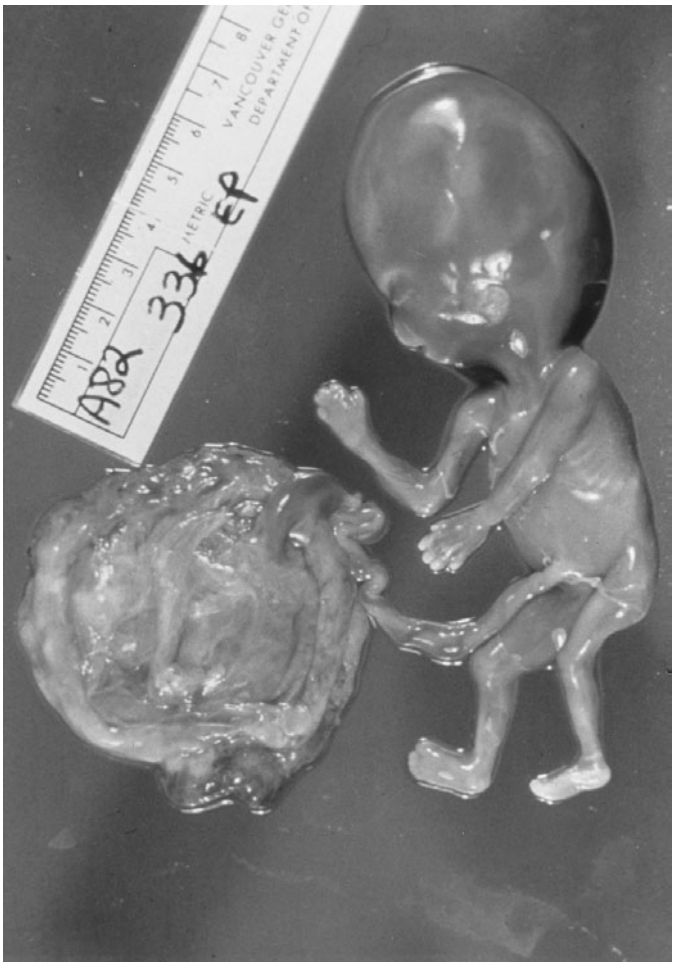
Triploidy syndrome

Triploidy is a frequent cause of fetal wastage (20%) prior to and during the second trimester of intrauterine development (2,3). It should be suspected when ultrasound shows fetal malformations, specifically intrauterine growth retardation, and/or cystic placental changes. Most newborns with triploidy die within the first few days of life, but some survive into early infancy (4,24,27). About 60% are 69,XXY with the rest mostly 69,XXX. 69,XYY conceptions are rare, as they abort early and grow in culture poorly. A digynic infant with triploidy has survived for 46 days (15).

Over 50 well-documented cases of newborns with true triploidy and 20 cases of diploid/triploid mosaicism have been reported. In general,



A



B

Fig. 3–16. *Triploidy phenotypes.* (A) Diandric fetus (type 1) with normal head and large cystic placenta. (B) Digynic fetus (type 2) with disproportionately large head and small placenta. (From DE McFadden and DK Kalousek, Am J Med Genet 38:535, 1991.)

the latter condition is less severe, more compatible with life, and harder to diagnose clinically, as peripheral lymphocyte cultures show a normal karyotype only (3). Fibroblast culture may be required to show the cell line with triploid complement.

The triploid fetus may show paternal genome dominance, being derived either from dispermy or from faulty meiotic division in the male. Errors in maternal meiosis produce triploid with maternal genome dominance or mitotic errors in female germ cell precursors (8,10,23,26,29,30). There has been recurrence in the same family (24a).

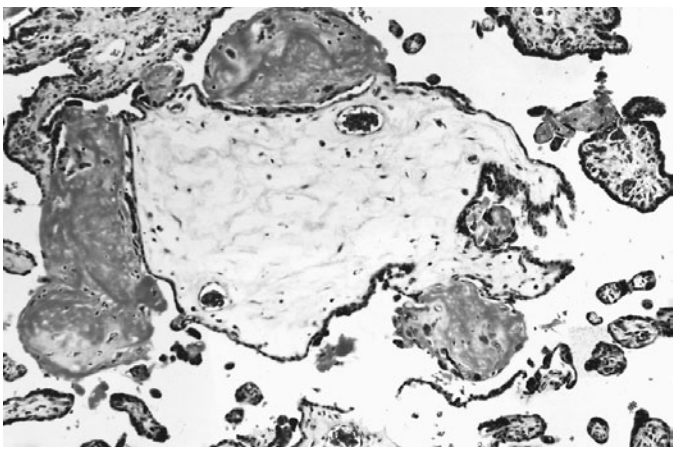
McFadden and Kalousek (17) showed two phenotypes of triploid fetuses: type 1 (diandric), in which the head is normal or somewhat small while the placenta is large and cystic (Fig. 3–16A) and type 2 (digynic), in which there is marked intrauterine growth retardation, the head is disproportionately large, and the placenta is small but noncystic, (Fig. 3–16B). The two different types are due to genomic imprinting (18) and reflect paternal or maternal genomic dominance. Microscopically, type 1 chorionic villi are hydropic and cystic (partial hydatidiform moles) (Fig. 3–17) whereas type 2 chorionic villi have fibrosis of the stromal core without trophoblastic hyperplasia. Zaragoza et al (31) found diandry to be predominant.

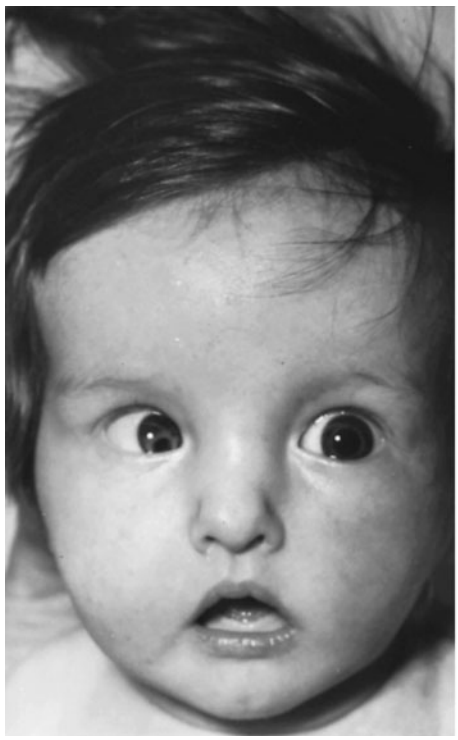
Miny et al (21) showed that maternal origin of the triploidy was often found in those fetuses that survived until late pregnancy.

Vertebral fusions were found in 6 of 15 triploid fetuses by Kjaer et al (15a). No correlation with genotype was found.

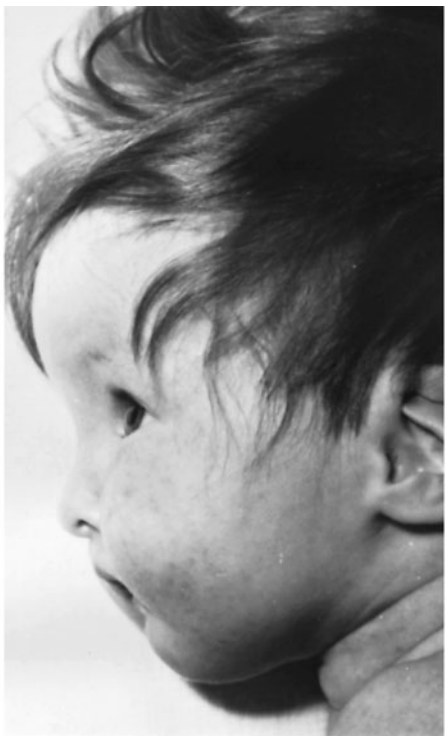
In true triploidy, polyhydramnios is common. Mosaic triploid pregnancy complications are unusual. About 70% exhibit birth weight below 1900 g. Pronounced asymmetry has been observed in about 50% with either pure or mosaic triploidy. This may lead to the misdiagnosis of *Silver-Russell syndrome* (19). The degree of asymmetry does not reflect the degree of mosaicism. Hypotonia has been documented in about 60%. Syndactyly of the third and fourth fingers (Fig. 3–18C) and variable syndactyly of toes, transverse palmar creases, and clubfoot have been noted in at least 60% of both true and mosaic triploids (3).

Fig. 3–17. *Triploidy syndrome.* Note both normal and hydropic and cystic villi. (Courtesy of S Walker, Liverpool, England.)





A



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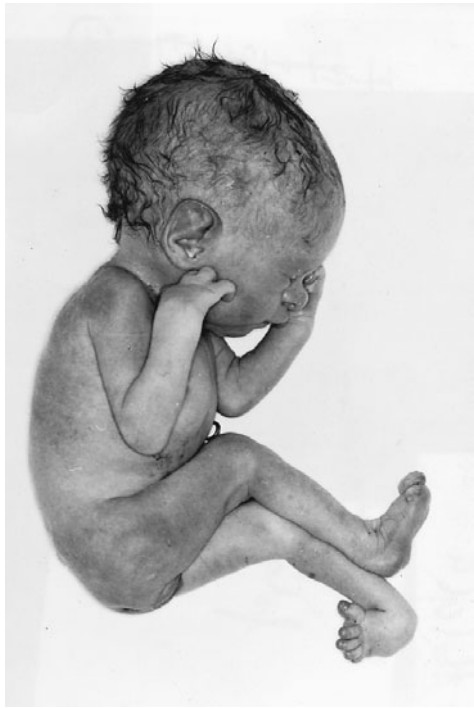

D

Fig. 3–18. *Triploidy syndrome.* (A,B) Frontal bossing, coloboma of iris, strabismus, and malformed ear. (C) Soft tissue syndactyly of third and fourth fingers. (D) Note talipes. (A–C from W Schmid and D Vischer, Cytogenetics 6:145, 1967. D courtesy of E Niebuhr, Copenhagen, Denmark.)

Camptodactyly of the fifth finger and an increased number of digital whorls have been reported (11,14). Mental deficiency has been noted in most true examples. Hydrocephalus (20%), absent corpus callosum (15%), dilated ventricles (35%), large posterior fontanel (90%), Dandy–Walker malformation, lumbosacral meningomyelocele (20%), and, frequently, Arnold–Chiari malformation and hydranencephaly have been reported. Holoprosencephaly has been noted (9). Microphthalmia, iris and choroid colobomas, and epicanthal folds are each seen in 25% of true triploidy (3). The ears are dysplastic and/or low set in 35%–50% (Fig. 3–18). Micrognathia is common. Isolated cleft palate (1,7,9) or cleft lip with or without cleft palate has been noted (1,27,29) in about 35%. Oral asymmetry, macroglossia, and smaller teeth on one side have been described (6,12,22,30).

The male genitalia in those with true 69,XXY are often abnormal (25). Hypospadias (40%), cryptorchidism (85%), micropenis (75%), and ambiguous genitalia (40%) are common. Scrotal abnormalities (60%) include bifidity and scrotal hypoplasia or agenesis. Leydig cell hyperplasia has been documented in 20% (3,13). Females (69,XXX) usually manifest gonadal dysgenesis. Kidney anomalies (cystic dysplasia, glomerulosclerosis, hydronephrosis), adrenal hypoplasia, and congenital heart defects, particularly ventricular septal defect, patent ductus arteriosus, and atrial septal defect, occur in 50% of those with complete triploidy but do not occur in the mosaic form (1,3,5,7). In true triploidy, abdominal wall defects such as omphalocele, gastroschisis, umbilical hernia, and diastasis recti are seen in 50% (3). Agenesis of the gallbladder has been reported.

Radiographic changes include harlequin orbits, small anterior fontanel, gracile ribs, upswept clavicles, diaphyseal overtubulation of long bones, vertical ilia, and proximal radioulnar synostosis (28). The posterior fontanel is always large at birth. Asymmetry of the occipitoparietal calvaria occurs in 50%.

Large placentas with molar changes (diandry) have generally been associated with increased maternal serum AFP (MSAFP) and high hCG levels; and those with digyry and small monocystic placentas have normal MSAFP and low hCG.

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Fragile X syndrome (Martin-Bell syndrome, macro-orchidism-marker X syndrome)

X-linked mental retardation (XLMR) is close in frequency to that of Down syndrome and fetal alcohol syndrome. More than 125 XLMR syndromes have been identified (50,55), of which fragile X (FraX) is the most common, accounting for approximately 50% of cases. Fragile X, the most common inherited form of mental retardation, is the only XLMR syndrome we shall consider here for extensive discussion. Several historical reviews of FraX have been published, including those of Schinzel and Largo (64), Goldson and Hagerman (22), de Vries et al (12), Stevenson et al (74), and Laxova (43).

The frequency of FraX has been estimated at approximately 1/4000 males and 1/8000 females (54,83,89). Its prevalence among mentally retarded males has been estimated to be about 2%–6% (3).

The term "fragile X" refers to its cytogenetic manifestation: a gap or break disrupting the long arm of the involved X chromosome. This abnormality was first described by Lubs (49) in 1969, and a scanning electron microscopy (EM) study has been carried out (29). Disruption of the long arm occurs at a specific site referred to as a fragile site. For the fragile X syndrome described here, it occurs within band Xq27.3, designated FRAXA. Several other fragile sites on the distal long arm of X have been described, only one of which, FRAXE at Xq28, appears to be associated with phenotypic consequences as well (16).

FRAXA differs from other chromosome abnormalities in that (*a*) the abnormality is only detectable if cells are cultured under specific conditions of folate stress; and (*b*) the abnormality is only seen in a proportion of cells from an affected individual (generally 10%–60% for lymphocytes of an affected male and 5%–30% for an affected female) (75).

The gene *FMR1*, responsible for FraX, has been sequenced, and its gene product, the FMR protein (FMRP) has been characterized; for review, see Fang et al (14) and Kaufmann and Reiss (38). Affected status appears to be caused by silencing of *FMR1*, resulting in absence of FMRP. Monozygotic female twins exhibited postzygotic X inactivation in one but not the other (90a).

In most cases of FraX, transcriptional silencing of *FMR1* is related to the presence of a greatly expanded and methylated CGG trinucleotide sequence (Fig. 3–19). Silencing has also recently been associated with histone diacetylation (10) (complete silencing and affected status have, in a few exceptional cases, been caused by single base pair mutations within *FMR1* or deletions). The CGG repeat is located in the 5′ untranslated region of the gene. The CGG repeat tract can be interrupted by one or more AGG triplets (40). Normal values of CGG repeats generally range from 6 to 60, and are transmitted without change from one generation to the next. *FMR1* alleles with 60–200 repeats comprise the so-called premutation range, and alleles with greater than 200 repeats designate full mutations (40). It is the full mutation that is typically associated with cytogenetic and phenotypic expression of the fragile X syndrome. In contrast, individuals carrying premutation alleles are not expected to be affected (18,31,72,84) and do not manifest the cytogenetic abnormality. However, such premutation alleles, when transmitted by a female, are unstable from one generation to the next—that is, the trinucleotide repeat tract can expand from premutation to full mutation size when passed from a mother to a child. Premutations are more stable in male carriers, who from pedigree analyses have been called "transmitting males." Daughters of transmitting males inherit such premutation alleles with little or no change in repeat number. However, during transmission from these daughters to their offspring, the premutations can expand to full mutations. Thus, daughters of transmitting males do not manifest FraX, whereas the grandchildren of transmitting males are frequently affected. Selective expansion of the CGG repeats associated with female meiosis explains the so-called Sherman paradox of very low penetrance (<20%) in brothers of nontransmitting males and high penetrance (>80%) in brothers of affected males (21). The instability and expansion of the triplet repeats also explains the basis for the observed genetic anticipation of FraX, that is, an increase in disease severity through successive generations (15,30,39,76,79,86).

Fragile X syndrome has variable expression in the hemizygote male and especially in the female heterozygote (46), about 35% of whom have cognitive impairment (26). In females, affected status appears to be related to the pattern of X-chromosome inactivation, and, as in males, to the ultimate level of FMRP expression.

Birth weight may be elevated (3). Adult height is somewhat decreased (47,48). Head circumference is relatively increased (42a), and there is dolichocephaly (6). Hand and foot lengths are slightly reduced (53). In the postpubertal male, only about 60% exhibit the triad of typical facies, mental retardation, and macro-orchidism (8,18). Occasionally, hemizygotes appear entirely normal (84).

Facies. A long narrow face is present in roughly 70% of postpubertal hemizygotes. The forehead is high, large, and quadrangular with prominent supraorbital ridges. There may be puffiness around the eyes.

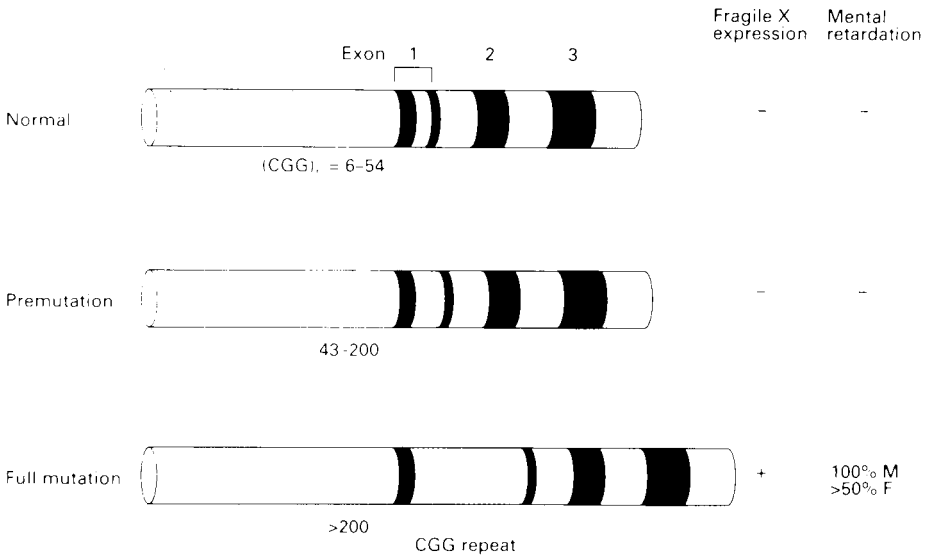
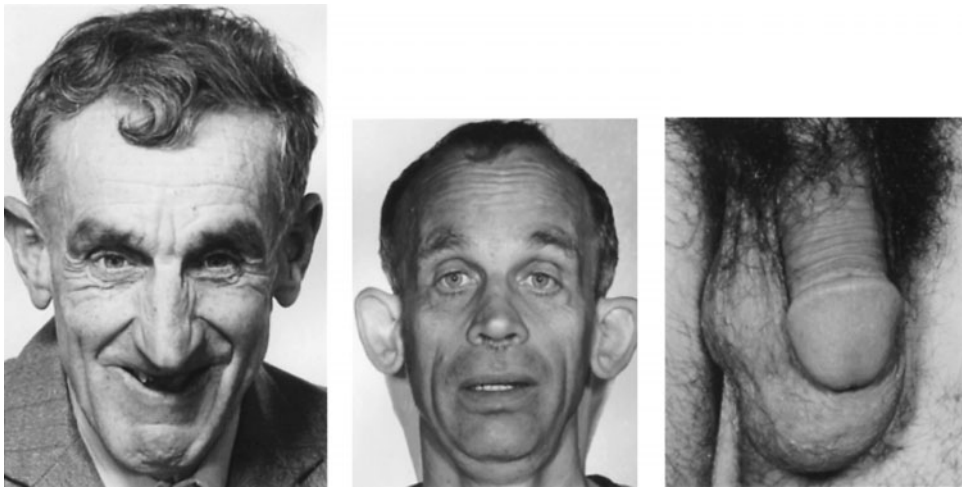
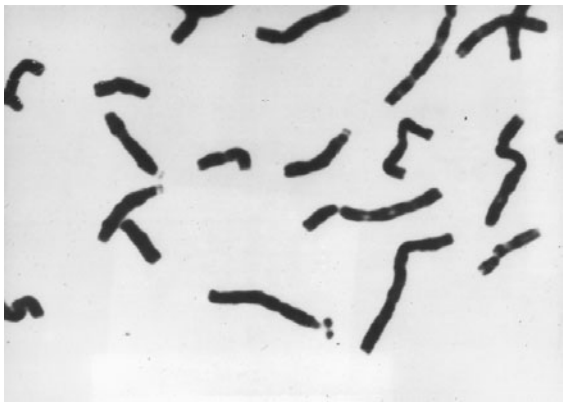


Fig. 3–19. *Fragile X syndrome.* Part of *FMR1* gene and its CGG related mutations in the first exon of the *FMR1* gene that contains the CGG repeat (gray). (From BBA de Vries et al, J Med Genet 35:579, 1998.)



A **B** **C**



D

Fig. 3–20. *Fragile X syndrome.* (A) Long, narrow face with large, quadrangular forehead, somewhat underdeveloped midface, broad-based nose, prominent chin, and prominent ears. (B) Compare facies to patient in A. (C) Macro-orchidism. (D) G–non-banded fragile X site. (A from A McDermott et al, J Med Genet 20:169, 1983.)

Palpebral length is increased and inter–inner canthal distance is decreased. Strabismus is noted in 10% and refractive errors in 25% of patients. The cheeks feel somewhat thickened (56). The chin becomes long and prominent during adolescence and there is some degree of midface retraction (77). The nose is usually broad based. The pinnae are very large (7 cm) in 70% of cases, and are somewhat soft, and outstanding or cupped with simple helices and absent lobes (5,25) (Fig. 3–20A,B). Otitis media occurs in 85%. Hull and Hagerman (34) have suggested that females with the premutation have outstanding ears. The palate is highly arched in 50% (3,18,53,80). Perhaps 25%–40% of carrier females, especially the more retarded ones, have the typical facies (long face, prognathism, large everted pinnae), are shy, and have poor eye contact (19,25,42a,45,81,87). In the newborn, relative macrocephaly and large fontanel may be noted, but not the long face. Ear infections are frequent (42a).

Central nervous system. Cognitive variability has been discussed by Theobald et al (78), Chudley and Hagerman (8), and Schapiro et al (62). Mental retardation in the hemizygote is moderately severe with IQs ranging from 20 to 69 (9,20). However, in over 75% of affected individuals, IQs are less than 39. Females with the full mutation have IQs of 50–107 (mean 81). Retardation seems to increase with age (91). Speech delay is constant. Those with a higher IQ exhibit cluttered speech (dysfluencies, stuttering). Often there is characteristic rhythmic intonation (litany speech). Those with low IQs are less verbal with short bursts of repetitive phrases. Patients exhibit delayed milestones (sitting, 10 months; walking, 21 months; speaking, 20 months), clumsiness, hyperactivity, mild hypotonia, increased deep tendon reflexes, emotional instability, and automutilation (especially handbiting). Approximately 25% exhibit autism (avoidance of eye contact, hand flapping or other stereotypic movements, perseverative speech, echolalia) (3,18,70,85). Hand biting is common. About 50% of patients manifest aggression. Seizures, noted in 20%, occur principally in those with the lowest intelligence. However, at least 50% of the adult males have abnormal EEG recordings. About 50%–75% of females who carry the full mutation have borderline to subnormal intelligence (IQs less than 85) (19,33,45,68) and another 15% have learning disability, especially in mathematics and reading. There is often a decrease in intelligence with age (33). Intelligence in female carriers appears to be inversely correlated with the expression of the fragile site. Higher functioning males have an incompletely methylated full mutation (27). Some female heterozygotes are psychotic (19). There is an overall enlarged brain with particular enlargement of hippocampus, caudate thalami, and ventricles with reduced size of vermis (58,66).

Connective tissues. Joint laxity, especially of the thumbs, metacarpals, fingers, knees, and ankles, is seen in 75% of children with FraX. The feet are flat in 70%. The skin feels velvety soft over the dorsum of the hand. It is somewhat lax, but hand calluses are seen in 30%. Single palmar creases are noted in 25%. Cutis verticis gyrata has been described (63). Mitral valve prolapse has been found in 80% of hemizygotes over 18 years, with mild aortic dilatation in about 15% (24,44). Younger children do not often have mitral prolapse (11).

Genitourinary. Macro-orchidism (Fig. 3–20C), unilateral or bilateral, first noted after 8 years and in only 40% prior to puberty, is found in about 75% of adult hemizygotes (8,41). The testes tend to be softer than normal. There is increased tubular length and interstitial edema (12,13). Hyperpigmentation of the scrotum and enlargement of the penis have been noted in over 50%. Carrier females exhibit high fertility, a higher frequency of twinning (19), premature ovarian failure, and an increased rate of miscarriages (33,45,65,67a). Premature ovarian failure is possibly due to paternal genomic imprinting (34a), but this was not confirmed by a subsequent study (85a).

Oral findings. The palate is high and narrow. Robin sequence has been reported (42). Crossbite and openbite are relatively common (67). Tooth crown diameter asymmetry is frequent (57). The lateral palatine ridges are prominent in 60% of patients (53).

Differential diagnosis. In the absence of a family history, one must exclude other forms of nonspecific mental retardation, especially Renpenning syndrome, which is characterized by relatively severe mental retardation without other central nervous system involvement, small head circumference, short stature, normal facies, normal ears, and normal or small testes. It should be emphasized, however, that fragile X syndrome, because of its variable expression, may be difficult to diagnose, especially before puberty. Several patients were initially thought to have *Sotos syndrome* or *Prader-Willi syndrome* (8,12,13). About 7%–15% of autistic males are positive for the fragile X chromosome (8). It should be emphasized that macro-orchidism is not an invariable finding in the fragile X syndrome. Conversely, one may find macro-orchidism in otherwise normal males.

There are an increasing number of X-linked mental retardation syndromes described that are beyond our attempt at coverage. Several are mentioned here because of orofacial involvement: Allan-Herndon syndrome [severe mental retardation, dysarthria, ataxia, athetoid movements, muscle hypoplasia ("limberneck") (73) , and spastic paraplegia with hyperreflexia], which maps to Xp21; macrocephaly with heterozygous expression (1,2,82); mental retardation, congenital heart anomalies, cleft palate, short stature, and unusual facies (28); microcephaly, growth delay, and hereditary bullous dystrophy, which maps to Xq24 (52); mental retardation and pseudoglioma (17); cleft lip/palate, broad nasal tip, and large hands mapping to Xp11.3–q21.3 (69); macrocephaly, macroorchidism, midface hypoplasia, triangular facies mapping to Xq12–q21 (37); hypertelorism, short nose, seizures, hearing loss, cardiomegaly, and early demise (at Xq28) (51); short stature, small hands and feet, seizures, cleft palate, and glaucoma mapping to Xq28 (65); unusual facies, hypogenitalism, congenital hypotonia, and pachygyria (93); unusual facies (35); unusual facies, epilepsy, ophthalmoplegia, and cerebellar atrophy, which maps to Xq24–q27 (7); and marfanoid habitus which maps to Xq22–q25 (19a,51a,57a). These and an inordinate number of other ones have been summarized in 1998 (50) and in 2000 (28a).

Laboratory tests. Although historically, cytogenetic assays were employed for detection of a fragile X chromosome and can still provide a reliable means of identifying affected males and females, molecular genetic assays now provide the methods of choice for diagnosis (36). The molecular methods are less labor intensive and, importantly, are the only means by which the premutation alleles can be identified and differentiated from normal alleles. Thus, the molecular methods can provide for identification not only of affected males but also of carrier females and transmitting males.

The molecular methods most commonly employed in laboratories include both PCR to amplify the CGG trinucleotide repeat segment within *FMR1*, and the Southern blot analysis, involving restriction enzyme digests and hybridization with a labeled nucleic acid probe complementary to the CGG repeat segment. The PCR methods provide the means for determining the number of repeats within premutation and normal *FMR1* alleles, while Southern blot analysis provides for the detection and characterization of the full mutations. (Classic PCR methods are generally unable to amplify reliably the very large repeats found within most full mutations.) A rapid antibody test for detection of the FMR1 protein has also been developed (90).

Although molecular methods are preferred for determining a diagnosis of FraX, cytogenetic analysis can provide a complementary test for ruling out the presence of other types of chromosome abnormalities that can be associated with similar developmental delays and mental retardation. As noted previously, differential diagnosis of FraX can be difficult, and most laboratories that perform parallel cytogenetic and molecular testing have found several-fold higher frequency of the "other" chromosomal abnormalities than FraX among their referrals (with the exception of those patients with a confirmed positive family history for fragile X) (59,61). Included among these other abnormalities are *47,XXY,* deletions of 17p11.2 (*Smith-Magenis syndrome*), deletions of 22q11.2 (*velocardiofacial syndrome*), various de novo balanced translocation, and others.

Testicular volume is usually measured by orchiometer and can be calculated by the formula $\pi/6 \times \text{length} \times \text{width}^2$. Testicular volume in the postpubescent male is significantly increased (25–127 ml) over

normal values (15–25 ml) (92). Prenatal diagnosis has been carried out on amniocytes, using molecular methods (23,32). Chorionic villus sampling, induction with at least two cytogenetic methods, and restriction fragment length polymorphism (RFLP) analysis have been advocated (66,88). Dermatoglyphic features of the hemizygote include increased radial loops, whorls, and arches on fingertips (especially the second and third fingers), abnormal palmar and plantar creases, absence of c-triradii on palms, dysplasia of papillary ridges, and low frequency of true patterns on soles. Female heterozygotes show some of the same changes (60,71). A metacarpal phalangeal index has been established for the syndrome (4).

Screening can be done by hair root analysis (79a).

References [Fragile X syndrome (Martin-Bell syndrome, macro-orchidism-marker X syndrome)]

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Chapter 4
Chromosomal Syndromes: Unusual Variants

It is impossible to provide a totally comprehensive review of the unusual variants of chromosomal syndromes, as some variations are extremely complicated, involving complex translocations; others represent single reports. Our goal here is to summarize what is known about these variants, especially where generalizations can be made on the basis upon several cases of the apparently same deletions or duplications. If sufficient numbers of examples have been reported, we have attempted to present the approximate frequency of a finding.

del(1p) syndrome

Deletion of the terminal short arm of chromosome 1 (1p36.22–pter) is relatively common (1–10), although a few examples of ring 1 have been reported [see del(1q) syndrome]. It has been estimated that the frequency of this syndrome is at least 1 in 10,000 live births (7). Others have found it to be as common as 1 in 500 (2a). Only the rare interstitial deletion has been noted (4); about 20 examples of deletion have been documented. The deletions are de novo, with most of them being maternally derived (11). Interstitial deletions have been reviewed by Stockton et al (9).

Terminal 1p deletions result in mental and somatic retardation (90%), hypotonia (90%), seizures (75%), microcephaly (40%), large anterior fontanel (100%), low-set dysmorphic pinnae with thickened helices (50%), flat nose (35%), depressed nasal bridge (65%), deep-set eyes with small, almond-shaped palpebral fissures (50%), relative prognathism (45%), cleft lip/palate (10%), congenital heart defects (20%), clinodactyly of fifth fingers (65%), small hands and feet (20%), cardiomyopathy (40%), and cryptorchidism (30%) (8) (Fig. 4–1).

There may be some correlation between phenotype and size of deletion (11).

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dup(1p) syndrome

The rarest of structural abnormalities involving chromosome 1, dup(1p) has been reported barely more than a dozen times.

In addition to growth and psychomotor retardation, most affected individuals had microcephaly, craniosynostosis, depressed nasal bridge, malformed pinnae, hypertelorism, cleft palate, brachydactyly, and cryptorchidism. Less constant features have included prominent pinnae, micrognathia, and clinodactyly of fifth fingers (1–9).

Some individuals with dup(1p) have shown facial resemblance to *Kabuki syndrome* (6).

References [dup(1p) syndrome]

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del(1q) syndrome

About 70 reports of patients with variable deletion of the long arm of chromosome 1 have been published. We have grouped these deletions into three categories: interstitial proximal (1q21–q24), interstitial intermediate (1q24–q32), and distal (1q42–qter). Most cases have been de novo. Rarely have ring chromosomes been reported (9,23).

Proximal interstitial deletion. Patients with proximal interstitial deletion (1q21–q24) have growth and psychomotor retardation, microbrachycephaly, sparse fine hair, up-slanting palpebral fissures, unusual pinnae, cleft lip/palate, small hands and/or feet, hernia, transverse palmar crease, clinodactyly of V, convex dysplastic nails, short neck, and hypotonia (2–4,10–12,21,22,24). External genital anomalies and talipes equinovarus have also been noted.

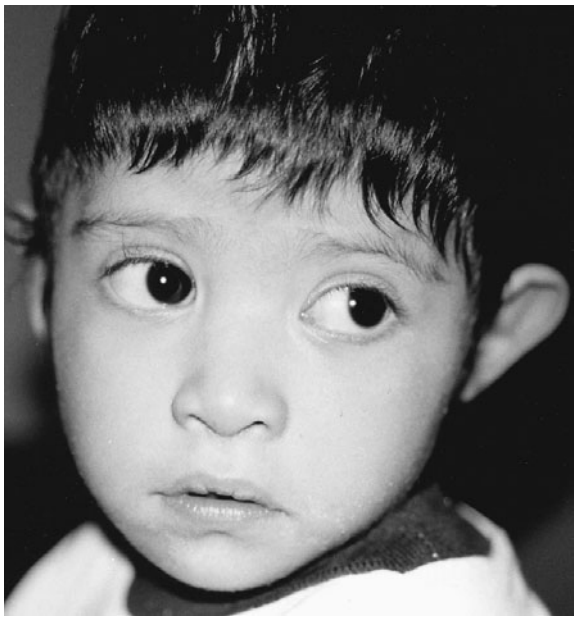
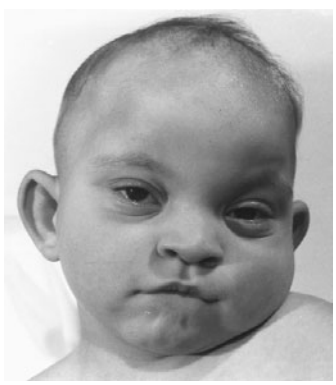


Fig. 4–1. *del(1p) syndrome*. Microcephaly, large anterior fontanel, dysmorphic pinnae, somewhat flattened nose. (Courtesy of SK Shapira and LG Shaffer, Houston, Texas.)

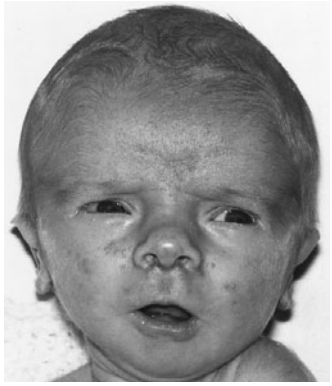
Intermediate interstitial deletions. Intermediate interstitial deletions (1q24–q42) are few in number. In addition to mental retardation, these infants have microdolichocephaly, prominent metopic suture, coarse scalp hair, preaxial hexadactyly, clinodactyly, hypospadias, cryptorchidism, and inguinal hernia (1,6,10,18,20).

Distal deletion. Patients with distal deletion (1q42–qter), the most common of the deletions, exhibit mental retardation, autism, hypotonia, seizures, microbrachycephaly, fine scalp hair, epicanthic folds, upslanting palpebral fissures, flat nasal bridge, downturned mouth, thin vermilion, long upper lip with smooth philtrum, congenital heart disease, broad nasal tip, cleft palate, micrognathia, short neck, weak or high-pitched cry, hypospadias, cryptorchidism, short fingers, and hypoplastic nails (5,7,8,13–17,19,25–27) (Fig. 4–2A). About 25% of cases have agenesis of the corpus callosum.

Fig. 4–2. (A) *del(1q) syndrome.* Microbrachycephaly, round flat face, upslanting palpebral fissures with apparent hypertelorism, epicanthal folds, heavy cheeks, malformed pinnae, short neck. (B) *dup(1q) syndrome.* Five-week-old infant presenting macrocephaly, craniofacial asymmetry, apparent hypertelorism, and anteverted nostrils. (A from M Andrle et al, Hum Genet 41:115, 1978. B from NL Chia et al, Clin Genet 34:224, 1988.)



A



B

References [del(1q) syndrome]

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dup(1q) syndrome

As in other duplications, examples of "pure" trisomy are rare. The clinical picture seems to reflect the size of the duplicated segment, and includes pre- and postnatal growth retardation and psychomotor retardation.

About 25 cases of trisomy for 1q42–qter have been reported, the phenotype consisting of relative macrocephaly (85%), large fontanels (60%), widely separated sutures in infancy (60%), prominent forehead (70%), hypertelorism (65%), flat nasal bridge, down-slanting narrow palpebral fissures (10%), low-set pinnae (55%), facial capillary nevi, and micrognathia (30%) (1). Various other anomalies have been found with lower frequency (2,3,5,7–10,13,16,17,21) (Fig. 4–2B). Cleft lip/palate

has been noted in about 15% of cases. Malformed fingers and toes are seen in 65%. Various forms of congenital heart anomalies have been found in about 40% of affected individuals (5).

In those cases with a longer duplicated segment, the above findings, especially cardiac abnormalities (60%) occur more frequently. Various digital anomalies (camptodactyly, syndactyly, brachydactyly, overlapping digits) have been noted in individuals with both small and marked duplications (4–7,11,12,14,15,18,19).

Schorry et al (20) have suggested that those with duplication for 1q31.1–q32.1 have pre- and postnatal growth retardation, narrow palpebral fissures, pituitary abnormalities, microphthalmia, and normal intelligence in some individuals.

References [dup(1q) syndrome]

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del(2p) syndrome

Deletion of part of the short arm of chromosome 2 must be lethal as we were able to locate but few examples. Duca et al (1) and Fryns et al (2) reported interstitial deletion of the 2p13–p15 region.

Other than mental retardation, both children had severe speech retardation and mild dysmorphism: wide bossed forehead, low hair implantation, wide mouth, short neck, narrow chest, kyphosis, and long and broad halluces.

There are at least 10 examples of r(2) chromosomes. In addition to mental and somatic retardation, the more common findings have included microcephaly, epicanthic folds, micrognathia, low-set pinnae, short neck, widely spaced nipples, hypogenitalism, and clinodactyly (3).

References [del(2p) syndrome]

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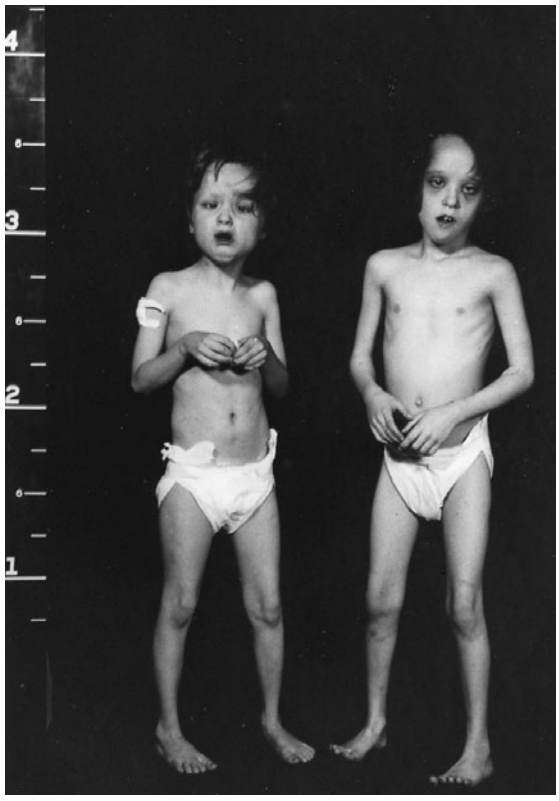
dup(2p) syndrome

Approximately 30 cases of trisomy of the 2p21 or p23pter region have been described (1–14). In addition to being severely retarded, all patients show microcephaly. Other features include a high, prominent forehead with frontal upsweep of hair, hypertelorism, strabismus, dysmorphic pinnae, short nose with prominent tip, maxillary hypoplasia, broad nasal bridge, small mouth, cleft palate, broad alveolar ridges, and micrognathia (Fig. 4–3).

Pre- and postnatal growth retardation are constant findings. The body build is slender with hypotonia, and the toes are widely spaced (40%). Skeletal anomalies include long, tapering, hyperflexible fingers (60%), scoliosis (15%), pectus excavatum (33%), increased internipple distance, and limited hip movement. Congenital heart anomalies (35%) are inconsistent in type. Micropenis (60%), shawl scrotum (15%), hypospadias (15%), and cryptorchidism (10%) have been found.

Fig. 4–3. *dup(2p) syndrome*. Slender body, thin extremities, wide spaced toes, high prominent forehead, wide flat nasal bridge, ptosis, pointed chin. (From U Francke and KL Jones, Am J Dis Child 130:1244,1976.)



References [dup(2p) syndrome]

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del(2q) syndrome

Interstitial deletion of bands 2q22.3–q23.3 has been associated with short neck and excess cervical skin. Deletion of the bands 2q23.3–q24.2 is seen with hypertrichosis and a high-pitched cry (11).

Children with deletion 2q21–q31 have somatic and mental retardation, relative macrocephaly, prominent nose, cataracts, microphthalmia, coloboma, ptosis, micrognathia, flexion deformity of fingers, syndactyly, ectrodactyly, and congenital heart anomalies (3,7,12,19) (Fig. 4–4). Several patients have cleft palate.

Most cases of del(2q) involve deletion 2q31–q33. In addition to mental and somatic retardation, these children exhibit the eye anomalies and finger deformities seen with del2q21–q31 (1,2,6,14–16,18). Blepharophimosis and microcephaly are common, and frequently there are seizures and brain anomalies. The midface is hypoplastic with a long philtrum. About 50% of affected individuals have cleft lip or cleft palate (1,2,3,6). Congenital heart anomalies are found in 50%.

Terminal deletion (2q35→qter) is associated with mental and somatic retardation, frontal bossing, macrocephaly, deep-set eyes, long eyelashes, down-slanting palpebral fissures, cleft palate, micrognathia, hypotonia, inverted nipples, and syndactyly (4,5,10,13,17,20,21).

There are at least 10 reported examples of r(2) chromosomes. In addition to mental and somatic retardation, the more common findings have included microcephaly, epicanthic folds, micrognathia, low-set pinnae, short neck, widely spaced nipples, hypogenitalism, and clinodactyly (9).

There is some evidence that an Albright hereditary osteodystrophy-like phenotype is associated with deletion of 2q (2a).

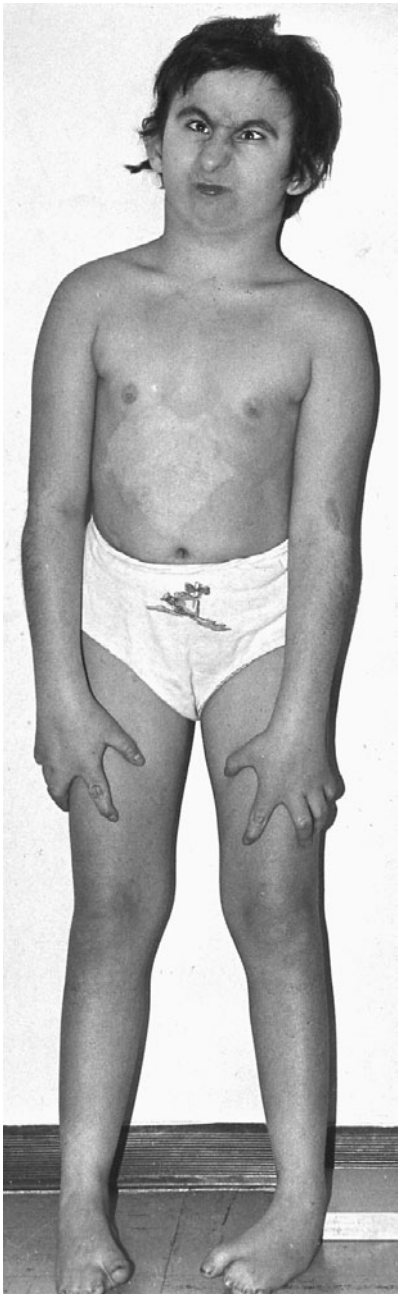

Fig. 4–4. *del(2q) syndrome*. Microphthalmia, strabismus, prominent nose, micrognathia, camptodactyly of fingers 3–5, hyperextensible index fingers, syndactyly of toes 2–5 in patient with interstitial deletion of 2(q31–q33). Cleft palate was also present. (From P Franceschini et al, Hum Genet 64:98, 1983.)

References [del(2q) syndrome]

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dup(2q) syndrome

Approximately 25 examples of various degrees of partial trisomy 2q have been analyzed by Kyllerman et al (3), Yu and Chen (8), and Siffroi et al (5). The phenotype seems to vary little with the degree of deletion q31→qter to q34→qter (2,3). Birth weight and length are usually normal. In addition to the constant mental retardation, frequent findings include frontal bossing, microbrachycephaly with temporal retraction, hypertelorism, short beaked nose, elongated philtrum, and abnormal pinnae (Fig. 4–5). Other eye findings include reduced vision, myopia, exotropia, glaucoma, nystagmus, iris defects, and fundus lesions (9). Some patients have thoracic kyphosis (1,6) and clinodactyly of the fifth finger. Visceral abnormalities have been extremely rare.

Cleft palate has been reported in several cases (1,4,7).

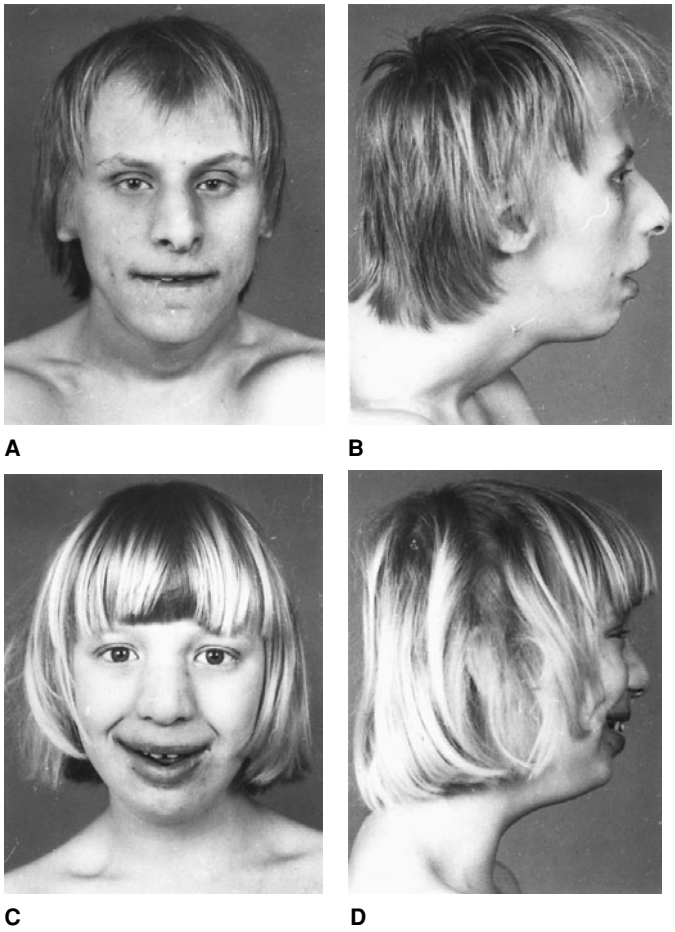

Fig. 4–5. *dup(2q) syndrome*. (A–D) Microbrachycephaly, beaked nose, wide mouth in brother and sister. (From M Kyllerman et al, Helv Paediatr Acta 39:499, 1984.)

References [dup(2q) syndrome]

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Chromosome 2 pericentric inversion of 2p12–q14

In 1995, Ramer et al (4) defined the syndrome of pericentric inversion of 2p12–q14. Findings included mental and growth retardation, lissencephaly, and trigonocephaly. The facies is characterized by ptosis, coloboma, epicanthic folds, hypertelorism, long philtrum, and large mouth. The pinnae are somewhat dysmorphic. About 50% of patients have sensorineural hearing loss.

References (Chromosome 2 pericentric inversion of 2p12–q14)

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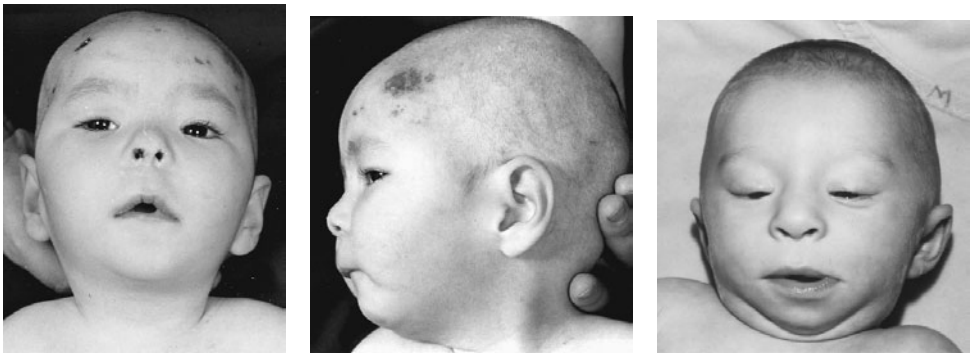
del(3p) syndrome

About 25 cases of del(3p) syndrome have been reported with most involving loss of the 3p25 (terminal) band. The most common features include low birth weight (70%), severe postnatal growth retardation (100%), severe mental retardation (100%), microcephaly (80%), brachycephaly, unusual facies, and developmental delay with severe psychomotor retardation (1–12,14–16).

The face is somewhat triangular (40%) with a high prominent forehead (25%), arched bushy eyebrows (15%), flat nasal bridge, up-slanting palpebral fissures, synophrys (30%), blepharoptosis (80%), epicanthic



A B C

Fig. 4–6. *del(3p) syndrome.* (A,B) Microcephaly, dolichocephaly, somewhat triangular face with high forehead, ptosis, thin lips with long philtrum and small mandible. (C) Microcephaly, ptosis, inverse epicanthus, small nose with prominent bridge, narrow vermilion, and small mandible. (A,B from DR Witt et al, Clin Genet 27:402, 1985. C from MC Higginbottom et al, J Med Genet 19:71, 1982.)

folds (50%), broad nasal tip (50%), and low and dysmorphic pinnae (95%). The lips are thin (25%), the philtrum long (75%), the angles downturned (30%), and the mandible small (65%) (Fig. 4–6).

Supernumerary postaxial digits of hands and feet (50%), renal malformations (45%), sacral dimple (20%), cryptorchidism (45%), small penis (25%), congenital heart anomalies (25%), and rocker-bottom feet have each been reported in about 30% of cases (7). About 15% of patients suffer premature death.

About 8 examples of interstitial deletion of 3p14 have been described (13). There does not appear to be a distinct phenotype.

References [del(3p) syndrome]

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dup(3p) syndrome

Approximately 50 patients with partial trisomy for the short arm of chromosome 3 have been reviewed by Reiss et al (11). The size of the trisomic segment seems to have little effect on the phenotype (14).

Prenatal growth is retarded in only 15% of patients and postnatal growth is slowed in about 35%. About 50% of infants have died within the first 2 years of life. All exhibit psychomotor retardation. Hypospadias, micropenis, or cryptorchidism has been found in 75% of males. Congenital heart defect has been documented in 70% of patients, and excessive fingertip whorls were noted in about 85%.

Facial features include brachycephaly (75%), frontal bossing (85%), temporal indentation (85%), hypertelorism (80%), epicanthal folds and square-shaped face with full cheeks (80%), prominent philtrum, large mouth, microretrognathia (60%), and short neck (85%). About 25% have cleft lip with or without cleft palate (Fig. 4–7). The facies become less distinctive with age (1–15). Possibly 10% of cases have associated holoprosencephaly (1,5–7,9).

References [dup(3p) syndrome]

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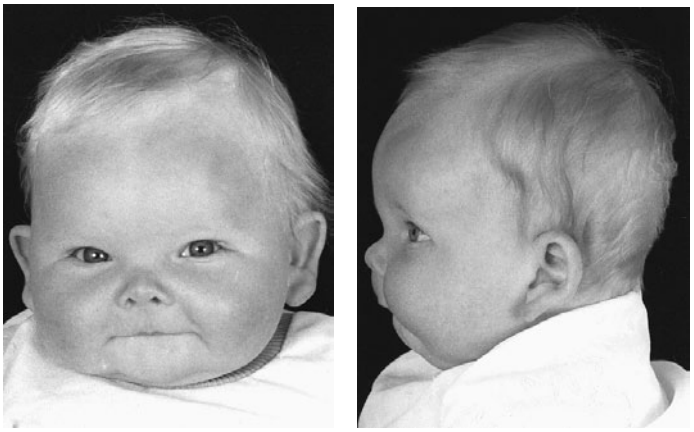
Fig. 4–7. *dup(3p) syndrome*. (A,B) Brachycephaly, frontal bossing, full cheeks, prominent philtrum, short neck. (From JA Reiss et al, Clin Genet 30:50, 1986.)



A B

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del(3q) syndrome

Approximately six cases of terminal deletion of the long arm of chromosome 3 have been reported (2–4,6,8), which have been sufficiently different so that no distinct syndrome can be discerned. However, two examples (2,4) seem somewhat similar, having hypoplastic supraorbital ridges, microphthalmia and broad nose with deep sulcus across the nasal bridge, short neck, and cardiac and limb anomalies.

Interstitial deletion (3q12–q25) results in microcephaly, blepharophimosis, ptosis, epicanthic folds, malformed large ears, talipes, joint contractures, and congenital heart anomalies in addition to short stature and mental retardation (1,5,7).

References [del(3q) syndrome]

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2. Alvarez Arratia AMC: De novo del(3)(q2800). Ann Genet 27:109–111, 1984.
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dup(3q) syndrome

Falek et al (2) first described the clinical features of dup(3q), reporting the condition as "familial de Lange syndrome." At least 40 examples have been reported, about 60% of these resulting from a familial translocation (9). The phenotype has been remarkably constant for dup3q21→qter. At least one-third of affected infants have died before the end of the first year of life as a result of heart malformation and infections (9). Mental retardation is severe, and underlying brain anomalies (polymicrogyria, hypoplastic olfactory bulbs) and seizures have been noted in at least 85% of cases. Craniofacial anomalies are remarkably constant. Hypertrichosis and synophrys are marked, and most infants have abnormal head shape due to craniosynostosis. Palpebral fissures are often up-slanting. There is a broad nasal root with anteverted nostrils, the upper lip is long, and the maxilla is prominent. The corners of the mouth are downturned. The pinnae are malformed, and approximately 80% have cleft palate. The neck is short and occasionally webbed (1–11) (Fig. 4–8).

Head anomalies include clinodactyly, camptodactyly, single palmar crease, and nail hypoplasia. In extreme cases, the hand may resemble that seen in trisomy 18. Talipes is present in at least 65% of cases.

Omphalocele occurs in about 25%. Various urogenital abnormalities (micropenis, hypospadias, cryptorchidism, ambiguous genitalia, absent scrotal folds) have been found in approximately 50% of patients, and

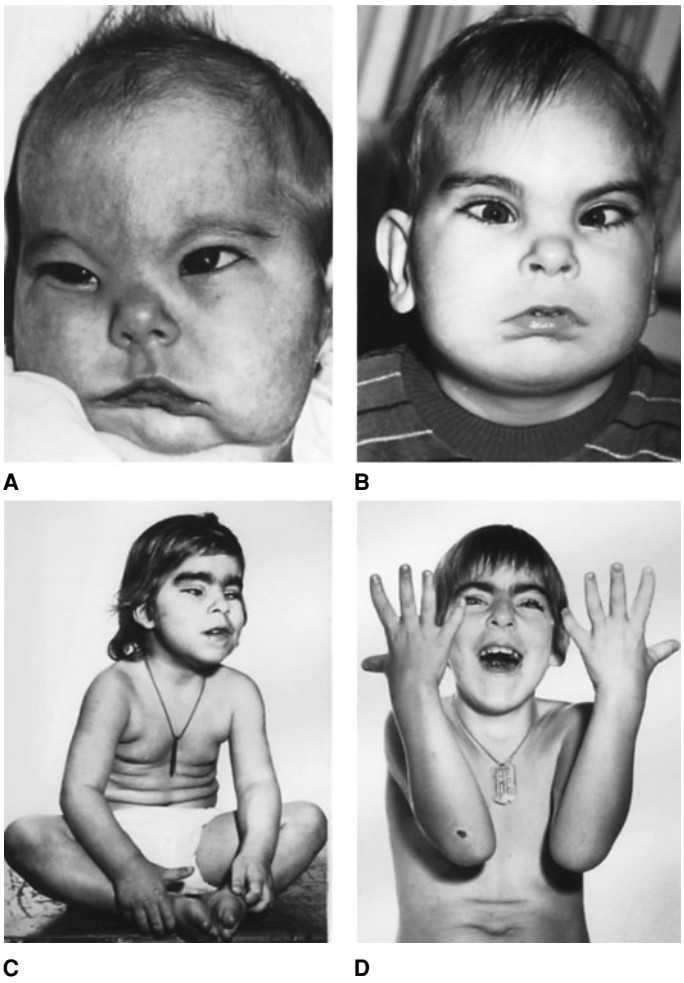

Fig. 4–8. *dup(3q) syndrome*. (A,B) Bushy eyebrows, synophrys, up-slanting palpebral fissures, broad nasal root, anteverted nostrils, long philtrum, downturned corners of mouth. (C,D) Similar phenotype in older children. (A from MT Mulcahy et al, Ann Genet 22:217, 1979. B from L Tranebjaerg et al, Clin Genet 32:137, 1987. C,D from A Falek et al, Pediatrics 37:92, 1966.)

cardiac defects [atrial septal defect (ASD), double outlet right ventricle, subaortic stenosis, aberrant right subclavian artery] have been noted in at least 75%.

The clinician should have little difficulty in differentiating dup(3q) syndrome from the *Brachmann-de Lange syndrome,* which far more frequently is marked by severe intrauterine growth retardation, prominent philtrum, oligodactyly, proximally placed thumbs, and syndactyly of the second and third toes. Also, craniosynostosis, cleft palate, and urinary tract anomalies occur far more frequently in dup(3q) syndrome.

Approximately 75% of the cases are derived from parental rearrangements involving a pericentric inversion of chromosome 3 or balanced translocation. Duplication of the 3q25→qter region is sufficient to generate the characteristic face, although a slightly more severe phenotype is produced by complete duplication of 3q.

References [dup(3q) syndrome]

1. Annerén G, Gustavson KH: Partial trisomy 3q(3q25→qter) syndrome in two siblings. Acta Paediatr Scand 73:281–284, 1984.
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3. Francke U: Clinical syndromes associated with partial duplications of chromosomes 2 and 3: dup(2p), dup(2q), dup(3p), dup(3q). Birth Defects 14(6C): 191–217, 1978.
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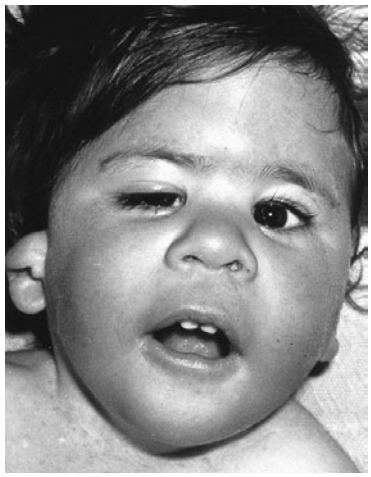

Fig. 4–9. *dup(4p) syndrome*. Round asymmetric face with chubby cheeks, somewhat bulbous nose, unilateral ptosis of eyelid, epicanthal folds, enophthalmos, malformed pinnae, short neck. (From JG Mortimer et al, Hum Hered 30:58, 1980.)

5. Ismael SR et al: Duplication 3q(q21→qter) without limb anomalies. Am J Med Genet 38:518–522, 1991.
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dup(4p) syndrome

Patients having duplication of at least the distal two-thirds to the entire short arm have a distinct phenotype. Over 75 cases have been reported (9) with no sex predilection. About 75% of reported cases have arisen from a balanced parental translocation, the most common recipient being acrocentric, especially chromosome 22. About 10% arise de novo. Death has occurred during early infancy in about 35%.

In addition to mental retardation (IQ: 20–25), about 25% of affected infants have prenatal and 65% postnatal growth retardation. Flexion contractures (55%), hypotonia (40%), hypertonia (35%), and seizures (25%) are also seen.

The following constitute the phenotype: microcephaly (75%), frontal bossing (20%), prominent glabella (30%), hypertelorism (45%), strabismus (40%), down-slanting palpebral fissures (20%), microphthalmia (15%), nystagmus (20%), synophrys and long, bushy eyebrows (25%), depressed broad nasal bridge with bulbous tip (60%), microstomia (30%), thin lips (25%), low-set, posteriorly rotated pinnae (75%), prominent mandible (50%), short neck with low hairline (50%), wide-spaced nipples (40%), micropenis (50%), cryptorchidism (35%), hypospadias (25%), and abnormal digits of the hands or feet (65%) (1–13) (Figs. 4–9 and 4–10).

References [dup(4p) syndrome]

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2. Crane J et al: 4p trisomy syndrome: Report of 4 additional cases and segregation analysis of 21 families with different translocations. Am J Med Genet 4:219–229, 1979.

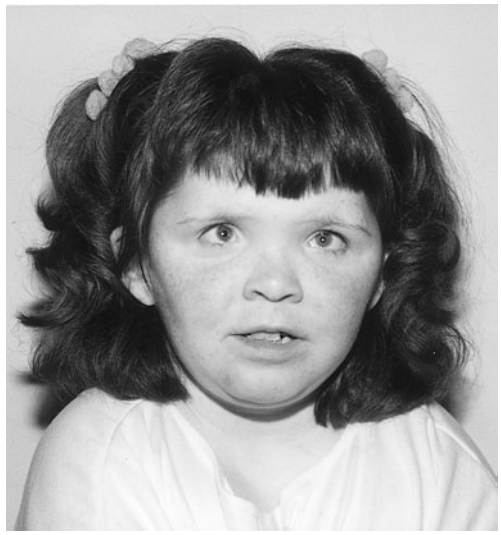

Fig. 4–10. *dup(4p) syndrome*. Prominent forehead and glabella, down-slanting palpebral fissures, telecanthus, strabismus, flat nasal bridge, bulbous nasal tip, long philtrum, thin upper lip, short neck. (From RC Rogers et al, Proc Greenwood Genet Ctr 5:29, 1986.)

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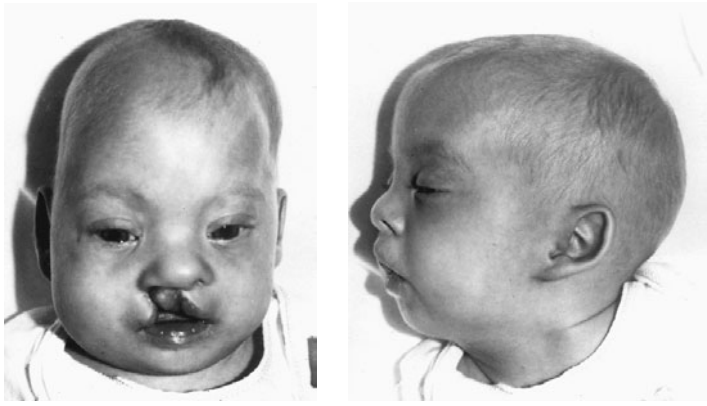
del(4q) syndrome

In about 10% of del(4q) cases, one of the parents is a balanced translocation carrier. The critical deletion segment is 4q31→qter. Over 30 patients have been described; a most comprehensive survey of this syndrome is that of Lin et al (9). About 70% die within the first two years of life from congenital heart disease or from aspiration pneumonia (1–17). Deletion of 4q34.2–4qter may be associated with a *velocardiofacial syndrome* phenotype (1,3,17).

Although birth weight is normal, mild postnatal growth retardation and mild to moderately severe mental retardation are common features. Craniofacial anomalies include microcephaly, low-set posteriorly angulated pinnae with malformed helices, short nose with a low nasal bridge and anteverted nostrils, and micrognathia. Cleft palate with or without cleft lip is common (75%), as are hypertelorism, epicanthal folds, and laterally displaced inner canthi (11,13,14) (Figs. 4–11 and 4–12A,B). Small, upward-slanting palpebral fissures, oropharyngeal hypotonia, cardiac defects (mostly ASD and VSD), limited extension at the elbows, clinodactyly and tapering of the fifth finger with a pointed or duplicated nail (which appears to highly suggestive of the syndrome), transverse

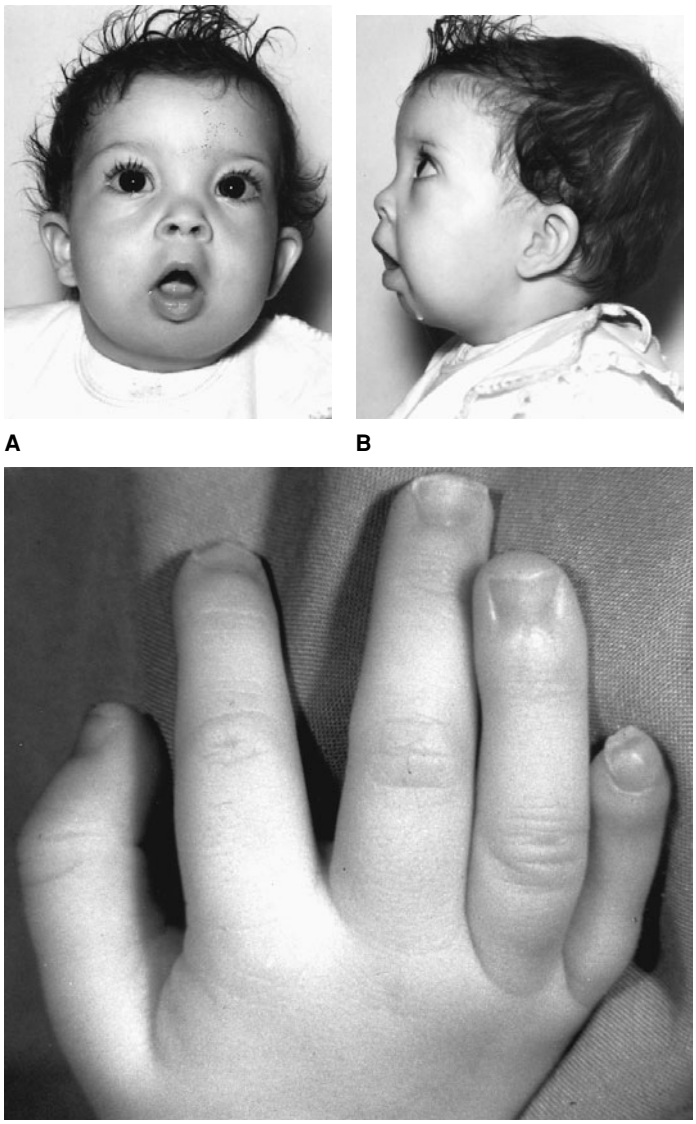


A B

Fig. 4–11. *del(4q) syndrome*. (A,B) Asymmetric forehead, up-slanting palpebral fissures, pointed helix, epicanthal folds, anteverted nostrils, cleft lip/palate. [From JL Frias et al, Birth Defects 14(6C):355, 1978.]

palmar crease, and overlapping toes also occur (Fig. 4–12C). Anomalies having a frequency of 25% or less include low-set posteriorly angulated pinnae and various skeletal anomalies (proximately implanted thumbs, camptodactyly, short distal phalanx of the fifth finger, absence of the fourth metacarpal, dislocated hips, and talipes equinovarus).

There is some evidence that del4q33–qter is associated with absorptive hypercalciuria (8).



A B C

Fig. 4–12. *del(4q) syndrome*. (A,B) Up-slanting palpebral fissures, short nose with anteverted nostrils, depressed nasal bridge, and micrognathia. Child had cleft palate. (C) Tapering and abbreviation of fifth finger with pointed nail. (A,B courtesy of SK Clarren, Seattle, Washington. C from AE Lin et al, Am J Med Genet 31:533, 1988.)

References [del(4q) syndrome]

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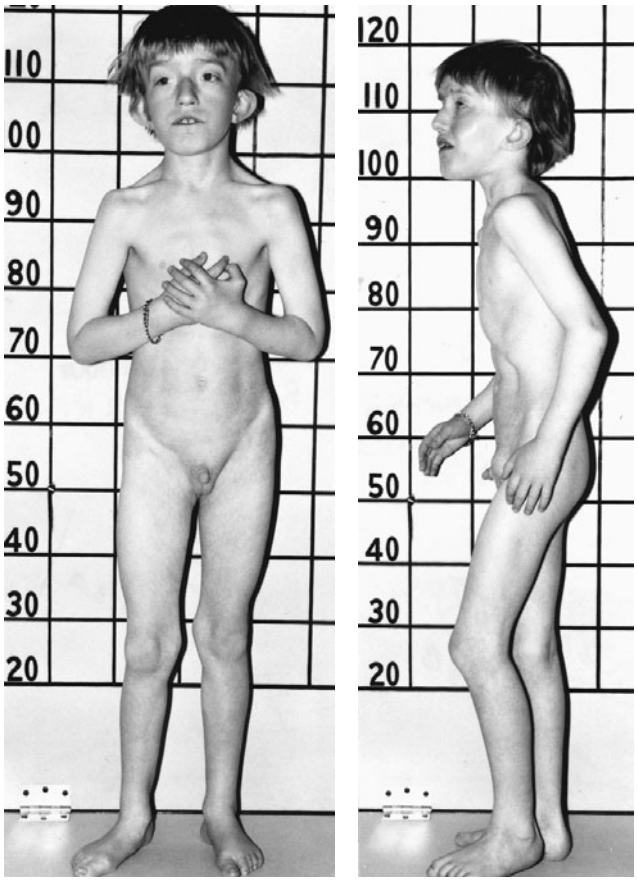
dup(4q) syndrome

In 90% of dup(4q) cases, one of the parents has a balanced translocation, which can range from 4q21→qter to 4q32→qter. At least 60 patients have been reviewed (3a). Poor correlation with clinical findings is noted (1–10). There is no sex predilection.

Neonatal mortality is about 30%, largely in those infants with more severe cardiac or renal anomalies. In addition to severe psychomotor retardation, cardiac and genitourinary anomalies are frequent. Birth weight is low in about half the cases.

The craniofacies is often characterized by microcephaly with sloping forehead (75%), epicanthal folds (40%), hypertelorism (75%), narrow down-slanting palpebral fissures (35%), large or prominent nasal bridge (40%), straight nasofrontal angle, short philtrum with protruding lateral margins (25%), downturned corners of mouth (35%), low-set, posteriorly angulated or malformed pinnae with prominent anthelix and hypoplastic tragus (90%), pointed chin, micrognathia (30%), and short neck (60%) (Figs. 4–13 and 4–14). Hyper- or hypotonia has been noted in over 60%



A B

Fig. 4–13. *dup(4q) syndrome*. (A,B) Broad forehead, down-slanting palpebral fissures, large outstanding pinnae, pectus carinatum, hypoplastic genitalia. (From RS Sparkes et al, Ann Genet 20:31, 1977.)

of cases and umbilical or inguinal hernia in about 30%. About half the patients have cardiovascular anomalies, including tetralogy of Fallot and various venous-return anomalies, and about 30% exhibit genitourinary abnormalities (horseshoe kidney, renal hypoplasia, urethrovesicular reflux with or without hydronephrosis). In males, cryptorchidism is a constant feature. The fingers are tapered, and the feet are edematous in 30% of patients.

Fig. 4–14. *dup(4q) syndrome.* (A,B) Down-slanting palpebral fissures, broad nasal bridge, pointed chin. (Courtesy of EM Bühler, Basel, Switzerland.)

A B

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dup(5p) syndrome

In addition to severe psychomotor retardation, the main features of this disorder are postnatal growth retardation, hypotonia, seizures, slender extremities with long fingers, short first toes, and club feet. Craniofacial findings include macrodolichocephaly, hypertelorism, up-slanting palpebral fissures, narrow palpebral fissures, epicanthic folds, low nasal bridge, bulbous nose, low-set pinnae, jowly appearance, long philtrum, full lips, cleft palate, and macroglossia (Fig. 4–15). Dermatologlyphic changes include excess ulnar loops and arch tibial patterns in the hallucal area (2,3).

An extensive review of this syndrome is that of Kleczkowska et al (6); about 50 cases have been reported (1–14). Duplications of segment 5p13 have more severe phenotypic changes (6,10) whereas duplication of 5p14→pter results in milder manifestations (4). Mosaic tetrasomic examples of 5p are associated with areas of skin hyperpigmentation (8,11), but otherwise the phenotype is similar.

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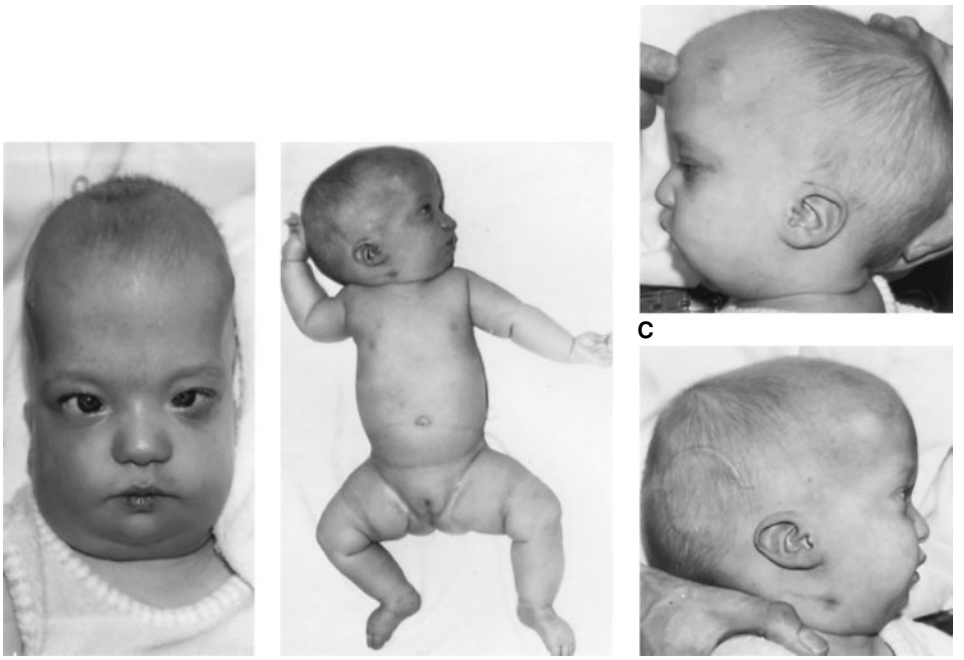

Fig. 4–15. *dup(5p) syndrome*. (A–D) Dolichocephaly, frontal bossing, strabismus, upslanting palpebral fissures, hypertelorism, unusually modeled pinnae, hypotonic posture. [From JM Opitz and K Patau, Birth Defects 11(5):191, 1975.]

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del(5q) syndrome

The effect of various deletions of the long arm of chromosome 5 has been well studied (2–5,7,9,10). Mental retardation is severe, but growth retardation has not been evident.

Micro- or macrocephaly; high, protruding forehead; telecanthus; epicanthic folds; anteverted nostrils; wide, flat nasal bridge; dysmorphic pinnae; long deep philtrum; microretrognathia; and short neck with redundant folds characterize the craniofacies (Fig. 4–16). Cleft palate has been noted in a few cases (6,8).

Various heart anomalies include ASD, VSD, and patent ductus arteriosus (PDA). Bilateral pes adductus, diastasis recti, short fingers, and inguinal hernias have been observed. Single palmar creases have also been described.

Megalokaryocytes may be abnormal (1).

References [del(5q) syndrome]

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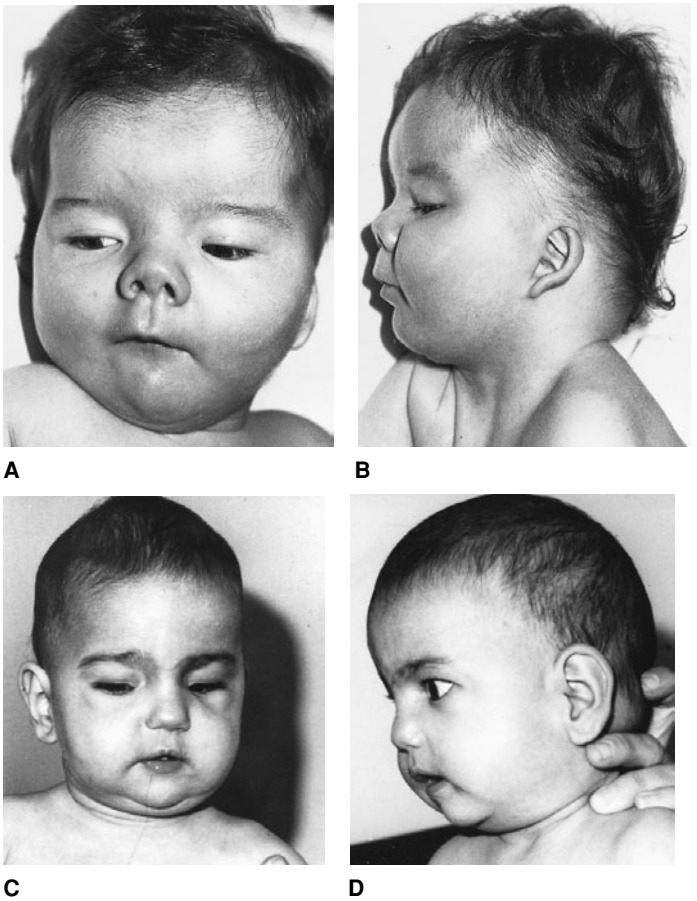
Fig. 4–16. *del(5q) syndrome.* (A,B) Brachycephaly, short nose with anteverted nostrils, long deep philtrum, microretrognathia. (C,D) Note similarity of phenotypes. (A,B from W Harprecht-Beato et all, Clin Genet 23:167, 1983. C,D from C Stoll et al, J Med Genet 17:486,1980.)



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dup(5q) syndrome

About 30 examples of various duplications have been reported. Trisomy for 5q31→5qter results in severe psychomotor retardation, low birth weight, microcephaly, high forehead, hypertelorism, downward slanting palpebral fissures, epicanthal folds, strabismus, large outstanding pinnae, prominent nasal bridge, long philtrum, large upper lip, and micrognathia. Musculoskeletal anomalies include brachydactyly, clinodactyly, preaxial polydactyly, and hernia (2–11). Various congenital heart defects, mostly VSD and ASD, are found in about one-half the cases.

In cases of trisomy 5q13→q22, the children have a high forehead, bulbous nose, short philtrum, large, protruding pinnae, and micrognathia (5). A smaller deletion, that of 5q34→qter, results in failure to thrive and strabismus (1,5).

References [dup(5q) syndrome]

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del(6p) syndrome

Most examples of this syndrome have involved a break point near 6p23 (2–7), but there are others (8,9). No sex predilection has been found. Involvement of ring chromosome 6 has also been discussed (2).

Mental retardation has been a constant feature of del(6p) syndrome. Most patients have microcephaly and abnormal cranial sutures. A broad, flat nasal bridge, eye anomalies (blepharophimosis, iris coloboma, strabismus, Peters anomaly, megalocornea), low-set dysmorphic pinnae with atresia of the canal, short neck with excessive skin folds, and micrognathia characterize the facies. About 35% of patients have cleft lip/palate. In reviewing the published cases, we have not been able to identify a common facies.

Pectus excavatum, hypoplastic nipples, and congenital heart anomalies (ASD, VSD, PDA, anomalous valves) are essentially constant features. Variable camptodactyly and minor genital hypoplasia occur frequently.

We have recently seen an infant with agenesis of the corpus callosum, Dandy-Walker cyst, diffuse cloudy corneae, and VSD.

References [del(6p) syndrome]

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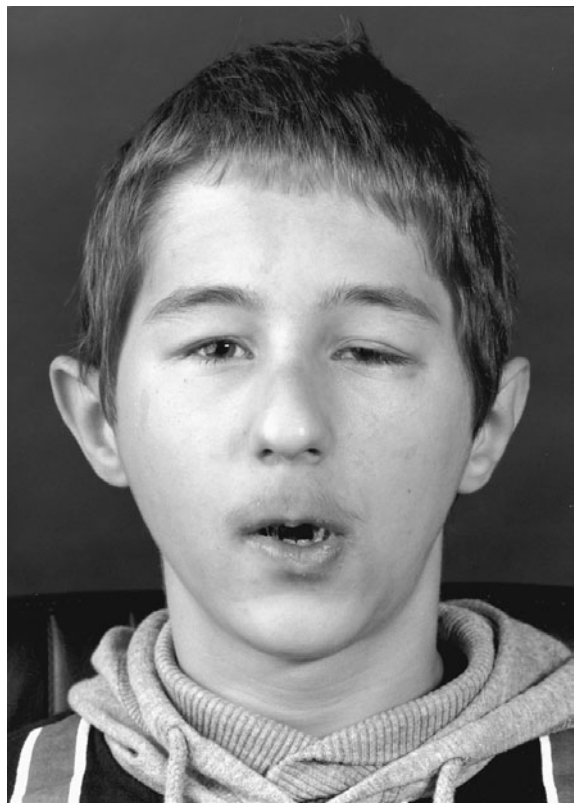
dup(6p) syndrome

About 40 cases of this partial trisomy have resulted from parental translocation or inversion duplication. Low birth weight has occurred in 95% of cases, and all survivors have had short stature. Most patients have died during infancy from respiratory or feeding problems (1–11). Developmental delay is a constant feature.

The facies is characterized by microcephaly (90%), high, prominent forehead (95%), craniosynostosis, flat occiput, wide fontanel, blepharophimosis/ptosis (90%), cataracts, microcornea (100%), strabismus, epicanthic folds, flat nasal root, very short nose, long philtrum (80%), thin lips, small mouth with cupid's bow, large, simple, low-set pinnae with poorly developed lobes (95%), and small pointed chin (80%) (Fig. 4–17).

Congenital cardiac abnormalities (ASD, VSD, PDA) are found in 65% of cases. Renal anomalies have included hydronephrosis and hypoplastic

Fig. 4–17. *dup(6p) syndrome.* Note high forehead, blepharophimosis, and microstomia. (From B Röthlisberger et al, Am J Med Genet 85:389, 1999.)



kidney (85%). Musculoskeletal abnormalities have involved umbilical or inguinal hernia and talipes equinovarus.

References [dup(6p) syndrome]

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del(6q) syndrome

About 60% of del(6q) cases have involved interstitial deletion and 40% have involved terminal deletion (3). At least 60 examples have been reported (1–16); these examples have been analyzed by Evers et al (1) and Hopkin et al (3). The latter authors have divided the cases into three groups; those with proximal deletions (6q11–q16), those with intermediate deletions (6q15–q25), and those with terminal deletions (6q25–qter). In all groups, mental retardation was a constant finding. Considerable overlap was evident among the groups. However, some findings were more often found in each group.

del(6)(q11–q16). This group was marked by growth failure (85%), ear anomalies (85%), epicanthic folds (65%), up-slanting palpebral fissures (85%), flat nasal bridge (50%), thin lips (55%), hypotonia (90%), hernia (70%), and limb anomalies (80%).

del(6)(q15–q25). This group was characterized by growth failure (65%), hypertelorism (60%), microcephaly (75%), broad nasal tip (65%), micrognathia (60%), ear anomalies (100%), limb anomalies (65%), and hypotonia (75%).

del(6)(q25–qter). Patients in this group had growth retardation (70%), microcephaly (80%), eye anomalies (50%), ear anomalies (90%), prominent nasal bridge (70%), long philtrum (55%), short neck (60%), and limb anomalies (70%).

A Prader-Willi-like phenotype has been noted (2).

References [del(6q) syndrome]

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dup(6q) syndrome

About 25 cases of this syndrome are known, all arising from balanced parental translocation or inversion (1–13).

The facies is striking and recognizable, characterized by microbrachycephaly or turricephaly, prominent forehead, flat face and occiput, prominent, almond-shaped eyes, microphthalmia, hypertelorism, downslanting palpebral fissures, broad flat nasal bridge, bow-shaped mouth with thin lips, short nose, short philtrum, micrognathia, short, webbed neck, and low-set ears with thickened earlobes. The lower lip may have a median indentation (Fig. 4–18). Cleft lip/palate or bifid uvula has also been reported (5,6).

In addition to severe somatic and mental retardation, there are joint contractures, flexed or deviated fingers and wrists, club feet, scoliosis, and single palmar crease. In the absence of congenital heart defects, survival is normal. Genital anomalies include hypoplastic labia, penis, and/or scrotum.

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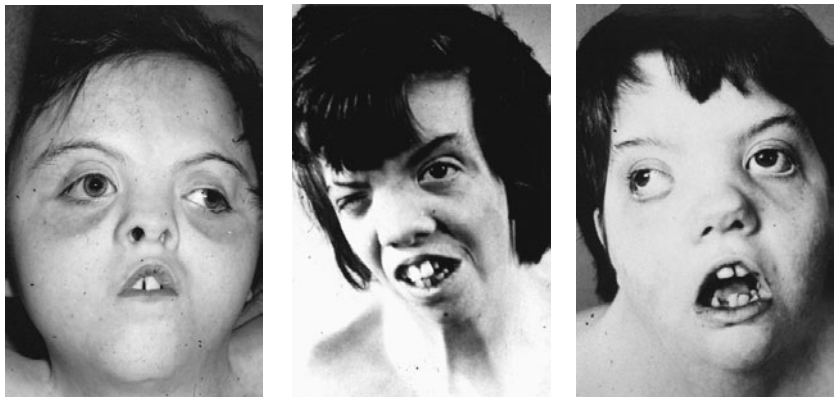

A B C

Fig. 4–18. *dup(6q) syndrome.* (A–C) Microcephaly, acrocephaly, prominent forehead, almond-shaped eyes, hypertelorism, down-slanting palpebral fissures, flat facial profile with depressed nasal bridge and malar areas, carp mouth, micrognathia, and extremely short webbed neck. B and C are sisters. (A courtesy of RE Tipton, Memphis, Tennessee. B,C courtesy of C Clark, Wilmington, Delaware.)

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del(7p) syndrome

This syndrome is characterized by variable craniosynostosis [turricephaly, microcephaly, flat occiput, prominent forehead, craniosynostosis (40%), trigonocephaly, cranial asymmetry] (3,5,6,9). The precise region involved in craniosynostosis has not been determined. Intelligence has varied from severe retardation to normal. Facial nevus flammeus, hypotelorism, downward-slanting palpebral fissures, ptosis, epicanthal folds, saddle nose, small, low-set dysplastic pinnae, and transverse palmar creases are frequent (1–14) (Fig. 4–19). Congenital heart disease and urogenital malformations are found in 50% of patients (12). Cleft palate has been described in association with this syndrome (3,9,10).

References [del(7p) syndrome]

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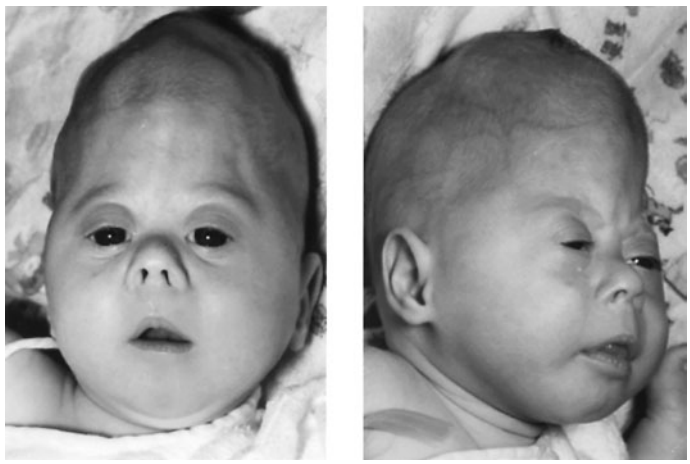
Fig. 4–19. *del(7p) syndrome.* (A,B) Turribrachycephaly with prominent metopic and coronal areas, hypotelorism, short palpebral fissures, epicanthal folds, prominent eyeglobes, short nose with anteverted nostrils. (Courtesy of JG Hall, Vancouver, British Columbia, Canada.)



A B

dup(7p) syndrome

Patients with duplication of 7p15→pter exhibit a syndrome comparable to those with larger deletions. The most common break points are 7p11,7p15 and 7p21. The critical segment appears to be 7p21→pter (1). The principal features, in addition to mental retardation, include asymmetric skull, wide anterior fontanel, brain malformations, high, large forehead, hypertelorism, choanal atresia, cleft palate, abnormal pinnae, congenital heart anomalies, joint dislocation or contractions, and broad digits (1–14) (Fig. 4–20).

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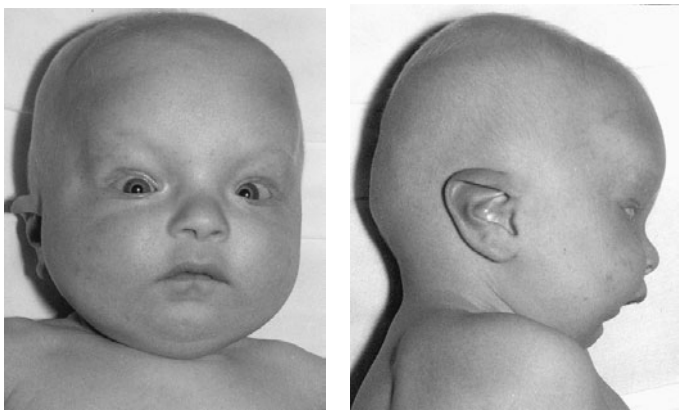

A B

Fig. 4–20. *dup(7p) syndrome.* (A,B) Large fontanel, hypertelorism, up-slanting palpebral fissures, full cheeks, short beaked nose, dysplastic pinna, downturned corners of mouth, micrognathia, short neck. (Courtesy of G Schwanitz, Erlangen, Nürnberg, West Germany.)

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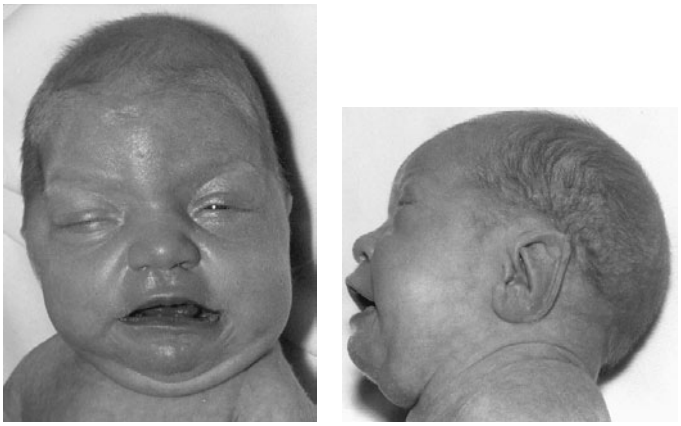
del(7q) syndrome

Among 25 examples of proximal interstitial deletions involving 7q21–7q32, no recognizable clinical syndrome was evident (6,12,16). However, findings among 30 examples of deletion of 7q32–qter included pre-and postnatal growth retardation (85%), feeding problems (35%), severe mental retardation (95%), microcephaly (90%) with prominent forehead (40%), broad nasal bridge with bulbous tip, hypertelorism (30%), hypotelorism (20%), epicanthus (25%), up-slanting palpebral fissures (20%), various other eye anomalies (50%), large dysplastic pinnae (40%), large, downturned mouth (35%), midface hypoplasia (35%), micrognathia (40%), and short neck (9,10,13,14) (Figs. 4–21 and 4–22). Cleft lip with or without cleft palate has been noted in 30% of cases (1,8,14,15). Clefting of the midline and single central incisor have been noted in those patients with variant holoprosencephaly (vide infra). Early death occurred in 25%.

Various congenital heart defects (15%), distal limb anomalies (30%), inguinal hernia (30%), hypospadias and small penis (60%), and abnormal palmar creases (50%) occur frequently. Typical holoprosencephaly may be seen in 30% of those with 7q32–qter deletions (2–5,7,11). Some have only a single central incisor (5).

Sacral dysgenesis has been noted with terminal 7q deletion (14a).



A B

Fig. 4–21. *del(7q) syndrome.* (A,B) Prominent forehead with broad nasal bridge and bulbous tip. Large dysplastic pinna, large mouth, micrognathia, and short neck. (Courtesy of G Schwanitz, Erlangen, Nürnberg, Germany.)

References [del(7q) syndrome]

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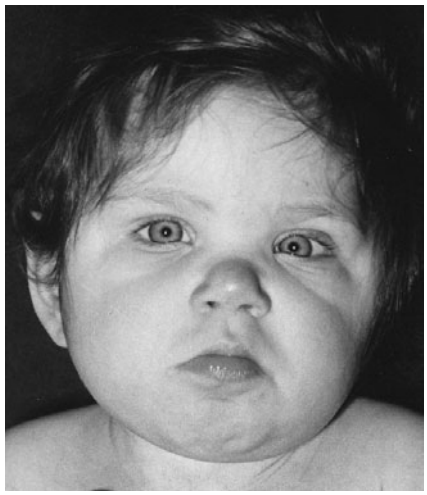
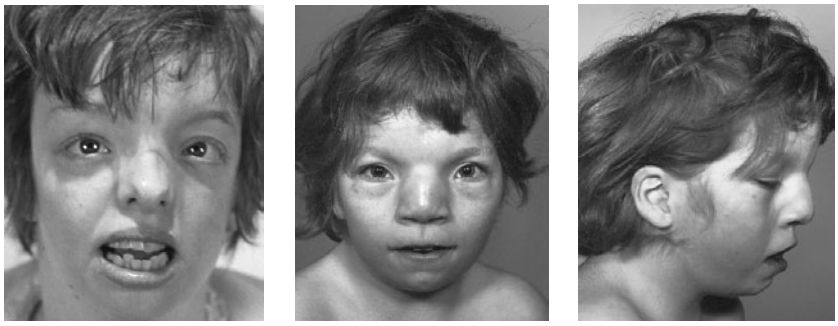
Fig. 4–22. *del(7q) syndrome.* Facies in older child similar to that seen in Fig. 4–21. (Courtesy of B Biederman, Edmonton, Alberta, Canada.)





A B C

Fig. 4–23. *dup(7q) syndrome.* (A) Prominent forehead, strabismus, hypertelorism, narrow palpebral fissures, bulbous nose, everted lower lip, micrognathia. *dup(8q) syndrome.* (B,C) Short protruding forehead, hypertelorism, upslanting palpebral fissures, broad flat nose with short septum, short upper lip, and small pinnae. (A from CE Clark et al, Am J Med Genet 7:21, 1980. B,C from A Schinzel, Hum Genet 37:17, 1977.)

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dup(7q) syndrome

About 50 patients with this syndrome have been documented; an excellent analysis is that of Johnson et al (8). For purposes of simpler presentation, two rather than six subgroups will be briefly described here. All patients exhibited mental and somatic retardation, with low-set abnormal pinnae and apparent hypertelorism (11a).

Patients with dup(7q31→7qter) have large fontanels; square, prominent forehead; short, down-slanting palpebral fissures; long eyelashes; short nose; long philtrum; thin vermilion; down-curved upper lip; and micrognathia. Most had cleft palate (Fig. 4–23A). Anomalies seen in a few cases include ventricular dilatation and severe hypospadias. Death is early (1,2,4,6,8,14,18).

Among 25 cases, those with dup(7q32–7qter) had no cleft palate. These patients also exhibited hypotonia, high forehead, depressed nasal bridge, macrocephaly with frontal bossing, large fontanelle, and hydrocephaly (3,5–13,15,18,20).

Total dup(7q) has been described in only a few cases (11a,19,21), but full trisomy 7 has been associated with Potter sequence (13,21). Renal anomalies have been seen in association with mosaicism for trisomy 7 (12,18,19).

References [dup(7q) syndrome]

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r(7) syndrome

About a dozen examples of ring chromosome 7 have been reported. Nearly all patients with r(7) have had skin lesions; among them vascular lesions (80%), large pigmented congenital nevi (50%), café-au-lait spots (30%), and achromic spots (10%) (1–9). Melanoma has been found in one case (3,7).

Intelligence has ranged from retarded (7,9) to normal (2–5). Microcephaly was noted in about 80% of patients (1,2,5–9). Short stature is a common feature, but major malformations are apparently rare. There is resemblance to *Silver-Russell syndrome* (8).

References [r(7) syndrome]

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del(8p) syndrome

At least 40 patients have been described with deletion of the distal portion of the short arm of chromosome 8. Intrauterine growth retardation (65%), abnormal facial appearance, and congenital heart defects (65%) have been observed in most patients, and genital anomalies have been found in males. Postnatal growth deficiency, mental retardation, seizures, developmental delay, microcephaly, dolichocephaly, and some lessening of facial changes become evident later in life.

The most prominent facial alterations during the first year of life include microcephaly (50%), a high forehead, wide low nasal bridge, epicanthic folds, short, broad nose (25%), malformed or malpositioned ears (70%), prominent alveolar ridges, microstomia (50%), and micrognathia and short neck (50%). Virtually all facial changes except epicanthal folds disappear with increasing age. Minor hand anomalies are present in about 50% of cases, taking the form of single transverse palmar crease, prominent palmar creases, clinodactyly, and puffy hands and feet (1–13). Various congenital heart anomalies have also been reported (9).

A variety of congenital heart anomalies (VSD, PS, ASD, transposition of great arteries), seen in 75% of patients, have been associated with a break point proximal to 8p23.1 (8,8a). Genitourinary abnormalities seen in 50% have included cryptorchidism, hypospadias, and hypogonadism (11). The nipples are widely set in most patients (6).

The use of FISH with 8p-specific telomeric probes may be used for detecting minor deletions (12).

References [del(8p) syndrome]

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dup(8p) syndrome

Approximately 35 cases of this syndrome which are either spontaneous or result from a parental translocation have been described. Mosaic tetrasomy 8p has also been reported in at least 10 patients (6,9).

dup(8p) results in a high forehead with frontal and parietal bossing, but with temple retraction, full cheeks, round face, low nasal bridge, anteverted nostrils, wide mouth, cleft palate and/or bifid uvula, everted lower lip with carp mouth, large earlobes, and a short neck with redundant skin folds. Severe mental retardation and absence of the corpus callosum have been reported as have various congenital heart malformations (1–8). An excellent phenotype–segment duplication correlation study is that of Walker and Bocian (8).

The trunk and extremities are long and contractures may restrict movement. Micropenis and cryptorchidism are frequent findings.

References [dup(8p) syndrome]

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Mosaic tetraploidy (8p) syndrome

Mosaic tetraploidy for the short arm of chromosome 8 has been reported several times (1–5). Associated features included prominent expressive language and motor delay, facial anomalies were very mild. The ventricles were dilated and the corpus callosum absent. Congenital heart anomalies (ASD, VSD, PDA) were evident in most patients.

Radiographically there were thoracolumbar hemivertebrae, fused vertebrae, and extra ribs or flail ribs.

References [Mosaic tetraploidy (8p) syndrome]

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dup(8q) syndrome

Approximately 50 cases of dup(8q) have been reported (8). Among those with trisomy for 8q23–pter, apart from mental retardation (IQ, 20–70), phenotypic changes have been very inconstant: low birth weight (35%), prominent forehead and flat occiput (65%), triangular face (50%), upslanting palpebral fissures (50%), strabismus (60%), short nose with broad base (40%), and low-set pinnae (65%) (1–9) (Fig. 4–23B,C). Cleft palate has been reported 1,5,9). Excellent phenotype–segment duplication analyses are those of Walker and Bocian (9) and Stengel-Rutkowski et al (7).

References [dup(8q) syndrome]

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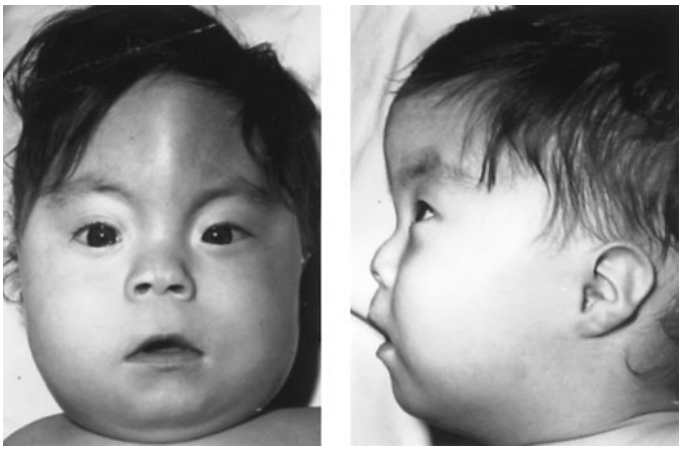
del(9p) syndrome

Approximately 100 cases of del(9p) have been described (1–13). In about 85%, the deletion occurs de novo at most often at 9p22, and has been shown to be of paternal origin in nine cases and of maternal origin in four cases (4). Several r(9) examples have been documented, most having the phenotype of del(9p) (7). In 15% of cases the disorder results from a parental translocation. Clinical findings include mental and somatic retardation but normal birth weight (100%), trigonocephaly (90%), flat occiput (70%), hypertelorism and upward-slanting, small palpebral fissures (75%), epicanthal folds, broad flat nasal bridge (90%), anteverted nostrils (100%), low-set malformed pinnae with abnormal lobules (85%), low hairline, long philtrum (95%), small mouth and protruding lips (75%), micrognathia (85%), short, somewhat webbed neck (95%), pterygium colli (75%), wide-set nipples (100%), congenital heart disease (VSD, PDA, PS) (65%), and omphalocele or umbilical hernia (65%). Scoliosis, inguinal hernia, long fingers or toes because of dolichomesophalangy, relative shortness of the metacarpals, square hyperconvex nails, and increased number of fingertip whorls (90%) (2,13) have also been reported (Figs. 4–24, 4–25, and 4–26). Infections, particularly those of sinus and middle ear, are common, as are genitourinary and gastrointestinal reflux. Muscle tone is low. Seizures may develop in mid-childhood. Many of these findings change with age (4). Among 30 cases, three had cleft palate or bifid uvula (11,13). Some patients developed leukemia or lymphoma (1,3).

Fig. 4–24. *del(9p) syndrome.* (A,B) Prominent forehead with trigonocephaly, mild up-slanting palpebral fissures, apparent hypertelorism, wide nasal bridge, anteverted nostrils, long philtrum, short neck. (From OS Alfi, Ann Genet 16:17, 1973.)



A B

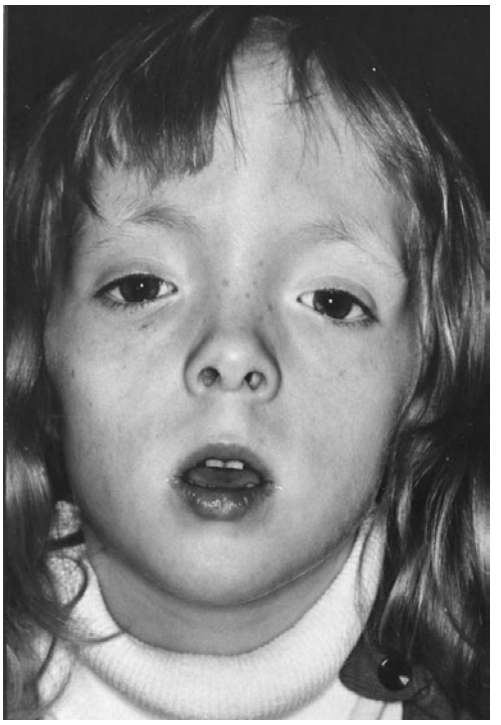


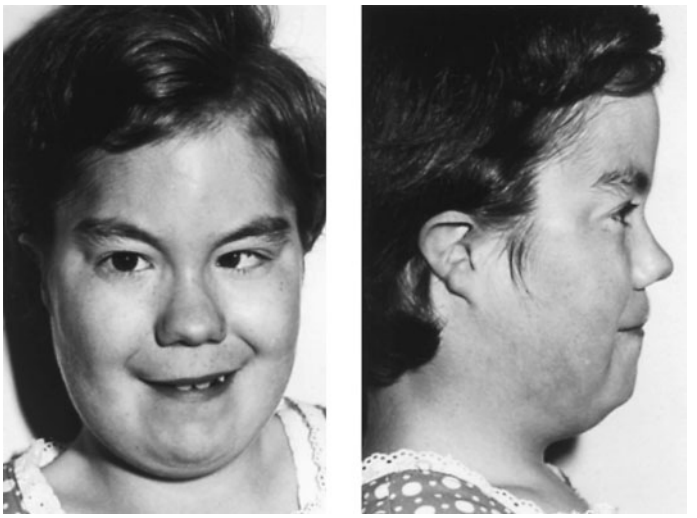
Fig. 4–25. *del (9p) syndrome.* Trigonocephaly, down-slanting palpebral fissures. (From RS Young, Am J Med Genet 14:751, 1983.)

Because of the upward-slanting palpebral fissures, at birth a child may be mistaken for having *Down syndrome.*

A dozen examples of r(9) have been reported (10). The features of r(9) resemble those of del(9p) syndrome: microcephaly, a facies similar to that of del(9p), flexion of major joints, ambiguous genitalia, hypospadias, inguinal hernia, and various cardiac defects (10).

Sex reversal has been reported (1a).

Fig. 4–26. *del(9p) syndrome.* (A,B) Trigonocephaly, up-slanting palpebral fissures, strabismus, broad flat nasal bridge, malformed pinna, long philtrum, short neck. (From FJ Rutten et al, Ann Genet 21:51, 1978.)



A B

References [del(9p) syndrome]

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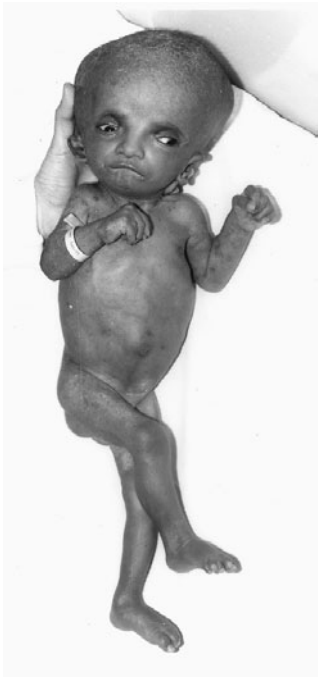
Tetrasomy (9p) syndrome

Tetrasomy (9p) is rare, having been first reported by Ghymers et al (7) in 1973, with less than three dozen reports having been written on this condition (1–18). It is very similar to *dup(9p) syndrome* (Fig. 4–27).

Fig. 4–27. *Teltrasomy 9p syndrome.* Note similarity to dup(9p). Infant also manifests Dandy-Walker cyst and Hirschsprung disease. (From MI Melaragno et al, Ann Genet 35:79, 1992.)



In addition to psychomotor and somatic retardation, the following have been found in 50% or more of cases: hypotonia, microbrachycephaly, hydrocephaly, wide sutures and fontanels, wide forehead, hypertelorism, enophthalmos, down-slanting palpebral fissures, epicanthal folds, strabismus, bulbous-beaked nose, low-set malformed pinnae, down-slanting mouth, retromicrognathia, and short neck. Approximately half the patients have cleft lip/palate (9a). Various congenital heart and urogenital anomalies have been reported in more than 80% of cases. Dysplastic finger nails, single palmar creases, and clinodactyly V are found in about 50%. Sacral dimple and redundant skin are common (14). The nipples are widely spaced.

References [Tetrasomy (9p) syndrome]

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del(9q) syndrome

Because only a few more than a dozen examples with various deletions of the long arm of chromosome 9 have been reported thus far, investigators have had difficulty in recognizing a distinct syndrome. Perhaps this situation will be resolved with the publication of more examples (1–4,7). The interstitial deletion reported by Ying et al (7) is unique.

Characteristics of del(9q) include frontal bossing with hypoplasia of supraorbital ridges, down-slanting palpebral fissures, epicanthic folds, and a short, flat nose. In addition to growth and mental retardation, hypotoniais frequent.

A dozen examples of r(9) have been reported, the features of which resemble those of *del(9p) syndrome:* mcrocephaly, a facies similar to that

of del(9p), flexion of major joints, ambiguous genitalia, hypospadias, inguinal hernia, and various cardiac defects.

Deletions of 9q have been noted in *Gorlin syndrome* (5).

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dup(9q) syndrome

Approximately 30 patients are known to have partial trisomy for various segments of the long arm of chromosome 9 (1–7). Mental retardation is severe in these patients, the relatively constant features being microdolichocephaly, deep-set eyes, prominent beaked nose, relatively large pinnae, overlapping upper lip, and microretrognathia (Fig. 4–28). Approximately 35% of those with tetrasomy for 9pter→q21–32 have cleft lip/palate.

The fingers and toes tend to be long. Flexion of fingers and/or limitation of joint mobility, dislocated hips, talipes equinovarus, hypoplastic genitalia, and congenital heart disease have also been found.

References [dup(9q) syndrome]

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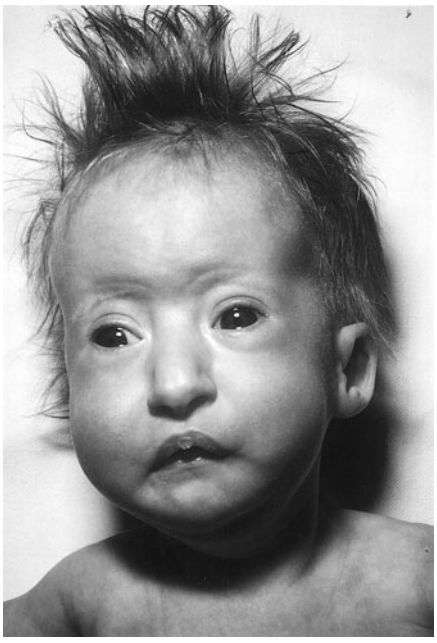
Fig. 4–28. *dup (9q) syndrome.* Microdolichocephaly, up-slanting small palpebral fissures, prominent beaked nose, short philtrum, microretrognathia. (From SF Aftimos et al, Am J Dis Child 134:848, 1980.)



Trisomy 9 syndrome

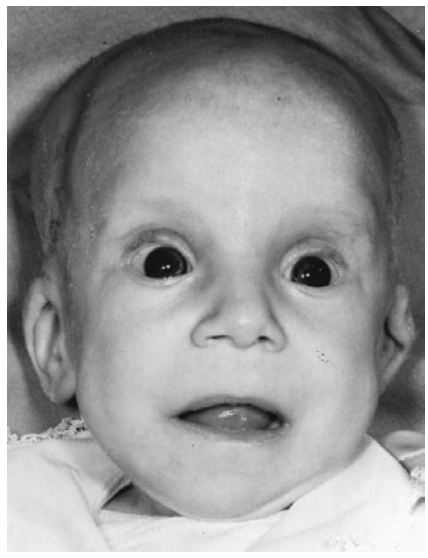
Trisomy 9 and trisomy 9 mosaicism do not appreciably differ in phenotype. All patients have psychomotor retardation. Most patients have low birth weight and/or failure to thrive and neurologic impairment, and most die before the fourth month of life (1–26); those with full trisomy 9 are not very viable. About 30 cases of trisomy 9 syndrome or trisomy 9 mosaicism have been reported. We suspect that one patient really had trisomy 8 (5).

Approximately 65% of patients exhibit microcephaly with narrow temples. The palpebral fissures are short in 75%. Microphthalmia and deep-set eyes are noted in 50% (8). In 70%, the nose is bulbous and prominent. Cleft lip/palate has been seen in 25% of patients (12–15,17,19,21,25). The ears are low set and/or malformed, the chin small, and the neck short or webbed (Fig. 4–29). Arhinia has also been found (8).

Musculoskeletal abnormalities are common: congenital dislocation of the hips or other joints, scoliosis, joint limitations or dysplastic hands and/or feet, rocker-bottom feet, and talipes. Congenital heart anomalies, seen in 60% of patients, include ASD, VSD, PDA, double-outlet right ventricle, and persistent left superior vena cava (6,9,13). Brain malformations have been noted in 65% of patients (18), with Dandy-Walker malformation constituting about one-quarter of these cases (24,26).

Urogenital abnormalities, noted in 65% of cases, include hydronephrosis, duplication of collecting system, cryptorchidism, micropenis, and hypospadias. The external genitalia of females are normal. Deep palmar and/or plantar creases occur frequently.

Fig. 4–29. *Trisomy 9 syndrome.* Microcephaly, dolichocephaly, and high forehead. Eyes are deeply sunken into the sockets. Palpebral fissures are up-slanting. Pinnae are dysmorphic.



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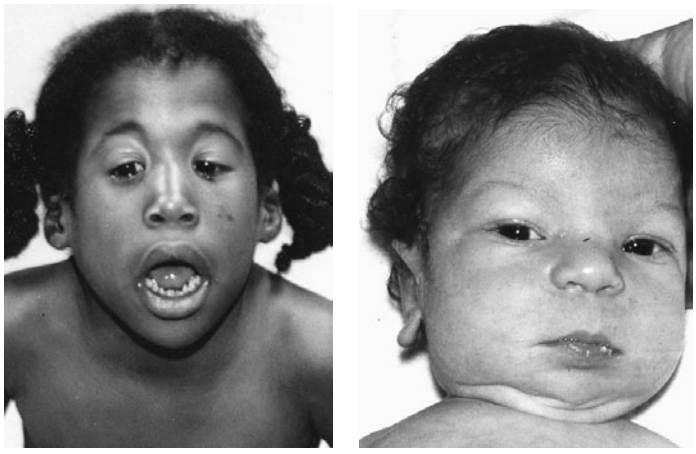
del(10p) syndrome

Less than 30 cases of this syndrome are known, about 75% of them being male (1–23). Several break points have been determined, most at 10p13, yielding various phenotypes. Nearly all have been de novo cases. Mental retardation is severe in all patients, and seizures occur in 20%. Postnatal growth retardation is a constant feature. About 40% of patients have died in infancy. The more constant facial features include microcephaly; frontal bossing; hypertelorism; short, down-slanting palpebral fissures; epicanthus; ptosis; strabismus; low nasal root with anteverted nostrils; small, low-set pinnae; prominent upper lip; micrognathia; and short neck (Fig. 4–30A). Cleft lip/palate has been reported in about 60% of cases (17,21,23).

The nipples are widely spaced in 60%. Various congenital heart anomalies have been found in about 60% of patients. Cryptorchidism, hernia, and renal abnormalities are noted in over 60%. Hypoplasia or aplasia of olfactory bulb and tracts have been found in those individuals with more proximal deletions (6). Various anomalies of the extremities have been noted in over 80%. Sensorineural hearing loss has been found in several patients (9,20). *DiGeorge anomaly* has also been noted (6,8,13–19,24). However, the facial features are different from those seen in 22q11 deletion. The nasal bridge is broad with very narrow palpebral fissures (15). There are two non-overlapping regions, the DiGeorge critical region II at 10p13–p14 and the hypoparathyroidism, sensorineural hearing loss, renal (HDR) region which is more telomeric at 10p14-pter. The GATA3 gene codes for a zinc finger transcript factor which is involved in vertebral skeletal development (24,25).

Ring chromosome 10 has no distinct phenotype.



A B

Fig. 4–30. *del(10p) syndrome.* (A) Narrow facies, low nasal root, anteverted nostrils, dysmorphic pinnae. dup(10p) syndrome. (B) Dolichocephaly with high, bulky forehead; wide, open, anterior fontanel; mild up-slanting palpebral fissures; prominent nasal bridge; small, triangular mouth; and micrognathia. [A from U Francke et al, Birth Defects 11(5):207, 1975. B from E Orye et al, J Genet Hum 33:63, 1985.]

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dup(10p) syndrome

Most examples of dup(10p) result from familial reciprocal translocation. Approximately 50 cases have been reported (1–11) with early death occurring in 25% of these patients. This syndrome is marked by severe mental and motor retardation with little or no speech. Birth weight is usually normal. Infants are often dolichocephalic (30%) with a high prominent forehead and wide open sutures and anterior fontanel (30%). Palpebral fissures have a slightly downward slant. The eyebrows are highly arched (30%), and hypertelorism is present in about 50% of patients. The maxilla tends to protrude. The nasal root, initially broad, becomes prominent in older patients and the mouth becomes triangular with a thin inverted upper lip (45%) (Fig. 4–30B). Cleft lip/palate has been noted in over 30%. The ears are often low set and somewhat angulated (75%). Elbows, wrists, and fingers are often hyperextensible (35%). Flexion deformities of fingers and toes and clubfeet are common (20%). The kidneys tend to be cystic. For various other anomalies, see Stengel-Rutkowski et al (10), Lurie et al (6), and Kozma and Meck (4).

References [dup(10p) syndrome]

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del(10q) syndrome

About 30 cases of terminal deletion have been reported (1–19), of whom about 25% died in the neonatal period. More females than males may be affected. In addition to severe mental and growth retardation, there are a few relatively nonspecific facial features of del(10q): microcephaly, brachycephaly, prominent beaked nose, apparent hypertelorism, down-slanting palpebral fissures, strabismus, deep-set eyes, malformed pinnae, bow-shaped upper lip, and short neck. Cleft lip has been noted (9).

In about a dozen cases of interstitial deletion, in addition to psychomotor retardation and hypotonia, unusual pinnae, hypertelorism, and VSD occurred (7).

A Prader-Willi-like phenotype (hypotonia, typical facies, hypogenitalism) may be seen in infancy with hyperactive behavioral pattern adolescence (7a). There is no obesity and no hyperphagia.

References [del(10q) syndrome]

1. Chung YP et al: Prenatal diagnosis of monosomy 10q25 associated with single umbilical artery and sex reversal. Prenat Diagn 18:73–77, 1998.
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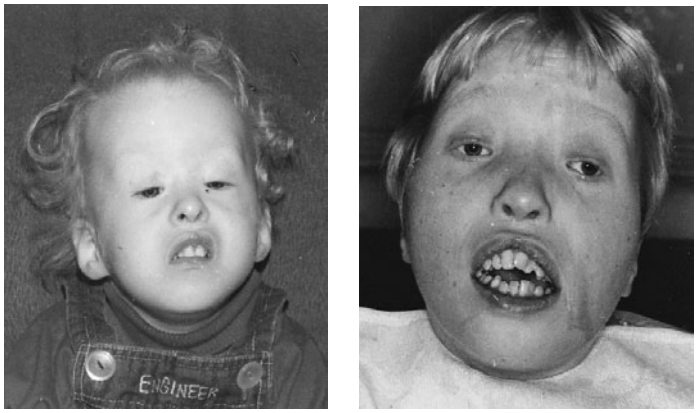
dup(10q) syndrome

Over 90% of cases of dup(10q) have resulted from a balanced translocation in a parent. A significant majority are male. The prognosis is poor with death occurring prior to the age of 4 years in approximately half the cases, largely because of cardiac, renal, or respiratory complications. Those who survive are severely retarded (12).

Duplication of 10q11–q22 produces a distinct phenotype: mental and somatic retardation, microcephaly, deep-set eyes, strabismus, small



A B

Fig. 4–31. *dup (10q) syndrome*. (A,B) Large forehead, round face, arched eyebrows, small palpebral fissures, hypertelorism, and bow-shaped mouth. (A courtesy of S Cho, Wichita, Kansas. B from S Kröyer and E Niebuhr, Ann Genet 18:50, 1975.)

upturned nose, short prominent philtrum, bowed mouth, and thick ear helix (2,4,11).

Trisomy (10q25→qter) produces a rather distinctive clinical picture: severe mental retardation, pre- and postnatal growth retardation, marked hypotonia, microcephaly, large, high forehead, somewhat flattened round face, fine arched eyebrows, narrow palpebral fissures, epicanthus, microphthalmia, flat nasal bridge, small short nose with anteverted nostrils, prominent cheek bones, bow-shaped mouth with prominent upper lip, small mandible, and low-set malformed pinnae (Fig. 4–31). About 35 cases have been reported (1,2a,3,5–10,12).

About 50% of patients exhibit ptosis, cleft palate, and long philtrum. Bilateral epicanthal folds create an illusion of hypertelorism, whereas reduced corneal diameter may simulate microphthalmia.

Anomalies of the hands and feet include camptodactyly, proximally implanted thumbs and/or great toes with a wide space between the hallux and second toe, overlapping and/or fusiform fingers, and rocker-bottom feet. Deep plantar furrows have been noted in over one-third of patients. At least half of the males exhibit cryptorchidism. Various congenital heart defects have been found. Delayed bone age, scoliosis, and thin ribs are noted in about one-third of patients. Various kidney abnormalities include hypoplasia, cystic alterations, hydronephrosis, and hydroureter.

References [dup(10q) syndrome]

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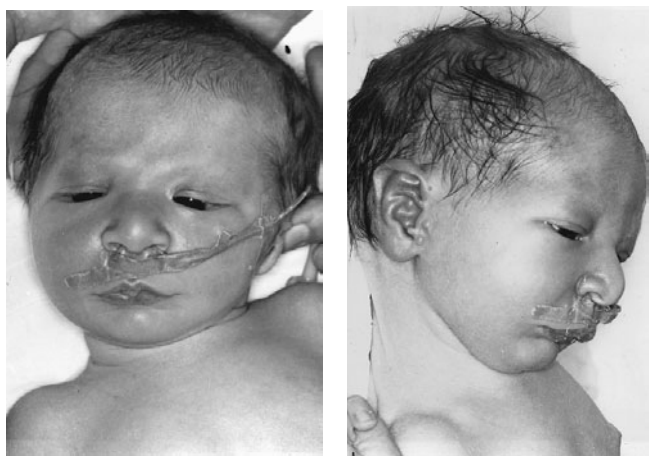
Unbalanced 11/22 translocation

This disorder, caused by unbalanced segregation of a translocation rcp(11;22)(q23;q11), is the most frequent non-Robertsonian balanced rearrangement in humans.

Mental deficiency is severe to profound. Survival is reduced, with at least 50% of liveborn patients not surviving the first 3 years. There is a tendency toward stereotypic movement, seizures, and autistic behavior (1,3,5). Causes of early death include cardiac failure, brain malformations, seizures, and infections. The clinical features overlap partly with those of *cat eye syndrome* [tetrasomy for (22)(pter→q11)] and (mosaic) trisomy 22. The facies is characterized by a broad and flat nose, long and well-marked philtrum, marked micrognathia, and abnormal pinnae. Preauricular pits, tags, or both, long narrow dysmorphic pinnae, and, less commonly, severe microtia with atresia or absence of the external canals are seen (Fig. 4–32). Severe conductive hearing loss or sensorineural hearing loss are common. Male genital hypoplasia with micropenis, small scrotum, and cryptorchidism is also found. Other malformations include cleft palate (>50%), heart defects (at least 50%), anal atresia with fistula, renal malformations, hypoplasia of diaphragm, intestinal malrotation, 13 pairs of ribs, bipartite clavicles, and cerebral malformations. In contrast to *cat-eye syndrome* and *trisomy 22,* coloboma of the iris does not occur in this disorder.

Karyotypes reveal an extra marker chromosome smaller than a 22 and with different staining qualities of the distal long arm. One parent, nearly always the mother, has an identical marker replacing a 22 and an abnormal 11 with an elongated long arm. The translocation is reciprocal, with break points probably at 11q23 and 22q11, and thus the unbalanced products are trisomic for a segment of 11(q23→qter) and a centromere-containing segment of 22(pter→q11). Unbalanced 2:2 segregations obviously do not survive in utero. The translocation is frequent and occurs in all populations and races. Family studies following the detection of a chromosomally unbalanced patient usually show multiple balanced carriers in several generations. There is also an excess of reproductive loss in these families.

Fig. 4–32. *Unbalanced 11/22 translocation.* (A,B) Atresia of auditory meatus, preauricular tags and pits, cleft palate, micrognathia, and torticollis. (From M Fraccaro et al, Hum Genet 56:21, 1980.)



A B

References (Unbalanced 11/22 translocation)

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del(11p) syndrome (Potocki-Shaffer syndrome)

Shaffer et al (4) reported that proximal deletions at 11p11.2p12 produce a phenotype that includes multiple cartilaginous exostoses, mental retardation, brachycephaly, biparietal foramina, large fontanels, craniosynostosis, and minor facial anomalies (ptosis, epicanthic folds, short philtrum, downturned upper lip) (1–4). This deletion involves EXT2 and appears to be contiguous. Loss of functional mutations of the homeobox gene *ALX4* is responsible for the syndrome (2).

For a more complete description of this syndrome, see *enlarged parietal foramina, craniofacial anomalies, mental retardation, and multiple exostoses (Potocki-Shaffer syndrome, del11p11.2p12 syndrome)* in Chapter 25.

References [del(11p) syndrome (Potocki-Shaffer syndrome)]

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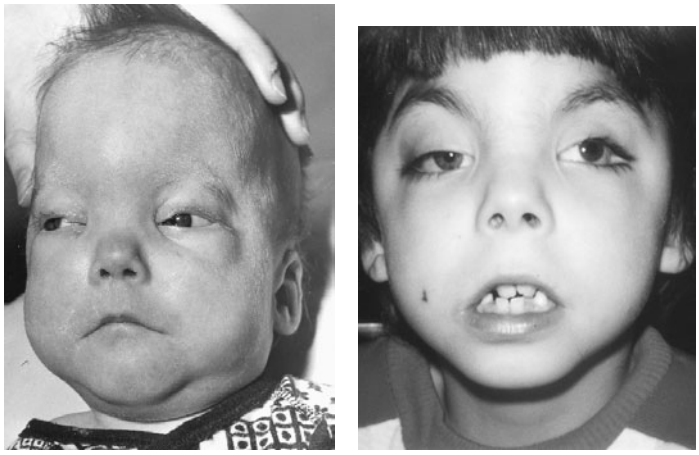
del(11q) syndrome (Jacobsen syndrome)

Patients with the most common del(11)(q23→qter) have exhibited mental retardation. This deletion is of a folate-sensitive site. Most 11q deletions are de novo deletions of paternal origin (11). At least 75 cases of del(11q) have been reported. Other deletions have been reviewed by Herz et al (7). A few individuals have been small for gestational age, but nearly all have poor postnatal growth. About 60% of patients have exhibited postnatal somatic retardation. Most have manifest frequent respiratory infections. About 25% die before 2 years of age, usually from congenital heart disease (1–18).

The facies is characterized by trigonocephaly (85%), hypertelorism (80%), microcephaly (60%), flat occiput (40%), deep-set short nose (100%), abnormally modeled pinnae (95%), carp mouth (95%), and micrognathia (90%). Eye anomalies have included intermittent strabismus, up-slanting palpebral fissures (75%), ptosis (85%), epicanthus (75%), hypertelorism (80%), and coloboma of iris (35%) (11,16) (Fig. 4–33).

Various congenital heart anomalies (VSD, single ventricle, ASD) (65%), joint contractures (camptodactyly, hammer toes) and/or minor digital anomalies (70%), and single flexion creases (65%) have been found. Systemic anomalies are unusual (17). About 40% of patients have exhibited isoimmune thrombocytopenia and recurrent infections (13). Some have giant platelet alpha granules (1). For unusual findings, see Hustinx et al (8).



A **B**

Fig. 4–33. *del(11q) syndrome (Jacobsen syndrome).* (A) Trigonocephaly, flat broad nasal bridge, carp mouth, epicanthal folds, mildly dysmorphic pinnae, hypertelorism, mild colobomas of eyelids, and micrognathia. (B) Trigonocephaly, hypertelorism, down-slanting palpebral fissures, epicanthic folds, short nose with anteverted nares, broad bridge, and "carp-shaped" mouth. (A from I Felding and F Mitelman, Acta Paediatr Scand 68:635, 1979. B from MG Obregon et al, Ann Genet 35:208, 1992.)

del(11q) syndrome shows clinical similarity with *Opitz trigonocephaly (C) syndrome.*

References [del(11q) syndrome (Jacobsen syndrome)]

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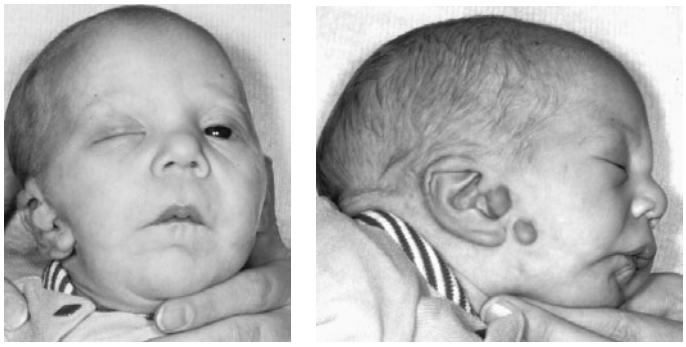

A B

Fig. 4–34. *dup(11q) syndrome.* (A,B) Facial asymmetry, epicanthal folds, ear tags, retracted lower lip.

17. Sirota L et al: New anomalies found in the 11q- syndrome. Clin Genet 26:569–573, 1984.
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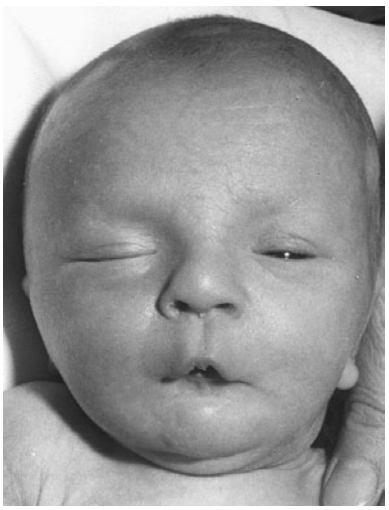
dup(11q) syndrome

In most cases, dup(11q) is associated with 11q/22q translocation, and is inherited in nearly all cases through the carrier mother and has a recurrent risk of 2%–6% (3,7). The frequency of this disorder appears to be far higher than estimated. There is also a group of cases representing dup(11q), most often 11q23→11qter (1,2,4–6,8–10). Although the first group may include trisomy for a small portion of 22q, the phenotypic overlap with the second group is marked.

Reduced birth weight and postnatal growth are nearly constant features. Mental retardation, ranging from low normal to moderate, is present in all cases. Hypertonia is found in about 50%.

Craniofacial asymmetry and microcephaly are present in 35% of affected individuals. Inconstant features include hypertelorism, epicanthal folds, and down-slanting palpebral fissures. The nose is short with a long philtrum. About 85% have low-set pinnae and preauricular (usually bilateral) ear tags or pits. The lower lip is usually retracted and the mandible small. Cleft palate has been found in 60% of patients (2–5) (Figs. 4–34 and 4–35). The neck may be short.

Fig. 4–35. *dup(11q) syndrome.* Hypertelorism, broad flat nasal bridge, small mouth, retracted lower lip, micrognathia, and short neck. (From HD Rott et al, Humangenetik 14:300, 1972.)



Genitourinary anomalies include imperforate anus or anal atresia (15%), associated with a fistula into the bladder, vestibule, or perineum. Cryptorchidism occurs in 35% of patients with micropenis occurring in 85%.

Musculoskeletal anomalies include bipartite clavicular defect and dislocation or dysplasia of the hips (30%). Inguinal or umbilical hernia has been described in 30%. Congenital heart anomalies, found in 60% of patients, are variable and nonspecific.

References [dup(11q) syndrome]

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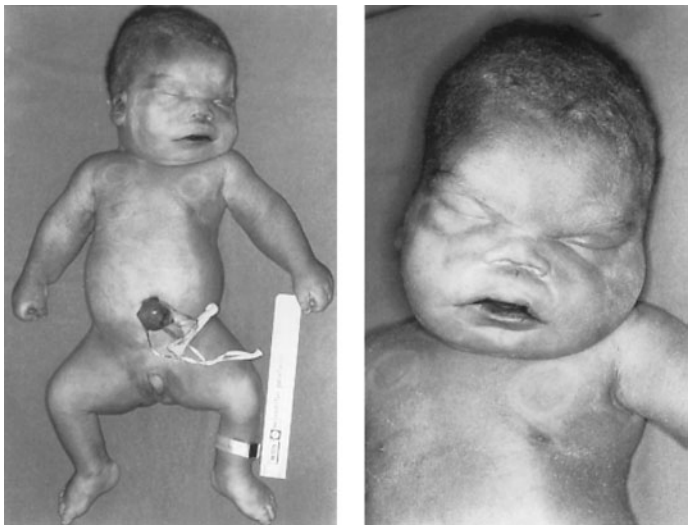
Pallister-Killian syndrome (mosaic tetrasomy 12p, isochromosome 12p syndrome)

Pallister et al (13) in 1977 and Killian et al (8) in 1983 independently described a syndrome consisting of profound mental retardation, coarse facies, localized alopecia, pigmentary skin anomalies, supernumerary nipples, diaphragmatic hernia, and cardiovascular anomalies. It is caused by isochromosome, i.e., tetrasomy 12p. The isochromosome is usually of maternal origin (27,30). Hexasomy produces the same phenotype (31). It should be pointed out that tetrasomy 12p ranges from classic Pallister-Killian syndrome to mild learning disability with pigmentary skin changes (23).

Although peripheral lymphocytes are usually normal, cultured fibroblasts, direct bone marrow analysis, and other soft tissues (33) will show the chromosome marker, but it may be lost in long-term culture (16) and with age (18,33). It may be diagnosed in amniocytes (16,25,28) or on chorionic villus sampling (3). Buccal smear of patients by means of FISH is effective in diagnosis (9a,12). A phenocopy has been reported (22). Mothers of affected infants tend to be older (34).

Birth weight is normal. Polyhydramnios is not rare (21,34,37). In infancy, the hair is sparse and fine, particularly in the frontal and temporal areas, extending to the vertex. With age, hair distribution becomes normal. Hypopigmented areas of the skin have been noted, reflecting mosaicism. The facies is coarse at birth and becomes more markedly so with age. The forehead is high and the metopic skin and eyelids are puffy (6). Eyebrows and eyelashes are sparse medially. Mosaic retinal pigmentation has been noted (14). Ptosis, strabismus, and hypertelorism also occur. The nose is short with a flat nasal bridge and anteverted nostrils, and the pinnae are fleshy. Hearing loss has been documented in nearly all patients. The philtrum is long and prominent; the mouth is large and downturned. The upper lip is thin and has a cupid-bow shape, and the lower lip protrudes. Clefting of the lip or palate is rare (10,11,24). The mandible is small and dental eruption is delayed. The neck is very short and often webbed with excess nuchal skin (Figs. 4–36 and 4–37). There is some phenotypic overlap with *Fryns syndrome* (11,21). The adult phenotype is one of severe retardation, epilepsy, coarse, flat facies, mandibular prognathism, macroglossia, hypertonia, and contractures (5,18).



A B

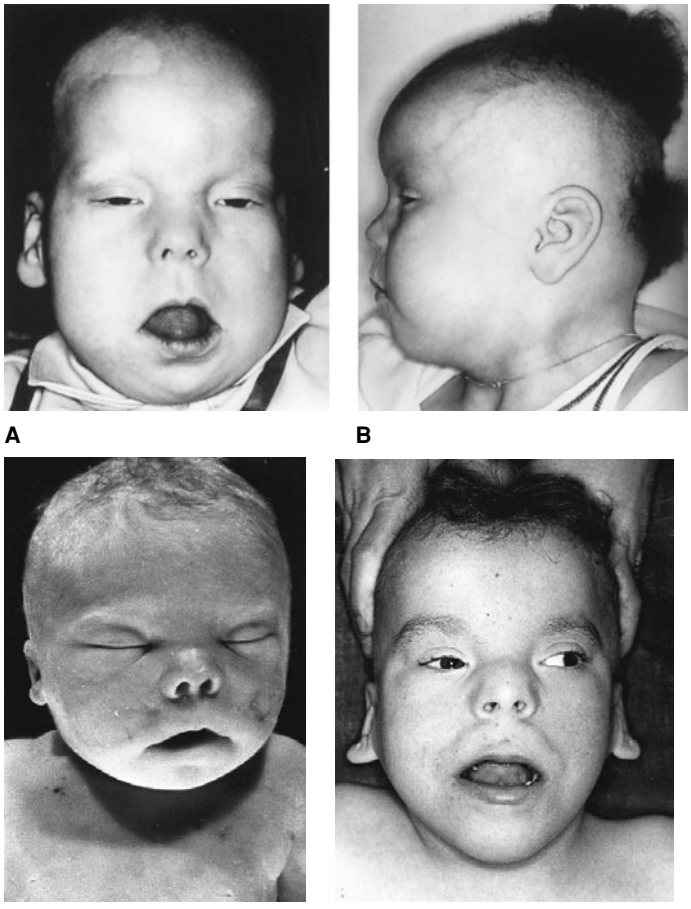
Fig. 4–36. *Pallister-Killian syndrome.* Tetrasomy i(12p). (A) Note altered body proportions and multiple depigmented areas. (B) Short depressed nasal bridge, prominent premaxilla, and large mouth. (From L Shivashankar et al, Prenatal Diagn 8:85, 1988.)

Developmental retardation is profound; speech is not attained. Neonatal asphyxia and death are frequent. Bone age is retarded. Postnatal growth deficiency and natal gigantism have been reported (20). Pineal tumor has been documented (9b). Marked hypotonia, hypermobile joints, and areflexia have been noted in infancy, but these improve with age (20). Pineal tumor has been documented (9b). Talipes has also been observed (4). Supernumerary nipples are a common finding.

Several children have had unexplained fever. Increased height of the vertebral bodies, mild thoracic scoliosis, and atlanto-occipital fusion have been documented (21,29,36). Cardiovascular anomalies, most frequently VSD, are found in about 25% of patients. Diaphragmatic hernia, which may be lethal, has been reported (15,21,32,36). Imperforate anus, anal atresia, or anteriorly displaced anus has been reported in several infants (4,24). The limbs and fingers tend to be short and there is often a sacral dimple (15,32–34). The thumb may be proximally inserted and the hallux may be large (7). Hexadactyly has been noted (14).

FISH has been used to confirm the identity of the chromosome (25,26). Fibroblast analysis is the best means of diagnosis, since the isochromosome tends to disappear with age (17,33). Maternal age effect is a factor in development of Pallister-Killian syndrome (34). Partial duplication of 12p is associated with a much milder phenotype (1,2,19).

Prenatal diagnosis has been made on nuchal translucency (8a).



A B C D

Fig. 4–37. *Pallister-Killian syndrome.* (A,B) Fine, sparse hair, particularly on frontal and temporal areas. Facies coarse. Note hypopigmented area of scalp, high forehead, eyebrows, medially sparse eyelashes, short nose with flat bridge and anteverted nostrils, downturned mouth, and thin upper lip. (C) Note similarity in facies to that of Fryns syndrome. (D) Observe microcephaly, ptosis, strabismus, flat wide nasal bridge, short upturned nose, prominent philtrum, dysplastic pinnae with upturned lobes. (A,B,D from W Killian et al, J Clin Dysmorphol 1(3):6, 1983. C from J Rodriguez, Am J Med Genet 53:176, 1994.)

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del(14q) syndrome

Most cases of del(14q) have ring chromosomes. Break points at 14q32 are most common. About 50 examples have been reported. There is a 2:1 female predilection. The main features include microcephaly with flat occiput, high forehead with lateral hypertrichosis, epicanthic folds, downward-slanting palpebral fissures, narrow elongated face, short, narrow palpebral fissures, flat nasal bridge, large, low-set pinnae, micrognathia, and short neck (Fig. 4–38A). Retinal dystrophy, seen in about 50% of cases, may be specific (hyperpigmentation and yellow-white spots of the macula) (1–12).

Mental retardation, hypotonia, and seizures are severe as are prenatal and postnatal growth retardation. The lateral ventricles are moderately enlarged. Ring 14 syndrome is compatible with extended survival but recurrent respiratory infections are common. Lymphedema of the hands and feet is not rare (2) (Fig. 4–38B).

References [del(14q) syndrome]

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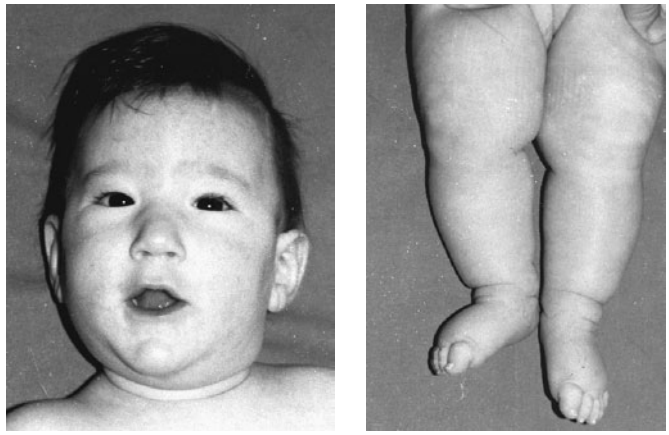

A B

Fig. 4–38. *del(14q) syndrome.* (A) Microcephaly, narrow palpebral fissures, flat nasal bridge. (B) Lymphedema of lower extremities. (From L Zelante, Ann Genet 34:93, 1991.)

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dup(14q) syndrome

In addition to mental retardation and pre- and postnatal growth retardation, this syndrome is characterized by a large face, chubby cheeks, facial asymmetry, hypertelorism, broad nose, short prominent philtrum, carp mouth, posteriorly rotated pinnae with prominent antitragus, and micrognathia (1–10). Cleft palate has been found in at least 50% of cases (1,3,4,9) (Fig. 4–39A)

The nipples are high and widely spaced. Males exhibit hypogenitalism. Brain, lung, and congenital heart defects are common.

References [dup(14q) syndrome]

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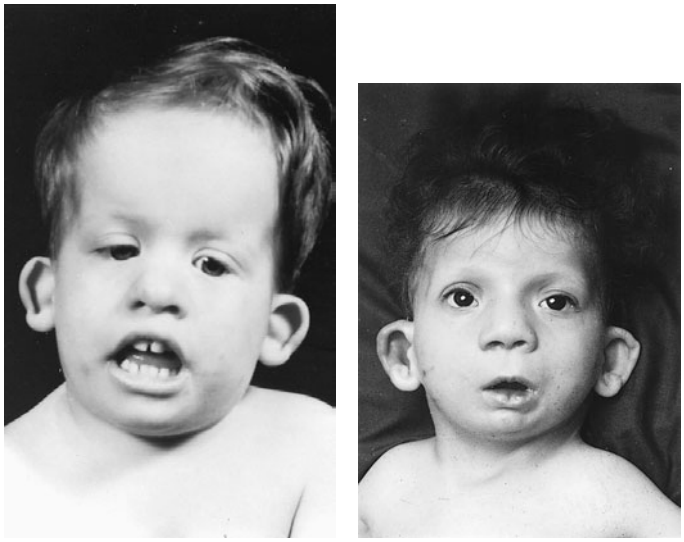

A B

Fig. 4–39. *dup(14q) syndrome.* (A) Microcephaly, broad flat nose with bulbous tip, down-slanting palpebral fissures, short philtrum with arched upper lip and downturned mouth. *Trisomy 14 mosaicism syndrome.* (B) Hypertelorism, broad saddle nose, asymmetric palpebral fissures, outstanding dysmorphic pinnae, long philtrum, micrognathia. (A from JQ Miller et al, J Med Genet 16:60, 1979. B from JD Murken et al, Humangenetik 10:254, 1970.)

Trisomy 14 mosaicism syndrome

Although trisomy 14 has been reported in abortuses, all living examples have been mosaic. About 20 examples have been reported. Polyhydramnios is frequent. Although weight is normal, postnatal growth and psychomotor development are severely retarded.

Prominent forehead, hypertelorism, wide nasal bridge and broad nose, narrow palpebral fissures, prominent maxilla, long philtrum, large mouth, thick lips, dysmorphic low-set pinnae, micrognathia, and short neck are characteristic. A number of patients have cleft palate (1–4,7,9,10,12) (Fig. 4–39B). This syndrome is similar in features to *dup(14q) syndrome.* Several patients have exhibited reticular hyperpigmentation of the skin, reflecting mosaicism. Body and facial asymmetry have been seen in about one-third of patients. Congenital heart anomaly, particularly tetralogy of Fallot, is found in nearly all examples (5,11,13). Micropenis and cryptorchidism are constant features in males (3).

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Uniparental disomy 14

There have been only a few examples of this very rare condition. Paternal and maternal uniparental disomy 14 differ in clinical findings.

Paternal disomy 14. In three of four examples of paternal isodisomy 14, polyhydramnios was observed. The facies was characterized by hirsute forehead, blepharophimosis, protruding philtrum, puckered lips, small pinnae, and small mandible. A webbed neck was seen in two of four examples. The thorax tended to be small with abnormal ribs. Other findings included ventral wall hernia, short extremities, and digital contractures (2,5,9,10).

Maternal disomy 14. Maternal uniparental disomy 14 is characterized by a phenotype of variable severity, including short stature, arrested hydrocephalus, small hands, scoliosis, mild developmental delay, and precocious puberty (1,3,4,6–8).

There is no evidence that uniparental disomy 14 is a cause of intrauterine growth retardation (4a).

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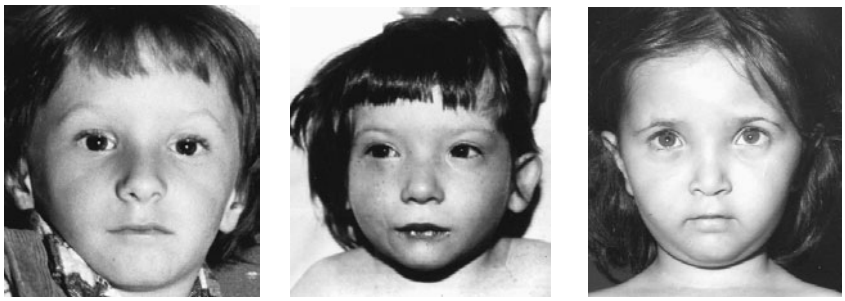
del(15q) syndrome

Deletion of the long arm of chromosome 15 usually results in a ring. At least 30 patients have been described (1–15).

In the young patient, the most characteristic findings include prenatal growth retardation (100%), short stature (100%), variable mental retardation (95%), microcephaly (85%), hypertelorism (45%), a triangular face resembling that of *Silver-Russell syndrome* (40%) (12), and limb anomalies including delayed bone age (75%), brachymesophalangy (45%), clinodactyly of the fifth fingers, and thumb hypoplasia. About 30% of patients have congenital heart anomalies. Café-au-lait spots are found in 30% of patients (Fig. 4–40).

During the adult years, severe mental and somatic retardation become evident. The forehead is bossed (35%), the face triangular (40%), and the pinnae anomalous (30%); the nose has a high bridge. Males are hypogonadal.



A B C

Fig. 4–40. *del(15q) syndrome.* (A) Patient having triangular face somewhat resembling that of Russell-Silver syndrome. (B,C) Note similar facies. (A from MG Butler et al, Am J Med Genet 29:149, 1988. B from E Yunis et al, Hum Genet 57:207, 1981. C from E Ferrante et al, Min Pediatr 29:2163, 1977.)

References [del(15q) syndrome]

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dup(15q) syndrome

Most examples of dup(15q) have resulted from unbalanced translocation (1–13). About 30 cases have been described.

Microdolichocephaly, occasionally hydrocephaly, narrow or short and downward-slanting palpebral fissures, bulbous nose, malformed pinnae, long philtrum, cleft palate, and micrognathia characterize the facies of trisomy for the proximal long arm of chromosome 15 (1,8,9,13) (Fig. 4–41). Other investigators deny any predictable phenotype (2,7).

Those individuals with distal 15q trisomy exhibit microcephaly with sloping forehead, facial asymmetry, down-slanting and short or narrow palpebral fissures, ptosis, prominent nose with broad bridge, long philtrum, downturned mouth, highly arched palate, midline crease of the lower lip, puffy cheeks, micrognathia, and short neck (10,11) (Fig. 4–42). Postnatal growth deficiency, scoliosis, pectus excavatum, cryptorchidism, arachnodactyly, camptodactyly, hyperextensible thumbs, and cardiovascular anomalies are relatively common. Severe mental retardation is constant and hypotonia is frequent. Seizures are noted in 30% of patients.

An example of complete trisomy 15 has been described (4).

References [dup(15q) syndrome]

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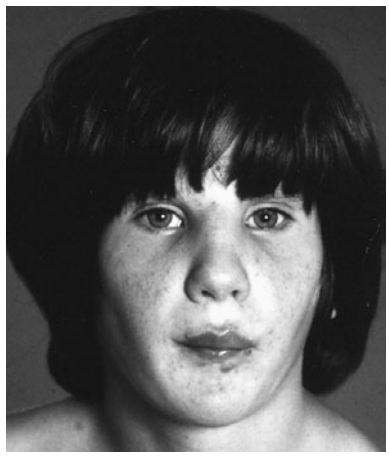
Trisomy and tetrasomy 15 mosaicism syndromes

An extremely rare and essentially lethal condition, trisomy 15 mosaicism is characterized by symmetrical growth retardation, distinct craniofacies, congenital heart anomalies, severe hypotonia, and minor skeletal anomalies (1,3–8). The facies has a low hair line, hypertelorism, broad nasal bridge, short bulbous nose, long philtrum, small mouth, dysmorphic pinnae, small mandible, and short neck.

Fig. 4–41. *dup(15q) syndrome.* Duplication of proximal chromosome 15. Patient has mental retardation, microcephaly, flat nasal bridge, cleft palate, small mouth, and micrognathia. (From G Annerén and KH Gustavson, Clin Genet 22:16, 1982.)



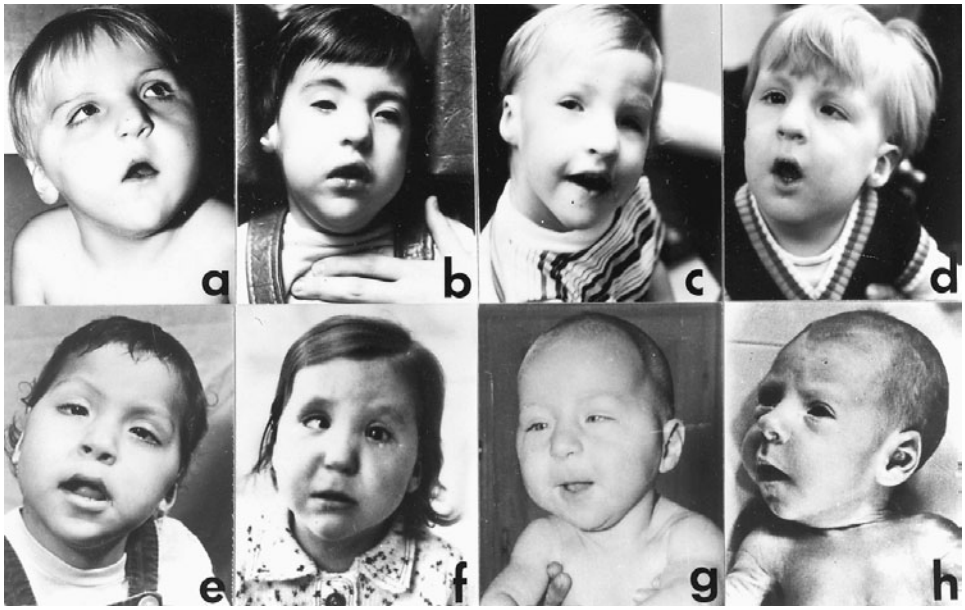


Fig. 4–42. *dup(15q) syndrome. Duplication of distal chromosome 15.* (A–H) Note facial asymmetry, narrow down-slanting palpebral fissures, ptosis, prominent nose, long philtrum, downturned mouth, and puffy cheeks in eight reported patients. (From P Schnatterly et al, Am J Hum Genet 36:444, 1984.)

Mosaic tetrasomy 15, usually the result of isochromosome formation, is even rarer than mosaic trisomy 15 (2,9).

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inv dup(15) syndrome

The inv dup(15) syndrome is caused by an extra marker chromosome, which is cytogenetically defined as inv dup(15)(pter→q12–13→pter) and, by FISH analysis, includes the Prader-Willi and Angelman syndromes' critical regions. The extra chromosome is maternally derived (8). When the critical region is included, there appears to be an abnormal phenotype.

In addition to developmental delay and moderate to severe mental retardation, features of this syndrome include seizures, diffuse hypotonia, and peculiar behavior such as lack of social interaction, absent or poor echolalic language, and nonfunctional use of objects (1–7). Affected individuals also have down-slanting palpebral fissures, epicanthic folds, low-set pinnae, coarse face, and multiple hypopigmented areas of the skin (1–7).

References [inv dup(15) syndrome]

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dup(16p) syndrome

Although trisomy 16 is the most frequent chromosome anomaly found in abortuses, the anomalies are quite lethal, and only a few examples of trisomy 16p are known (1–8). Anomalies include severe developmental delay, round face, prominent glabella, hypertelorism, narrow palpebral fissures, scant brows and lashes, broad, depressed nasal bridge, anteverted nares, long philtrum, thin vermilion of upper lip, cleft palate, micrognathia, severe mental retardation, and growth delay (1–8). Congenital heart anomalies were found in 50% of patients (1,2). The skin is loose in about 50% of patients (5). The thumbs are abnormally placed.

References [dup(16p) syndrome]

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del(16q) syndrome

Over 25 examples of interstitial and terminal deletions of the long arm of chromosome 16 have been reported (1–15). It has been shown that 16q21 must be deleted for the typical syndrome changes to occur (12).

The phenotype is characterized by mental retardation (100%), low birth weight (50%), delayed growth and development (90%), feeble suck (100%), and hypotonia (100%). The distinct craniofacies includes microcephaly (70%), high forehead (70%), prominent metopic suture (65%), large anterior fontanel with or without wide cranial sutures (100%), short, up-slanting palpebral fissures (40%), hypertelorism (60%), small, upturned nose with flat bridge (70%), low-set folded helices (100%), micrognathia (65%), and short neck (65%). Cleft palate has been described (11), as well as natal teeth (4) (Fig. 4–43A,C).

Diverse musculoskeletal anomalies [narrow thorax (50%), small hands and feet (50%), talipes, umbilical hernia, polydactyly, flexed fingers, broad halluces (80%)] have been reported (Fig. 4–43B). Cardiac anomalies [coarctation of aorta, VSD (40%)], renal anomalies [cystic dysplasia (35%)], and intestinal anomalies [ectopic anus, malrotation (35%)] anomalies have also been described.

References [del(16q) syndrome]

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dup(16q) syndrome

Trisomy 16 is the most common trisomy among spontaneous abortions during the first trimester, thus there are only a few known liveborn examples (2,4,9,10).

In addition to low birth weight and severe psychomotor and mental retardation, common features of dup(16q) include round face, high forehead, frontal bossing, prominent glabella, hypertelorism, depressed nasal bridge, round nasal tip with anteverted nostrils, low-set small pinnae, prominent maxilla, asymmetric skull, small palpebral fissures, hypertelorism, malformed long philtrum, hypertrichosis, flexion contractures, cryptorchidism, VSD, and foot deformities (1,3,5–7). Breast asymmetry has been noted (8). Early death is common.

References [dup(16q) syndrome]

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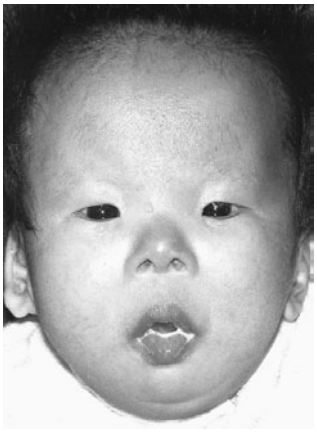

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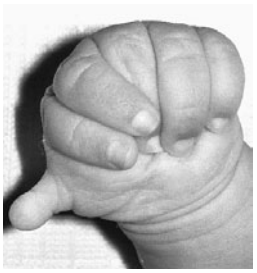

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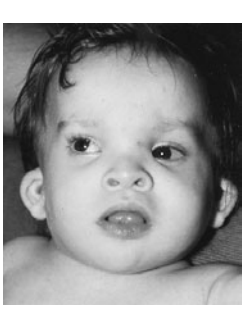

C

Fig. 4–43. *del(16q) syndrome.* (A) High forehead, large anterior fontanel, narrow palpebral fissures, small upturned nose, malformed pinnae, and short neck. Child had cleft palate. (B) Polydactyly and overlapping flexed fingers. (C) High forehead, strabismus, hypertelorism, dysmorphic pinnae. (A,B from CC Lin et al, Hum Genet 65:134, 1985. C from FFB Elder, Hum Genet 67:233, 1984.)

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Trisomy 16 and partial trisomy 16

Trisomy 16 is the most common trisomy among spontaneous abortions during the first trimester, but there are relatively few liveborn examples (2–4,8,9).

In trisomy 16p, in addition to low birth weight and severe psychomotor and mental retardation, common features include dolichocephaly, round face, frontal bossing, prominent glabella, hypertelorism, depressed nasal bridge, round nasal tip with anteverted nostrils, low-set pinnae, high palate, prominent maxilla, micrognathia, and short neck. Atrial septal defects and tetralogy of Fallot have also been observed. Various other features include scoliosis, talipes, clinodactyly, and camptodactyly.

In trisomy 16q, common features include low birth weight, psychomotor retardation, low-set small pinnae, asymmetric skull, high forehead, small palpebral fissures, hypertelorism, flat nasal bridge, malformed long philtrum, high palate, hypertrichosis, flexion contractures, hypospadias, cryptorchidism, ASD, VSD, PDA, and foot deformities (1,2,5–7). Sacral dimple has been noted. Early death is common.

Single umbilical artery and umbilical hernia have been noted in both trisomy 16p and 16q.

References (Trisomy 16 and partial trisomy 16)

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Smith-Magenis syndrome [del(17p11.2)]

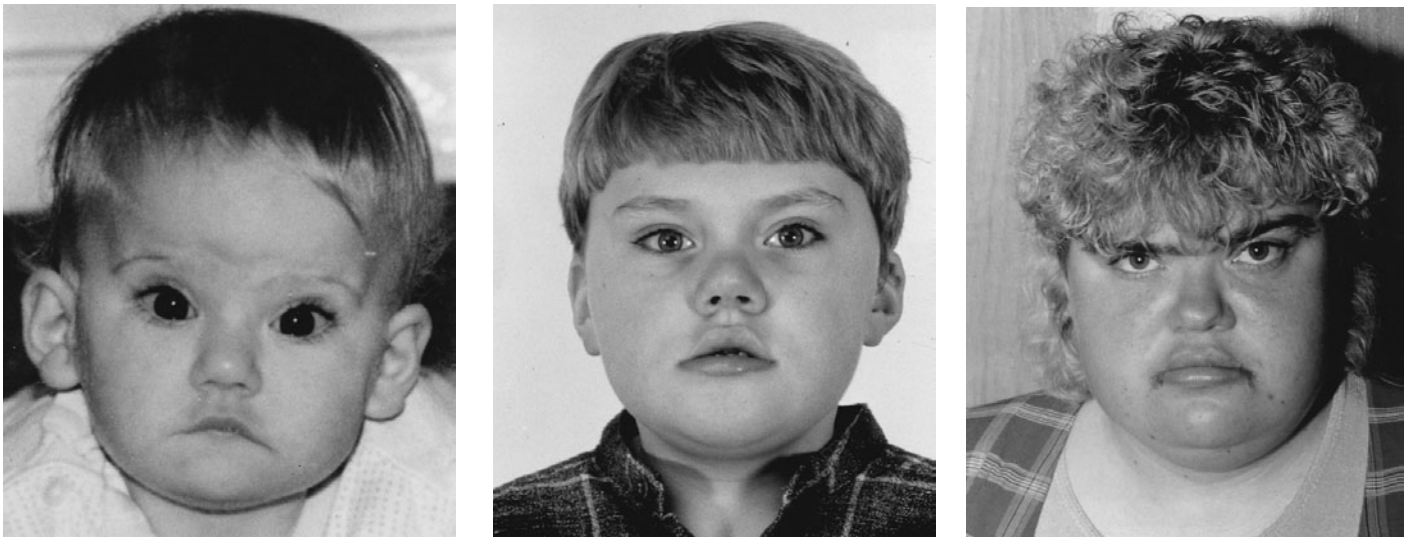
Smith-Magenis syndrome, or interstitial del(17p11.2), is characterized by growth retardation, mental deficiency, typical behavior abnormalities, and a relatively nonspecific combination of congenital minor or, occasionally, major anomalies. At least 100 patients with this syndrome have been described (16). Incidence has been estimated at 1 in 25,000 births (8).

The face is distinctive, even in the young child (1): there is brachycephaly (85%), a broad, square face with frontal bossing, flat midface, prominent chin, synophrys and lateral extension of eyebrows, telecanthus, epicanthic folds, up-slanting palpebral fissures, deep-set eyes, strabismus, Brushfield spots, myopia, retinal detachment, depressed nasal root, broad nasal base, full nasal tip, wide mouth with downturned corners, full lips, short philtrum with tenting, prominent lower jaw, and midface hypoplasia (2–4,6,7,12,13,15–17) (Fig. 4–44). Cleft lip/palate is found in 10% of patients. The external ears are misshapen and posteriorly angulated. Large ears, small ears, prominent ears, asymmetric ears, or thick helices have been noted. At least 65% of affected individuals have conductive hearing loss, and about 35% have sensorineural loss (7). Repeated middle ear infections are frequently reported. An excellent facial anthropometric study is that of Allanson et al (1).

The hands are broad with short fingers and fifth finger clinodactyly. Fingertip pads are often present (11). A characteristic metacarpophalangeal pattern has been discerned (11). The feet are flat with syndactyly between toes 2 and 4. Scoliosis, seen in 65% of patients, increases with age. Heart anomalies and renal malformations, especially duplication of collecting system, are found in about 35% (9).

Mental deficiency varies from moderate to, more often, severe. Speech is disproportionately delayed (95%), and the voice is hoarse or deep in 80% of cases. A constant pattern of behavioral abnormalities is characterized by low tolerance of frustration, sudden changes of mood, hyperactivity, distractibility, self-injury, irritability, sleep disturbance, impulsive, violent, and aggressive behavior, bruxism, reduced REM

Fig. 4–44. *Smith-Magenis [del(17p11.2)] syndrome*. (A–C) Facies in individuals of different ages. Overall shape is broad and square, brows are heavy with lateral extension of eyebrows, upslanting palpebral fissures, deep set nose with scooped bridge, short nose with broad tip. Mouth is wide with full lips. Central part of upper lip is fleshy and everted, producing a tented appearance. Increased mandibular width and prognathism. (From J Allanson et al, J Med Genet 36:394, 1999.)



A B C

sleep, and self-mutilation. Peripheral neuropathy is seen in 75% of patients, and about 25% have seizures of no predominant type. Ventriculomegaly is found in over 50%.

The diagnosis is based on prometaphase chromosome examination, which is usually prompted by the characteristic physical and behavioral abnormalities. The deletion is not easily detected in routine karyotypes unless the examiner pays special attention to 17p. FISH probes aid in diagnosis (10), although fibroblast study is preferable. All deletions have occurred de novo. Smith-Magenis syndrome has been detected prenatally (5,18). Molecular studies have shown that both paternal and maternal origin may occur, without any differences in clinical presentation (8).

Potocki et al (14) have described dup17p11.2, the reciprocal of Smith-Magenis syndrome.

References (Smith-Magenis syndrome [del(17p11.2)])

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dup(17p) syndrome

Severe mental and somatic retardation, microcephaly, narrow, downslanting palpebral fissures, midface hypoplasia, hypertelorism, broad nasal bridge, dysplastic low-set ears, smooth philtrum, chronic open mouth, micrognathia, and short, webbed neck are characteristic of this syndrome (2,3,5,7). Some patients have mild to severe retardation (6).

Flexion abnormalities of the first four digits with extension of the fifth finger are common. The fingers tend to be long and tapered. Inguinal hernia has also been noted. A transverse palmar crease has been found in most patients. The male genitalia are hypoplastic (1–10).

References [dup(17p) syndrome]

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del(17q) syndrome

Deletion of the long arm of chromosome 17 is essentially lethal. Only a few examples of interstitial deletion of 17q21–q24 can be cited (1,3). Clinical findings have encompassed prominent glabella, hypertelorism, up-slanting palpebral fissures, anteverted nares, long philtrum, cleft palate, proximally placed thumbs, symphalangism, tracheoesophageal fistula, and cerebral abnormalities. Ring 17 is also rare. Growth retardation, seizures, café-au-lait spots, microcephaly, and broad nasal bridge with anteversion of nostrils are common features (2).

References [del(17q) syndrome]

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dup(17q) syndrome

Duplication of the distal portion of 17q is quite rare. Most cases have involved bands q21, q22, or q23–qter (1–10).

The phenotypic alterations appear to be remarkably similar. Stature is short and psychomotor retardation is profound. Most patients exhibit microcephaly, plagiocephaly, frontal bossing, temporal retraction, facial asymmetry, and widow's peak. Several patients have manifested downward slanting palpebral fissures, hypertelorism, and epicanthal folds with a flat nasal bridge. The mouth is often wide with a thin upper lip and downturned corners. Over half of patients have either cleft lip or cleft palate (1,2). The pinnae are often low set, posteriorly angulated, and malformed. The neck is short and broad and may occasionally be webbed with low posterior hairline (Fig. 4–45). Postaxial polydactyly of the hands and/or feet has been reported in several patients, as have hyperlaxity of limb joints and brachyrhizomelia (6). Serious congenital heart anomalies have been present in about 50% of patients. Central nervous system abnormalities have been a constant feature; renal anomalies (hydronephrosis, cystic kidneys) are also common. All males have exhibited cryptorchidism.

Examples of liveborn mosaic trisomy 17 have been reported, in whom mental and somatic retardation, seizures, autism, microcephaly, and hearing loss were found (6,9). An extra ring 17 results in severe retardation, microstomia, eye coloboma, unusual pinnae, polydactyly, contractures, and hearing loss.

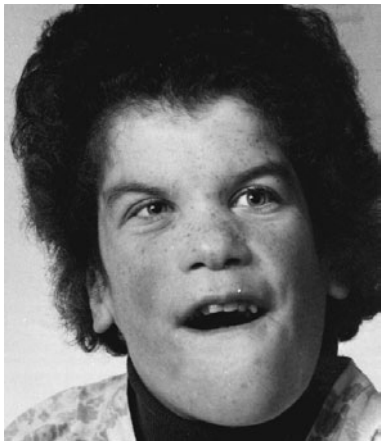

Fig. 4–45. *dup(17q) syndrome*. Narrow bifrontal diameter, temporal hair, widow's peak, and thin upper lip. [From M Berberich et al, Birth Defects 14(6C):287, 1978.]

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dup(19q) syndrome and mosaic trisomy 19

Less than a dozen cases of trisomy for the distal third of the long arm of chromosome 19 are known (1–3,4,6–9). There is no sex predilection. In addition to mental retardation, the phenotype includes low birth weight and length, marked postnatal growth retardation, microbrachycephaly, widely open sutures, downward-slanting palpebral fissures, hypertelorism, ptosis, prominent glabella, short nose, short philtrum, downturned mouth, cleft lip and/or palate, and short neck with redundant skin (Fig. 4–46). The thorax is barrel shaped. Musculoskeletal disorders include hypotonia, diastasis recti, kyphosis, duplicated thumb, valgus deformity of feet, and laterally curved halluces. Survival into late childhood has been reported. FISH probes have been used for diagnosis of distal trisomy 19q (3).

Mosaic trisomy 19 has been described (2,5) with features in one case including hydrops, hypertelorism, flat nasal bridge, short nose, small mouth, dysmorphic pinnae, narrow meati, short neck, and talipes. Another case showed a pointed nose, short upper lip, up-slanting palpebral fissures, and laryngeal stridor.

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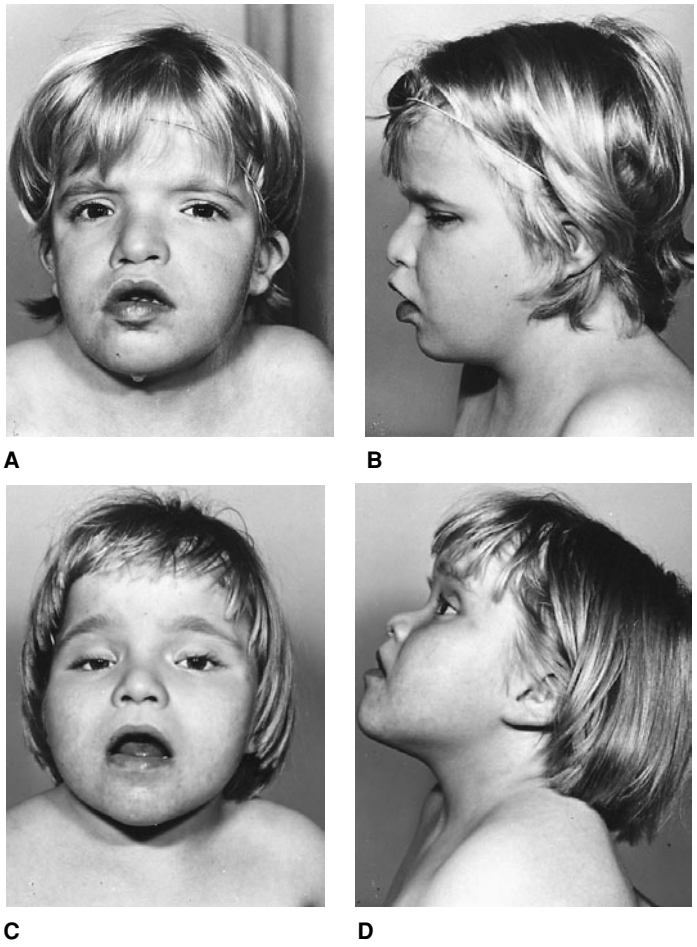

Fig. 4–46. *dup(19q) syndrome*. (A–D) Sisters with microbrachycephaly, ptosis, short philtrum, downturned mouth, short neck. (From W Schmid, Hum Genet 46:263, 1979.)

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del(20p) syndrome

Among a dozen cases of del(20p), the following clinical features have been noted: psychomotor and growth retardation, frontal bossing, hypertelorism, prominent nasal root, flat nasal bridge, anteverted nares, long philtrum, malformed helices with variable hearing loss, micrognathia, short neck with redundant skin, cardiovascular anomalies, chronic cholestasis, vertebral defect, and single palmar creases. Many of the features are those of *Alagille syndrome* (1,3–7).

Ring 20 cases, analyzed by Brandt et al (2), have, in addition to mental retardation and seizures, few clinical features: behavioral abnormalities, variable microcephaly, and facial dysmorphism.

References [del(20p) syndrome]

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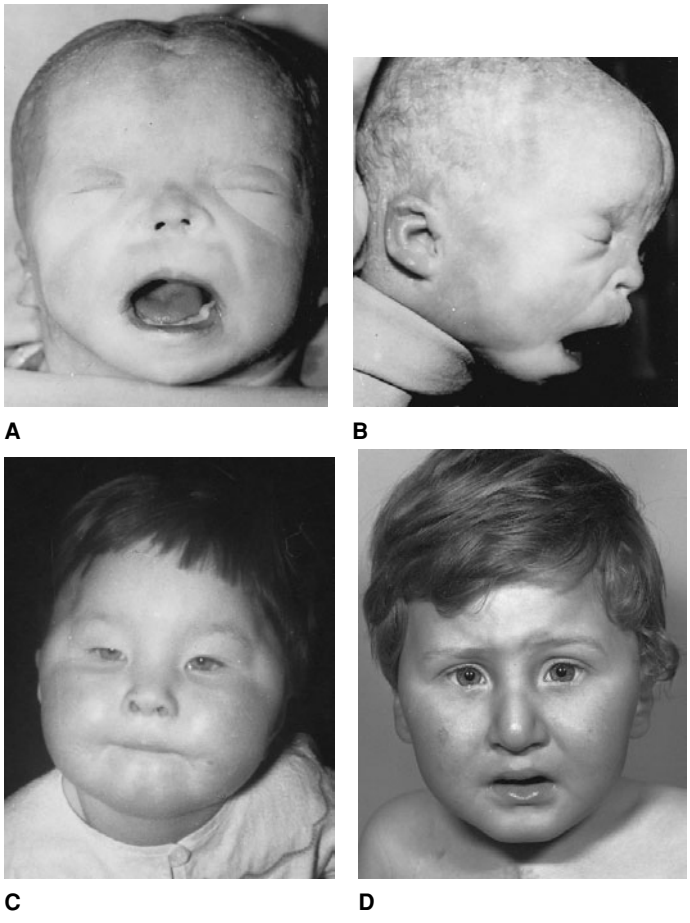
dup(20p) syndrome

The clinical picture of patients trisomic for the short arm of chromosome 20 is quite variable. Approximately 35 cases have been analyzed, about 90% of which originated from parental translocation, more often in the female parent (1–14).

Clinical features of dup(20p) syndrome uniformly include mild to severe, but usually moderate, psychomotor retardation, poor motor coordination, and rudimentary, delayed speech. Also found are flat occiput (80%); coarse hair; round face; full cheeks; sloping forehead; deep widely set eyes with up-slanting palpebral fissures; strabismus (40%), short nose with large, upturned nostrils (50%); low-set, large, and posteriorly angulated pinnae; microretrognathia; and positional abnormalities of the feet, fingers, and toes (11) (Fig. 4–47). Various vertebral abnormalities resulting in scoliosis have also been noted. Cardiac anomalies have been found in about 35% of patients, most frequently VSD and tetralogy of Fallot.

Trisomy 20 mosaicism, a not uncommon finding in amniotic fluid cell cultures, has no clinical significance.

Fig. 4–47. *dup(20p) syndrome*. (A,B) Front and side views showing widened sagittal suture, hypertelorism, posteriorly rotated pinnae, and micrognathia. (C) Craniosynostosis, up-slanting palpebral fissures, prominent cheeks, broad nasal bridge. (D) Beaked nose, small mouth, and full cheeks. (A,B from SF Pan et al, Clin Genet 9:449, 1976. C from IW Lurie et al, J Genet Hum 33:67, 1985. D from A Schinzel, Hum Genet 53:169, 1980.)



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dup(20q) syndrome

Trisomy for the long arm of chromosome 20 is extremely rare as is trisomy for complete trisomy 20. Features include brachycephaly, low hairline, frontal bossing, epicanthic folds, microphthalmia, alar hypoplasia, cleft lip and/or palate, large pinnae, chin dimple, and congenital heart anomalies (1–4).

References [dup(20q) syndrome]

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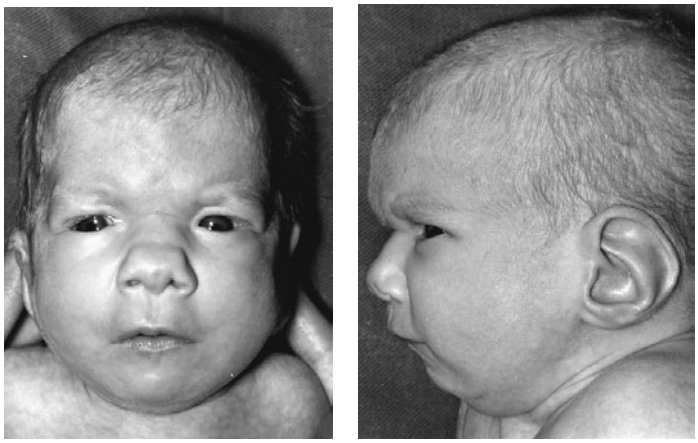
Monosomy 21 and del(21q) syndrome

Cases of del(21q) are usually due to maternal translocation. Because of the difficulty in differentiating chromosomes 21 and 22 prior to chromosome banding, we have carried out critical analysis of cases published since 1973. A good review of 25 cases is that of Huret et al (12).

The infant is small at birth and fails to thrive, often succumbing within the first year of life. Head circumference measures between the 3rd and 10th centiles. The occiput is prominent and the hairline is low. The facies is characterized by down-slanting small palpebral fissures, thick eyebrows, hypertelorism, broad nasal base with large tip,



A B

Fig. 4–48. *Monosomy 21 syndrome*. (A,B) Down-slanting palpebral fissures, broad nasal base, large nose, large dysmorphic pinna, micrognathia, and short neck. (From M Mikkelsen and S Vestermark, J Med Genet 11:389, 1974.)

no alar furrows, anteverted nostrils, low-set large pinnae with prominent anthelix and large lobes, large carp mouth, long philtrum, thin vermilion, micrognathia, and short neck (Fig. 4–48). Most have cleft lip and/or cleft palate (4,7,10). Skeletal anomalies include overlapping and/or flexed fingers and toes, kyphoscoliosis, pseudoarthrosis of clavicles, short thorax, and narrow pelvis (1,11,19). Inconstant features include wide-set nipples, ambiguous genitalia or micropenis, cryptorchidism, and imperforate anus (17).

Cardiac anomalies have included preductal coarctation and patent ductus arteriosus. Thrombocytopenia has been described in about 20% of cases, most of which were hypertonic.

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Tetrasomy 22pter→q11 or cat eye syndrome

Cat eye syndrome is defined as the combination of an extra small chromosome (an inverted duplicated 22 with a break at 22q11) with a particular pattern of congenital anomalies. The clinical phenotype may have been first recognized in 1978 (4). Highly unusual for an autosomal chromosome duplication, mental development is often normal or only mildly to moderately impaired. Less than 50% of patients show growth retardation, and a minority are microcephalic. Hypertelorism, down-slanting palpebral fissures, and uni- or bilateral, total or partial, inferior coloboma of iris, choroid and retina (rarely microphthalmia) are found. The external ears usually exhibit preauricular pits, tags, or both (Fig. 4–49). This is the most consistent finding in the syndrome. Occasionally, the pinnae are malformed, rarely with severe reduction or even absence, with atretic or absent canals and severe conductive hearing loss (1–15). Moderate to severe sensorineural hearing loss has also been found.

Congenital heart malformations occur in about 35% of patients. Especially characteristic is false pulmonary venous return. About 50% exhibit various renal anomalies, most often horseshoe kidneys, congenital hydronephrosis, or unilateral agenesis/hypoplasia. Less than 35% of patients have anal atresia, always with a fistula into the bladder, vagina, perineum, or urethra. Some patients have a covered anus or anteriorly displaced anus. Males may have cryptorchidism (2,3).

Diagnosis is based on the finding of an extra 21–22-like chromosome that is usually shorter than a 21 chromosome and has a different morphology. The chromosome may be unstable and thus present in a mosaic state. It varies in form within families (5). It is often bisatellited, showing short and long arm association with other acrocentrics. Centromere staining unmasks a second centromere. The marker represents a rearranged chromosome derived from one or two 22 chromosomes with break(s) at the proximal long arm followed by reunion that results in an isodicentric, inv dup(22)(pter→q11) (3). This finding was proved by a molecular study with a polymorphic marker on 22q11, which revealed a quadruple dosage in patients with cat eye syndrome (15). The FISH technique may be used to identify partial or complete cat eye syndrome (1,6).

The cat eye chromosome, which by definition is an inv dup (22)(pter→q11) chromosome, cannot be secondary to a familial balanced rearrangement. However, partial trisomy (and not tetrasomy) of the analogous segment can and does result in a quite similar, but milder, clinical picture and can be transmitted to the offspring of an affected patient (5).

References (Tetrasomy 22pter→q11 or cat eye syndrome)

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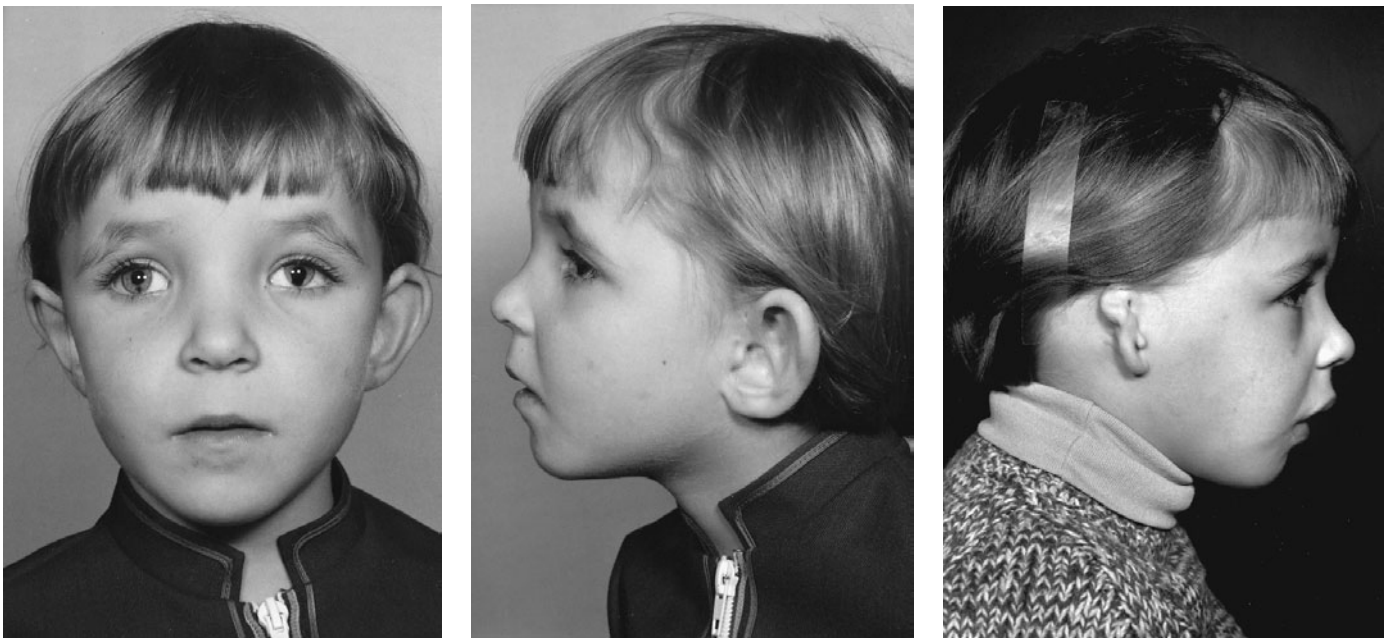

A B C

Fig. 4–49. *Cat eye syndrome.* (A,B) Seven-year-old patient. There is complete coloboma of iris (left) and incomplete, peripheral coloboma (right). Note preauricular fistula (left). (C) Microtia, atresia of external ear canal, ear tag. (From A Schinzel, Hum Genet 47:148, 1981.)

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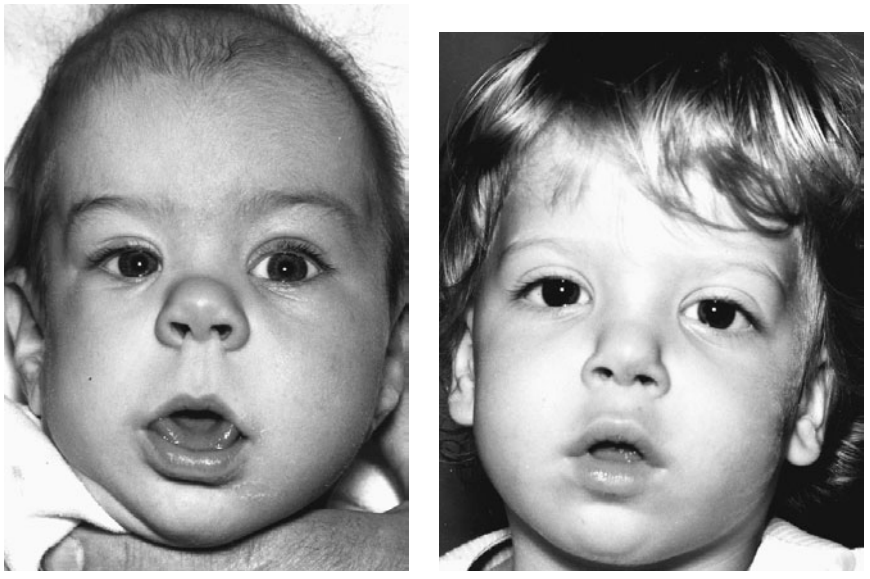
del(22q) syndrome

Loss of the distal portion of the long arm of chromosome 22 usually results in a ring. Approximately 40 patients with this syndrome have been described (1,5,8,13). The phenotype is not striking (1a). The head circumference is reduced in about 65% of patients. The face tends to be round in young children, with horizontal and wide, almond-shaped palpebral fissures. Epicanthic folds are frequent. Ptosis is present in approximately 35%. The eyebrows tend to be full, the nose has a bulbous tip in infancy, and the pinnae are often large (6,7,10,11,16,17) (Fig. 4–50). Mental retardation is usually severe and becomes even more pronounced with age. Hypotonia is constant, with poor motor coordination.



A B

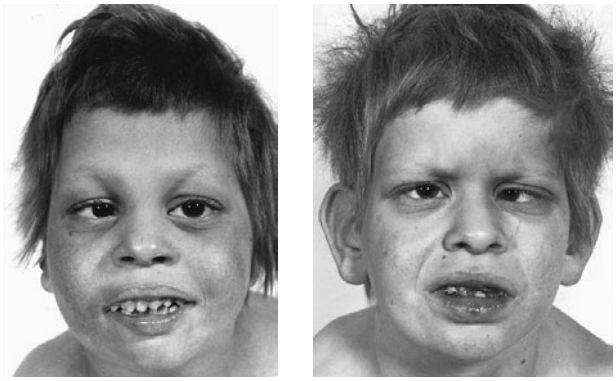
Fig. 4–50. *del(22q) syndrome.* (A) Epicanthal folds, ptosis, broad upturned nose and long philtrum. (B) Compare facies with that of older child. (A courtesy of D Hoefnagel, Dartmouth, New Hampshire. B courtesy of R Warren, Miami Florida.)

Deletion of 22q11 has been found in about 75% of those with *velocardiofacial syndrome,* in the autosomal dominant form of *Opitz BBB/G syndrome,* and in almost 90% of infants with *DiGeorge sequence* (thymic aplasia, congenital heart anomaly, hypoparathyroidism) (4). In some cases, the chromosome abnormality has resulted from de novo rearrangements and, in others, from unbalanced transmission of familial translocations.

DiGeorge sequence, a developmental field defect, involves failure of the thymus and parathyroids to develop, resulting from disturbances of the third and fourth pharyngeal pouches (2,14). This sequence is usually isolated but may be seen in *CHARGE association.* Occasionally, DiGeorge sequence may be transmitted by autosomal recessive or dominant inheritance (9,12,15). Some of these examples may represent chromosome translocation. However, in several cases, no chromosome change has been detected with high-resolution cytogenetics (15).

Congenital heart anomalies, mostly conotruncal abnormalities, vary from VSD (most common) to interrupted aortic arch, right aortic arch, truncus arteriosus, tetralogy of Fallot, PDA, and single ventricle (3).

Cleft lip and/or palate have been noted. The pinnae may be malformed or posteriorly rotated. Hypertelorism, short palpebral fissures, prominent nose, short philtrum, and micrognathia are frequent features.



A B

Fig. 4–51. *Trisomy 22 syndrome.* (A,B) Esotropia, broad flat nose, prominent upper lip, everted lower lip. Female had preauricular tag on right, severe microtia on left. (A,B from A Schinzel et al, Hum Genet 56:269, 1981.)

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Trisomy 22 (dup22q) syndrome

Trisomy 22 is the second most common anomaly seen in embryos lost spontaneously during the first trimester. However, it is rare in liveborn babies. Some of the early cases represented undetected unbalanced 11/22 translocations or were composed of part of chromosome 22 and material from other chromosomes (17). However, there are numerous examples of true trisomy 22 that have been demonstrated by chromosomal banding and FISH analysis (4,9,10,18,21–24). Examples of trisomy 22 mosaicism (5) have been described, with origin being shown in paternal nondisjunction at the second meiosis shown (7). Parental age is advanced. Early cases of trisomy 22 were tabulated by Cervenka et al (4) in 1977. It has been described with *holoprosencephaly* (8) and with *Fryns syndrome* phenotype (12).

Life expectancy is limited for patients with pure trisomy, but the mosaic state is compatible with prolonged survival. Intrauterine growth retardation is seen in almost all cases. The head is microcephalic. Hypertelorism, epicanthic folds, and down-slanting palpebral fissures are noted in over 90% of patients. Coloboma has been described (1,4). The nasal bridge is flat and the nasal tip is often flat as a result of a short septum. About 65% have preauricular tags or sinuses. Complete atresia of the external auditory canal has been reported (2). The pinnae are low set with prominent anthelix. Cleft lip and/or palate are present in about 50% of patients (7,9,11,14–16,18,19). The mandible is small in 85% and many patients have been classified as having *Robin sequence* (Fig. 4–51). Webbed neck or redundant skin has been noted in over 80%.

The fingers have hypoplastic nails and distal phalanges in 90% of cases. The thumbs are digitalized in 50% (3). Clinodactyly is not rare. About 40% exhibit hip dysplasia and/or luxation. Hypotonia has been noted in about 50% of cases.

Abnormal external genitalia described in about 90% of males include micropenis, bifid scrotum, and cryptorchidism (12). Anal atresia is found in 30% of patients (3), and various renal malformations have been noted in 50% (6).

Congenital heart anomalies, present in 85%, have included a diverse group of abnormalities without an obvious pattern: pulmonary stenosis (PS), VSD, ASD of secundum type, PDA, tricuspid valve atresia, hypoplastic right ventricle, aberrant subclavian artery, coarctation of aorta, left superior vena cava, and bicuspid aortic valve (9,13,17,20). An excellent survey of congenital heart anomalies seen in this syndrome is that of Lin et al (13).

Those individuals with mosaicism have failure to thrive, mental retardation, ptosis, hearing loss, low posterior hair line, syndactyly, hemihypoplasia, streaky pigmentation, and ovarian failure (5).

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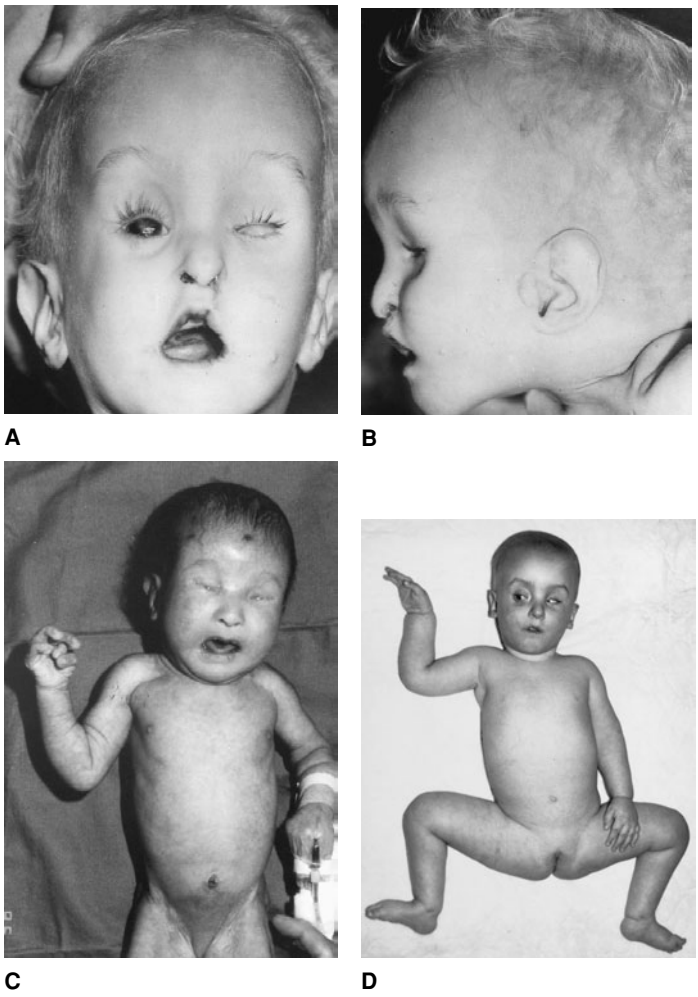

Fig. 4–52. *Tetraploidy syndrome.* (A,B) Microcephaly with narrow bifrontal diameter, sparse blond hair, lowset simplified pinnae, pretragal tags, anophthalmia and micrognathia, short philtrum, and beaked nose. (C) Newborn female with tetraploidy. Note microphthalmia, beaked nose, and overlapping fingers. (D) Note facies similar to that seen in (C). (A,B from M Golbus et al, J Med Genet 13:329, 1976. C from H Shiono et al, Am J Med Genet 29:543, 1988. D from C Lafer et al, Am J Med Genet 31:375, 1988.)

Tetraploidy and tetraploid/diploid mosaicism syndrome

Although relatively common (2%–3%) in embryos lost spontaneously during the first trimester, tetraploidy or tetraploid–diploid mosaicism (mixoploidy) in liveborn infants is so rare (not more than a dozen examples of tetraploidy having been recorded) that few generalizations can be made (8). Some cases have been 92,XXYY and others 92,XXXX. They arise either from post-fertilization mitotic cleavage error or trispermic fertilization of a haploid egg (2). Trispermy causes molar changes. The origin of mixoploidy may be failure of cytokinesis at some time after the first mitotic division, resulting in mosaicism. In at least one case, AFP was low while hCG was elevated (2). Tetraploidy is not uncommon as an artifact in amniotic cell cultures. Most true examples abort spontaneously in early gestation. Of embryos lost in the first trimester, about 5%–6% have tetraploidy (5,8).

All living examples have exhibited severe mental retardation, low birth weight, hypotonia, and most have microcephaly. The majority have died within the first year. The forehead is narrow and prominent, the nose beaked, and the philtrum short. The pinnae are often low set and often lack cartilage (4,12,15). Some infants have microphthalmia or anophthalmia and short palpebral fissures (4,10,15,16), whereas others have corneal opacity, colobomas, aphakia, and retinal detachment (10,11). The nose appears pinched and the mouth, small (Fig. 4–52). Cleft lip and/or cleft palate has been found in a few cases (9–11).

Anomalies of the extremities are common: positional limb defects, arachnodactyly (11,12,15,16), syndactyly of toes (15), talipes (12,15), and single palmar creases (4,12,15). About 35% of patients have major congenital heart anomalies (8,11,15).

Among 13 examples of tetraploid–diploid mosaicism (1,3,6,7,10, 13,14,17–21), the phenotype was very similar to that described above for tetraploidy but milder. The hands and feet are slender with long tapering digits, and growth deficiency is often asymmetric. Skin pigmentation changes reflect the mosaicism.

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Nijmegen breakage syndrome (Seemanová syndrome)

Nijmegen breakage syndrome is a chromosomal instability disorder characterized by pre- and postnatal growth retardation, microcephaly, "bird-like" facies, and recurrent infections (16). It has been called "ataxia-telangiectasia variant," sharing with it cellular, immunological, and chromosomal but not clinical findings.

Severe microcephaly becomes evident after a few months of life. The forehead is often low and receding. The palpebral fissures have an upward slant. The eyes may be prominent (1). The face is triangular and narrow with a rather long, straight nose and a high nasal bridge. The philtrum is smooth and the chin small (10) (Fig. 4–53).

An immunodeficiency is characterized by low immunoglobulin levels and cellular immune defect. Various infections, especially sinopulmonary, are extremely common. Urinary and gastrointestinal infections have been noted in 15% of patients. Death has resulted from bronchopneumonia (15%) and lymphoid malignancy (20%) (12).

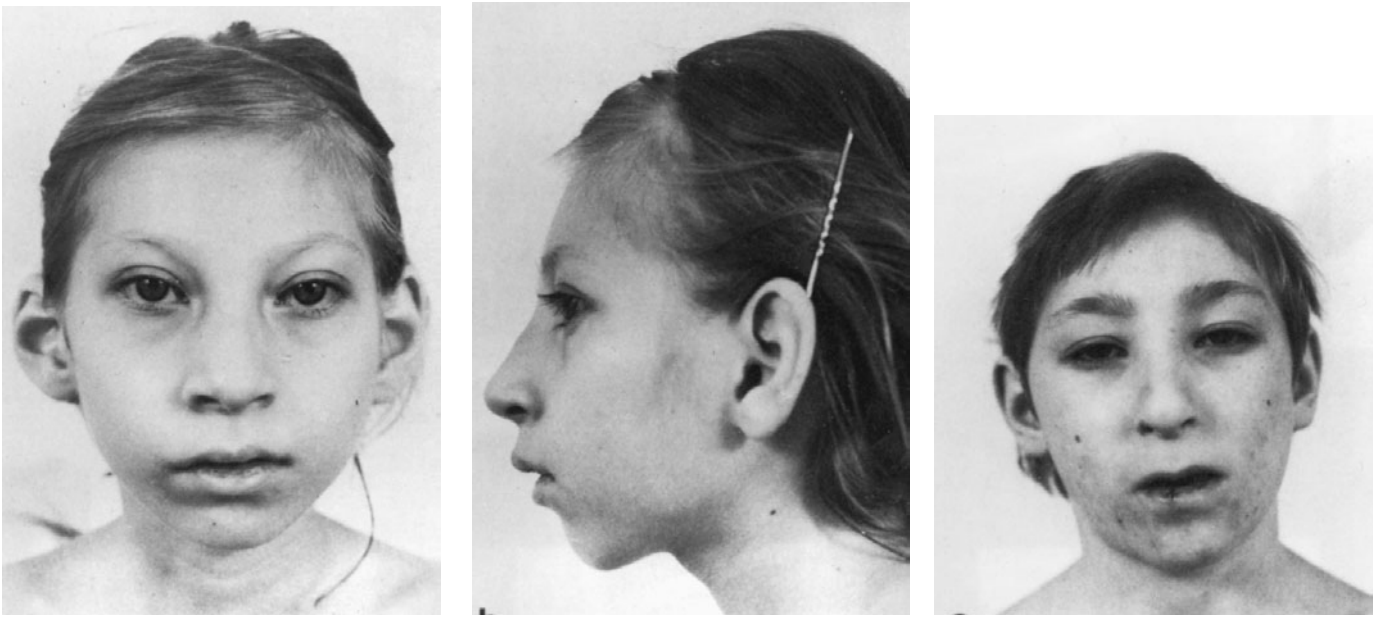
Chromosomal rearrangements involving chromosomes 7 and 14 are seen in 15%–35% of patients; these rearrangements are very similar to those noted in ataxia telangiectasia. The sites most frequently involved are 7p13, 7q34, and 14q11 (10) (Fig. 4–54). There is increased sensitivity to ionizing radiation and bleomycin (7,9,11). Malignancies seen in 30% of cases have included acute lymphoblastic leukemia, malignant lymphoma, neuroblastoma, glioma, medulloblastoma, and rhabdomyosarcoma (3,4,9,13). Most affected individuals have normal intelligence, but some have mental retardation (12).

The syndrome is caused by an autosomal recessive radiosensitivity gene (8,13) that has been mapped to 8q21–24 (2,6,8). Mutation in nibrin, a protein involved in double strand break repair, has been shown (5a,14). Heterogeneity has not been found (5), but allelic mutations have been noted (11).

Clinical and cytogenetic (chromosomal rearrangement) similarities are seen not only in *ataxia telangiectasia* but in *Bloom syndrome* and Fanconi anemia. Other features such as growth retardation, immunodeficiency, and a high incidence of malignancy are also shared. However, patients with Nijmegen breakage syndrome have microcephaly and do not have ataxia, oculocutaneous telangiectasia, or progeric skin change (5). Also, there is no elevation in serum AFP levels. Complementation analyses have shown that Nijmegen breakage syndrome and ataxia telangiectasia are different disorders (16), but both may be part of the same protein complex or pathway (8,18).

A new autosomal dominant chromosomal instability syndrome characterized by less breakage than in ataxia-telangiectasia and Nijmegen breakage has been reported. Anticipation was observed (4a). Stature

Fig. 4–53. *Nijmegen breakage (Seemanová) syndrome.* Severe microcephaly, low sloping forehead, triangular facies, long nose with high bridge, smooth philtrum. (From E Seemanová et al, Am J Med Genet 20:639, 1985.)



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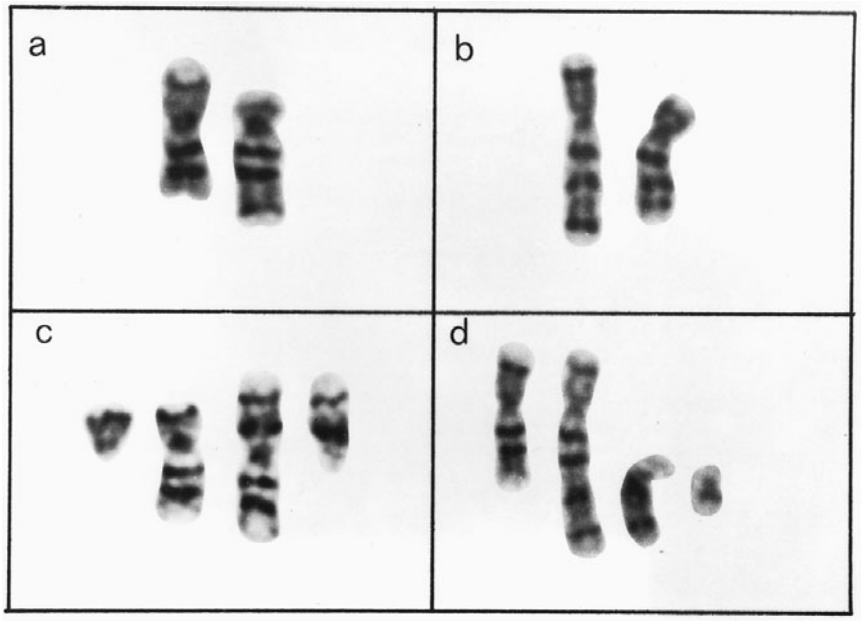

Fig. 4–54. *Nijmegen breakage (Seemanová) syndrome*. Chromosomal arrangements involving chromosomes 7 and 14. Sites most often involved are 7 q13,7q34, and 14q11. (From RDFM Taalman et al, Am J Med Genet 32:425, 1989.)

was short, and there were mental retardation, depression, dysarthria, and ataxic gait.

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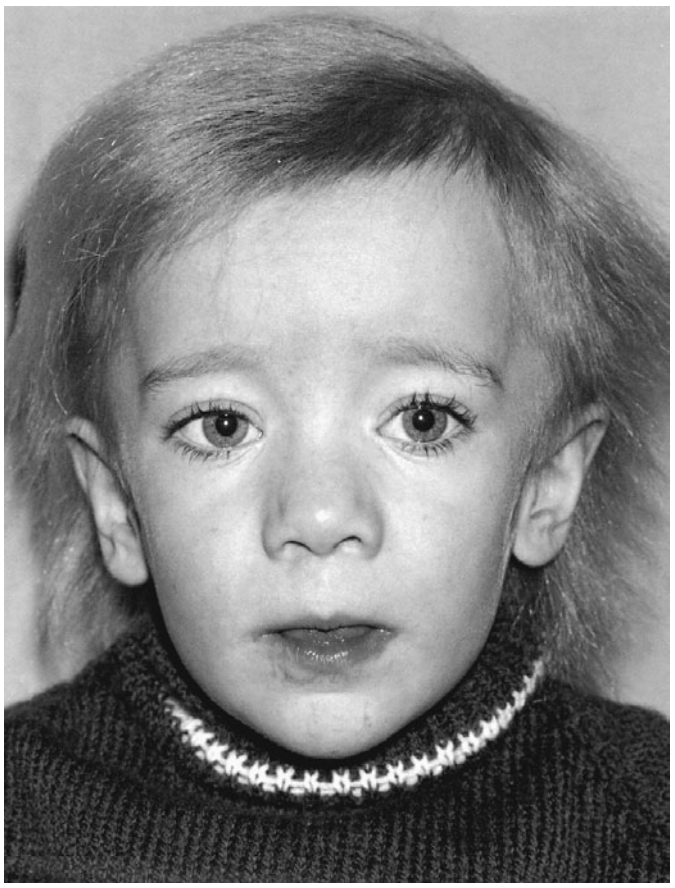
Immune deficiency with centromeric instability of chromosomes 1, 9, and 16 (ICF syndrome)

This syndrome, first reported in 1978 by Tiepolo et al (19) and briefly by Hultén (9), has been described in about 20 patients (1–22), including sibs (4,7,20,22). Parental consanguinity has been noted on a few occasions (2,4). There is no sex predilection. Autosomal recessive inheritance has been shown (21); the gene maps to 20q11–q13 (22). It has been characterized (24), but there may be genetic heterogeneity (23). The name ICF is an acronym for *I*mmunodeficiency, *C*entromeric heterochromatin instability, and *F*acial anomalies (14).

Facial changes. The facies is characterized by frontal bossing, hypertelorism, flat nasal bridge, small, upturned nose, epicanthic folds, and micrognathia. Protruding tongue has been a variable feature (6,7,11,14,17,21) (Fig. 4–55A). Cleft palate has also been found (8).

Growth and mental retardation. Mental retardation varies from mild (2,8) to severe (4). Most authors have indicated that growth has been below the 3rd centile.

Immune deficiency. Recurrent skin and chronic respiratory infections include bronchitis, bronchiectasis, pneumonia, sinusitis, and otitis media (3). Variable immune deficiency associated with at least two depressed immunoglobulin levels is a constant feature (7,13). Some patients suffer from persistent diarrhea (3,7,14,17). Others have defective cell-mediated immunity (3,4,9,20,22). Death from pneumonia has occurred in infancy or childhood in a number of children (4,9,22).



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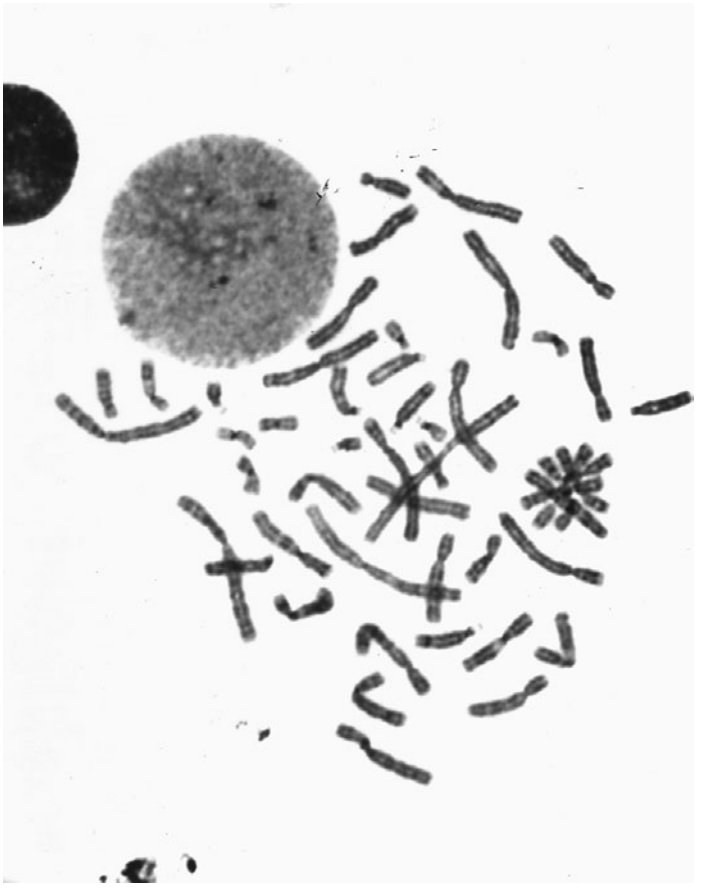

B

Fig. 4–55. *ICF syndrome.* (A) Facies characterized by frontal bossing, flat nasal bridge, small upturned nose, micrognathia, protruding tongue. (B) Multibranched configuration involving chromosomes 1, 9, and 16. (Courtesy of H Hinkel, Dresden, Germany.)

Other findings. Miscellaneous findings have included hydrocephalus (22), short stature (9), macrocornea (4), sparse, dry hair (2), hyperpigmented skin spots (3,5), bipartite nipples (5), umbilical hernia (22), shawl scrotum (5,8), and hypospadias (5,11).

Laboratory findings. In all cases there has been instability of paracentromeric heterochromatin of chromosomes 1, 9, and 16 (12). This has been manifest by despiralization, chromosome and chromatid breaks, triradials, somatic pairing and interchanges between homologous and nonhomologous chromosomes seen in variable numbers of peripheral blood lymphocytes. These appear as multiple branched configurations. Abnormalities can be seen in interphase nuclei using in situ hybridization with a probe specific for pericentromeric regions of chromosomes 1, 9, and 16 (12,15,18)(Fig. 4–55B). Fibroblast chromosomes appear to be essentially normal (12). Undermethylation of satellite DNA has been shown (10,16).

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Chapter 5
Metabolic Disorders

Mucopolysaccharidoses

As in the last edition of this book, coverage of the mucopolysaccharidoses is essentially limited to those metabolic disorders that cause alteration in the facies of patients.

The mucopolysaccharidoses (MPS) are a family of inherited metabolic diseases that result from the deficiency of lysosomal enzymes involved in the degradation of the glycosaminoglycans (mucopolysaccharides; also designated MPS). These glycosaminoglycans (GAGs) include dermatan sulfate (DS), heparan sulfate (HS), and keratan sulfate (KS). Chondroitin sulfate (CS) may also be involved (11).

On the basis of clinical and biochemical studies, these disorders have been designated MPS I through MPS VII (11) (Table 5–1). Extensive reviews on various aspects of the MPS have been published (6,7,14,18). A deficiency of a specific lysosomal enzyme has been demonstrated in each of the MPS disorders. Each has autosomal recessive inheritance with the exception of Hunter disease (MPS II), which is X-linked recessive. Considerable progress has been made in the field of molecular genetics toward understanding these disorders (11) (Table 5–2).

Although the clinical phenotypes of these disorders are very heterogeneous, they share many features and permit provisional clinical diagnoses. For example, all of the disorders have characteristic skeletal abnormalities (termed "dysostosis multiplex"), with the exception of Morquio disease (MPS IV), which has quite different skeletal changes (15). Hearing, vision, and cardiovascular function may be affected (19). Joints are often stiff and marked short stature is observed, except in Scheie disease (MPS I-S). In addition, unusual hair, corneal clouding, hepatosplenomegaly, hearing loss, arteriosclerosis, and stiffening of the thoracic cage are common findings (16,17).

There is clinical similarity among different enzyme deficiencies and, conversely, a remarkable clinical heterogeneity within each of these diseases. For example, patients with MPS I-H, MPS I-S, and MPS I H/S have in common deficiency of α-L-iduronidase, an enzyme activity required to degrade DS and HS. The genes appear to be allelic (11). Patients with MPS I-H have severe dysostosis multiplex, short stature, and mental retardation and expire in childhood, whereas patients with MPS I-S have mild skeletal abnormalities, normal height, and normal intelligence and survive into adulthood. Patients with MPS I-H/S have an intermediate phenotype. The genes appeared to be allelic (10). Molecular genetic studies will make genotype–phenotype correlations possible (12). There have been several reports on the relative frequencies of the various types of MPS (8).

The suspected clinical diagnosis of patients with MPS is confirmed by the demonstration of the specific enzymatic defect in isolated leukocytes, cultured skin fibroblasts, or serum. Prenatal diagnosis following amniocentesis or chorionic villus biopsy is possible for all MPS (11). Identification of heterozygotes is becoming more definitive as specific mutations are identified.

Progressive deterioration generally leads to death in childhood, with the exception of MPS I-S, MPS IV, and the mild form of MPS VI; patients with these disorders survive into adulthood. Animal models that have facilitated the development of therapeutic strategies by supplying enzyme exogenously (3) have been described for MPS I (9,13), MPS VI (4), and MPS VII (5). The partial therapeutic success of bone marrow transplantation (BMT) has shown that cells of donor hematopoietic origin can assist in the removal of GAGs stored in various tissues of the host. But allogenic BMT is a high-risk procedure, thus development of somatic gene therapy, using retroviral vectors to introduce cDNA encoding the missing lysosomal enzyme into the patient's own bone marrow cells (11), has been encouraged.

Retrovirally transduced cDNA encoding α-L-iduronidase can restore normal GAG metabolism in deficient fibroblasts (1). Neither enzyme replacement nor retroviral vector-mediated gene therapy is thought likely to affect the central nervous system (11). However, MPS I patients with normal IQ scores before BMT maintained normal scores from 2 to 7 years post-transplantation (18). After BMT, cardiac function, e.g., left ventricular restriction, may be ameliorated (2,6).

The relative frequency of the mucopolysaccharidoses has been addressed and reviewed by Poorthuis (11a).

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Table 5–1. Classification of the mucopolysaccharidoses

Type	Synonym	Clinical dysmorphism	Skeletal dysplasia	Corneal opacities	Mental retardation	Excessive urinary AMPS	Defective enzyme	Genetic transmission
I-H	Hurler	Severe	Severe	Yes	Yes	DS and HS	α-L-Iduronidase	AR
I-H/S	Hurler/Scheie	Intermediate	Moderate	Yes	No	DS and HS	α-L-Iduronidase	AR
I-S[a]	Scheie	Mild	Mild	Yes	No	DS and HS	α-L-Iduronidase	AR
II-A	Hunter A	Late (moderate)	Moderate	No	No	HS and DS	Iduronate sulfate-sulfatase	XR
II-B	Hunter B	Early (moderate)	Moderate	No	Yes	DS and HS	Iduronate sulfate-sulfatase	XR
III-A	Sanfilippo A	Mild	Minimal	No	Yes	HS	Heparan-*N*-sulfatase	AR
III-B	Sanfilippo B	Mild	Minimal	No	Yes	HS	α-*N*-acetyl glucosaminidase	AR
III-C	Sanfilippo C	Mild	Minimal	No	Yes	HS	Acetyl CoA:α-glucosaminide-*N*-acetyltransferase	AR
III-D	Sanfilippo D	Mild	Minimal	No	Yes	HS	α-*N*-acetylglucosaminide-6-sulfatase	AR
IV-A	Morquio A	Severe	Severe	Yes	No	KS	Galactosamine-6-sulfate-sulfatase	AR
IV-B	Morquio B	Severe	Severe	Yes	No	KS	β-galactosidase	AR
VI-A	Maroteaux-Lamy A	Mild to moderate	Moderate	Yes	No	DS	Arylsulfatase B	AR
VI-B	Maroteaux-Lamy B	Severe	Severe	Yes	Mild	DS	Arylsulfatase B	AR
VII	Sly	Severe	Severe	None	Late	DS and HS	β-glucuronidase	AR

[a]Formerly classified as type V.
AMPS, acid mucopolysaccharide; DS, dermatan sulfate; HS, heparan sulfate; KS, keratan sulfate.

Mucopolysaccharidosis I-H (Hurler syndrome). Mucopolysaccharidosis I-H (MPS I-H) was first described in 1919 by Hurler (20) at the suggestion of Von Pfaundler who was from the same clinic. It is the classic prototype of the MPS, having the following cardinal features: growth failure after infancy, marked mental retardation, characteristic craniofacial dysmorphism and physical habitus, dysostosis multiplex, corneal clouding, histochemical and biochemical evidence of intracellular lysosomal storage of GAGs, and excessive urinary excretion of DS and HS.

The onset of symptoms is in the first year of life (8). During the first months of life there are a few relatively nonspecific findings, such as hernias, macrocephaly, limited hip abduction, and recurrent respiratory infections.

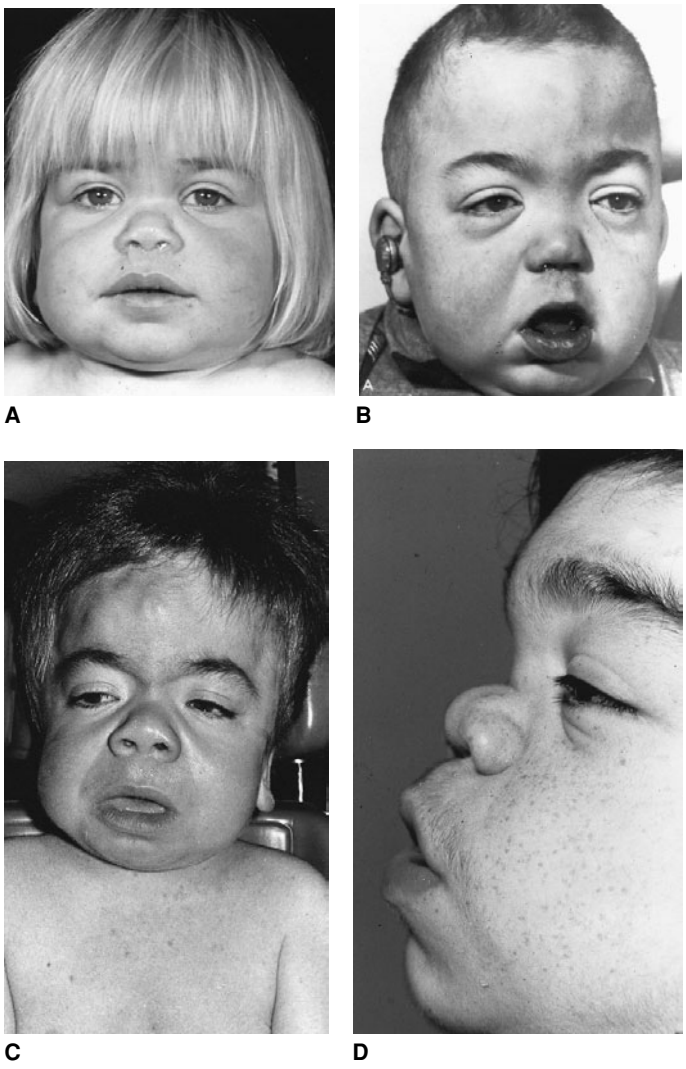
Skeletal abnormalities become apparent at around the age of 6 months. Acute cardiomyopathy associated with endocardial fibroelastosis has been a presenting feature in several infants with MPS I less than 1 year of age (4,12). The full clinical picture usually develops in the second year of life (Figs. 5–1 to 5–5). Death most often occurs before 10 years of age from pneumonia and cardiac failure. Intrafamilial variability in Hurler syndrome has been reported in a limited number of families in which sibs with comparable deficiencies of α-L-iduronidase in vitro showed a divergence in clinical severity and disease progression (25).

The frequency of mucopolysaccharidosis I-H is approximately 1/144,000 births (23). Similar data stem from the Netherlands (33a). More recent data from Northern Ireland revealed an incidence of approximately 1/76,000 live births (29). The specific enzymatic defect is

Table 5–2. Chromosomal assignment of structural genes for lysosomal enzymes that degrade glycosaminoglycans

Mucopolysaccharidosis	Enzyme	Chromosome region
MPS I	α-L-iduronidase	4p16.3
MPS II	Iduronate 2 sulfatase	Xq28
MPS III-A	Heparan-*N*-sulfate	17q25.3
MPS III-B	α-*N*-acetylglucosaminidase	17q21
MPS III-C	Acetyl CoA:α-glucosaminide-*N*-acetyltransferase	14(?)
MPS III-D	α-*N*-acetylglucosamine-6-sulfate sulfatase	12q14
MPS IV-A	Galactosamine 6-sulfate sulfatase	16q24.3
MPS IV-B	β-galactosidase	3p21-p14.2
MPS VI	Arylsulphatase B (*N*-acetylgalactosamine-4-sulfatase)	5q13
MPS VII	β-glucuronidase	7q21.11

Fig. 5–1. *Hurler syndrome*. (A–D) Characteristic facies with large head, prominent forehead, coarse features, hypertelorism, heavy lids, low nasal bridge, snub nose, long philtrum, and open mouth. (A,D courtesy of RJ Desnick, New York, New York. C courtesy of E Passarge, Hamburg, Germany.)



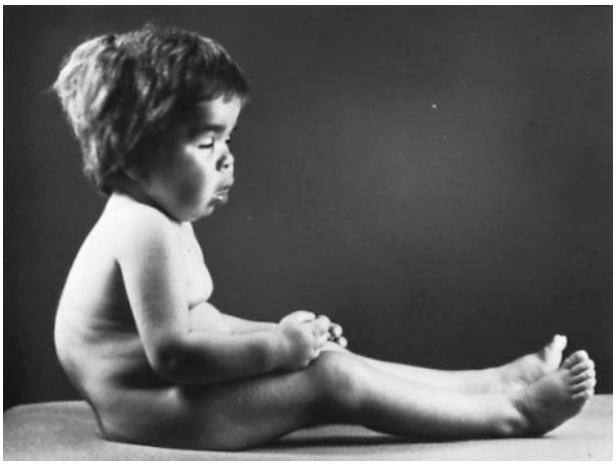


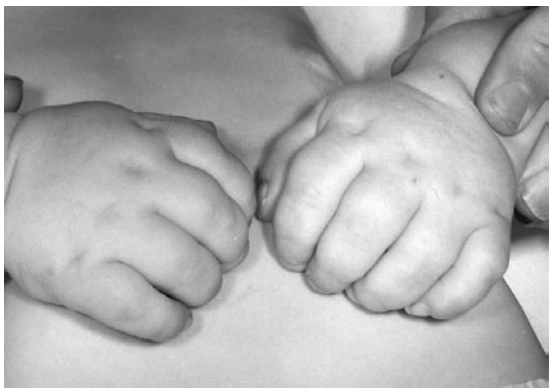
Fig. 5–2. *Hurler syndrome*. Two-year-old girl. Note characteristic facies and gibbus.

deficiency of α-L-iduronidase (IDUA) activity, lack of which precludes intralysosomal degradation of the α-L-iduronide-containing GAGs, DS, and HS. IDUA has been localized to chromosome 4p16.3 by in situ hybridization and confirmed by Southern blot analysis (35,36). In MPS I, molecular heterogeneity has been reported (7). It has been treated by bone marrow transplantation (13,18).

Facies. A slight coarsening of facial features at 3–6 months of age is usually the first abnormality noted. The head is large, and the frontal bones bulge. Premature closure of the sagittal and metopic sutures and hyperostosis in this area frequently lead to scaphocephaly. Hirsutism is represented on the face only as synophrys. The nasal bridge is depressed, the tip of the nose is broad, and the nostrils are wide and anteverted. The interpupillary distance is greater than normal. Generally, corneal clouding appears during the third year of life. Glaucoma may be an early complication (31). The lower eyelids and nasolabial folds are prominent, and the cheeks are full. The earlobes are thick. The lips are enlarged and patulous, and the mouth is usually held open, particularly after the age of 3 years. Chronic nasal discharge is usually marked, even between the frequent bouts of upper respiratory infection (Fig. 5–1). Nasal congestion with stertorous breathing through the mouth is severe, as it is related to hyperplastic adenoid tissue and a deep cranial fossa that narrows the airway between the sphenoid bone and the hard palate. Gag and swallowing reflexes become progressively diminished (22).

Musculoskeletal system. Length at birth is not below the norm. Most MPS I-H patients between the ages of 6 and 12 months are at or above the 87th centile for total body length. Some remain among the tallest infants until 18 months, but growth ceases in all patients before 2 years of age. By age 3 years, all MPS I-H patients are below the third centile for stature. The neck is short; a serious complication is subluxation of C1–C2 (3,45). Both pectus carinatum and excavatum occur, and usually there is lumbodorsal kyphosis or gibbus (Fig. 5–2). Range of motion is limited in all joints; in the hands, the so- called clawhand deformity (Fig. 5–3) results.

Fig. 5–3. *Hurler syndrome*. Clawhand deformity.



Radiographically, in infancy, bone trabeculation is coarse. In late infancy and early childhood, a pattern of skeletal changes called "dysostosis multiplex" emerges: the skull becomes large and deformed, the sphenoidal plane is depressed, and the sella is J-shaped, possibly from arachnoid cysts (Fig. 5–4A). The sagittal and lambdoid sutures close prematurely. The cranial base and orbital roofs are particularly thick and dense. The orbits are shallow. Communicating hydrocephalus, which is usually associated with increased intracranial pressure, is often present. The stylohyoid ligament is almost always calcified (normal, 25%) and thicker than normal (32). The ribs are wide in their lateral and ventral portions, with overconstriction at their paravertebral ends (Fig. 5–4B). The vertebral bodies are dysplastic, with biconvex endplates and hook-shaped configuration of the lower thoracic and upper lumbar bodies, after 12–18 months of age (Fig. 5–4C). The basilar portions of the ilia are underdeveloped, with flaring of the iliac wings (Fig. 5–4D). The long tubular bones show marked diaphyseal widening and distortion, with small and deformed epiphyses. The shafts of the short tubular bones are underconstricted, with bullet-shaped phalanges and proximal pointing of the second to fifth metacarpals (Fig. 5–4E) (42).

The abdomen protrudes because of hepatic and splenic enlargement, deformity of chest, shortness of spine, and laxity of abdominal wall. These changes are noted during the second year of life. Hepatomegaly may be detected as early as 1 month of age.

Inguinal hernia, present at birth or developing within the first 3 months of life, is a constant feature in boys. The hernias tend not to recur following surgery; they are a classic part of the patient's history before diagnosis is established but are not common during the subsequent course of the disorder. Umbilical hernias, usually small at birth in both sexes, gradually reach major proportions.

Other findings. The skin is pale, coarse, and dry and is covered with fine, lanugo-like fuzz, particularly on the back and extremities. Mental retardation is conspicuous and progressive. Moderate cardiomegaly, as a result of deposition of acid mucopolysaccharide (AMPS) in the myocardium and valves, is usually present (43). Echocardiographic mitral valve deformity has been demonstrated (21). Hypertension is a frequent finding in older patients (44).

Oral manifestations. Oral changes (Fig. 5–5) have been reviewed by Gardner (15). The lips are enlarged and patulous, with flattened philtrum, and the upper lip is particularly long. The mouth is usually held open, with protruding tongue, from about 3 years of age. Lip and tongue enlargement becomes marked after the age of 5 years (22).

The teeth are widely spaced, often exhibiting severe attrition. The incisors may exhibit some degree of conical crown form but are otherwise normal structurally. Because of macroglossia, there may be anterior open bite. Eruption is probably delayed in at least half of the patients (6), particularly in areas of bone destruction. The second primary molars or first and second permanent molars are often distoangularly positioned, with the distal surface of the crown being situated more deeply than the mesial. In some cases, there is dilaceration of the distal roots (48). These changes occur more frequently in the mandible.

Extremely common are localized areas of bone destruction that have been designated "dentigerous cysts." These are often present by 3 years of age and more often involve the second primary molars and first and second permanent mandibular molars. The margins of the radiolucencies are usually smooth and clearly defined (6,14,19). We believe that the cysts represent pooling of dermatan sulfate in hyperplastic dental follicles, since they also occur in MPS I-S and MPS VI but not in MPS III. However, the material in the follicles in MPS VI has been shown to be hyaluronic acid (vide infra).

The alveolar ridges are nearly always hyperplastic, resulting in spacing of the teeth. Some patients exhibit hyperplastic gingivitis, because of poor oral hygiene and mouth breathing. Rarely, there is true hyperplastic

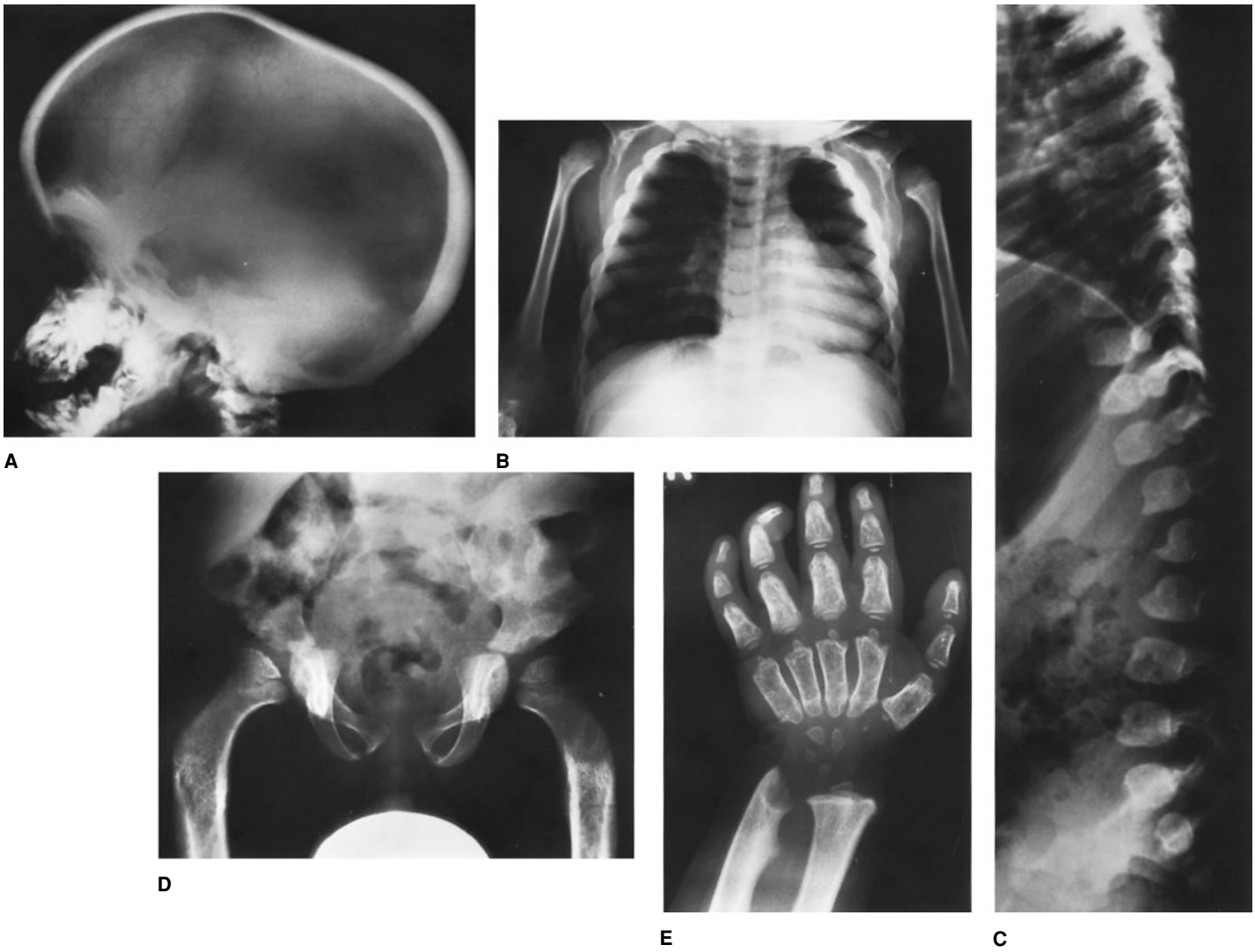


Fig. 5–4. *Hurler syndrome*. Radiographs. (A) Skull of 8-year-old patient with macrocephaly, dolichocephaly, thickened calvaria, and wide sella. (B) Chest of same patient, showing wide, oar-shaped ribs, expanded medial portion of clavicle, valgus deformity of humeral neck, submetaphyseal overconstriction of proximal humerus, and expansion of distal shaft of humerus. (C) Spine of 4-year-old patient with flattening and biconvex endplates of vertebral bodies, and hooked-shaped configuration of first two-thirds of the lumbar vertebrae. (D) Pelvis of 8-year-old patient, showing hypoplasia of basilar portion of ilia, flared iliac crest, long femoral neck, and coxa valga. (E) Hand of 6-year-old patient, with expanded shafts of short tubular bones, bullet-shaped phalanges, proximal pointing of second to fifth metacarpals, small carpal bones, and tilted distal ends of radius and ulna.

gingiva with eruption cysts (14). Histochemical study of the gingiva has demonstrated metachromatic cells (14).

The mandible is short and broad, with a wide bigonial distance (48). The rami are short and narrow, and the condyle is replaced by a flat, inclined surface or cup-shaped excavation (24). The mandibular notch is irregular or cleft. The temporomandibular joint may exhibit limited motion. Airway obstruction and sleep apnea have been reported (28,41).

Diagnosis. The earliest diagnostic tests for the MPS syndromes were based on the urinary excretion of GAGs. A great number of methods have been devised, ranging from semiquantitative spot tests to precise qualitative and quantitative measurements (33). Spot tests are quick and inexpensive but have the disadvantage of both false-positive and false-negative results (11).

Although the reported ratios vary significantly, there is generally more DS than HS found in MPS I-H. It is generally more efficient to omit extensive analysis of urinary GAGs and to proceed to the enzyme assay directly. In MPS I-H, the deficiency of α-L-iduronidase can easily be detected in isolated leukocytes or cultured fibroblasts (17), using artificial (fluorogenic, chromogenic, or radioactive) substrates. Heterozygote testing has been complicated by the marked overlap of normal and carrier groups (47), but presently DNA analysis can be used to give unambiguous information on the carrier state. Prior to undertaking carrier testing in a family, it is necessary to identify the mutant allele in that particular family, because there is a marked genetic heterogeneity in MPS-I, leading to a broad range of clinical phenotypes (35,40). Prenatal diagnosis is possible on cultured amniotic fluid cells, but because of the long waiting time for culturing and testing, rapid enzyme testing in chorionic villus biopsies has been developed. Diagnosis of MPS I on the enzyme level may present some difficulties because normal villi may have low activity (50). When the specific mutation in a given family is known, DNA analysis can be used for prenatal diagnosis, giving the most reliable results.

Laboratory aids. α-L-iduronidase, the 653 amino acid enzyme protein deficient in the MPS-I disorders, has been purified to homogeneity from a number of human sources and has been extensively characterized (9,10). The enzyme is a monomer that is proteolytically processed within the lysosome to a number of unique peptide species, which have been shown to form catalytically active aggregates (9).

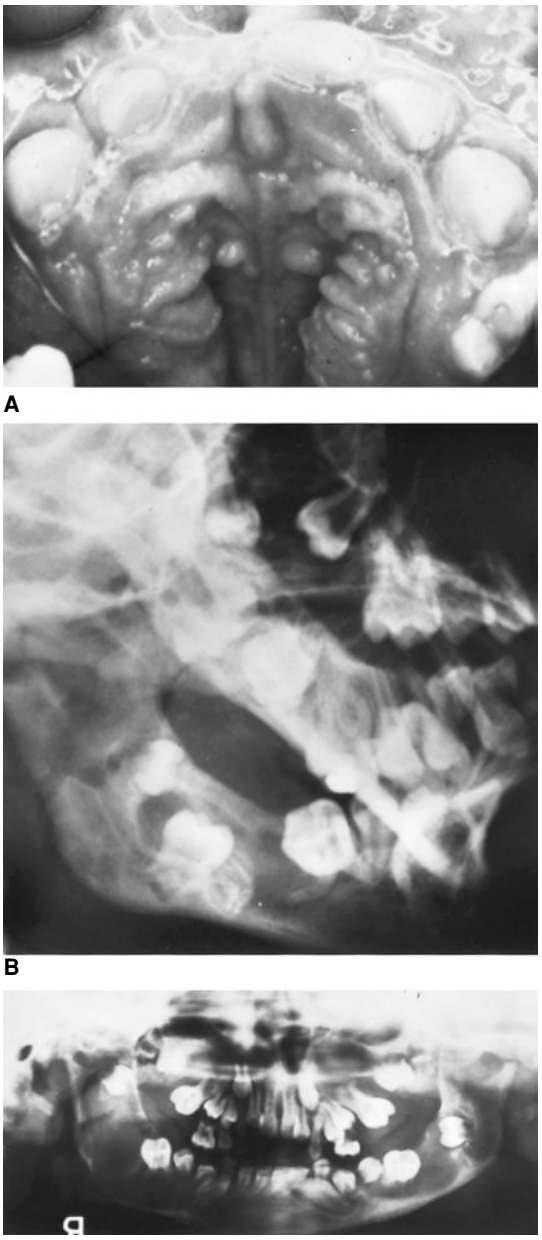


Fig. 5–5. *Hurler syndrome*. (A) Widened alveolar processes. (B) Note distoangular mandibular first molar with dilaceration of distal root, cystic bone destruction around first and second mandibular molars, partially inverted mandibular third molars in ramus, and clearly discernible cleft in mandibular notch. Condyle is hypoplastic. (C) More extensive alterations in a 9-year-old male with mucopolysaccharidosis. (A courtesy of Maj J Fay, US Army. B from HM Worth, Oral Surg 22:21, 1966. C from MA Germann, Dtsch Zahn Mund Kieferheilkd 59:59, 1972.)

Individuals with MPS-IH have from 0.0% to about 1% of normal enzymatic activity, depending on the substrate and assay conditions used. The milder forms of MPS I, Scheie and Hurler-Scheie syndromes, are likely to have at least one mutant allele that permits some residual activity (30).

The gene encoding α-L-iduronidase (*IDUA*) has been mapped to chromosome 4p16.3 (36). It consists of 14 exons spanning a distance of 19 kb, and contains a large intron (13 kb) that separates the second from the third exon (38). In the canine *IDUA* gene, a similar architecture has been found (26). There is also a murine counterpart (34).

Scott et al (37,39) found *W402X, Q70X* and *P533R* to account for over half the MPS mutations in a population of European origin. In a group of 27 Italian patients, the two most common mutations in northern Europeans (*W402X* and *Q70X*) (4) accounted for 11% and 13% of the alleles, respectively (16). In Caucasians, homozygosity or compound heterozygosity for the nonsense mutations *W402X* and *Q70X* are the common causes of MPS-I with a severe form of Hurler syndrome while the presence of *R89Q* may lead to a milder phenotype (49). In contrast, the 704ins5 and the *R89Q* mutations were the two most common MPS-I mutations in Japanese populations (49). Additional studies in a Libyan/Jewish patient (27) and in Druze and Muslim Arab patients in Israel (2) have indicated that there is marked genetic heterogeneity of MPS I-H alleles both between and within ethnic groups (5,46).

α-L-iduronidase pseudodeficiency has also been described, the proband showing clinical features of MPS I and II (1). The proband, his sister, and his father were found to be heterozygous for the common *W402X IDUA* mutation. The novel *IDUA* mutation *A300T* was identified in the proband, his sister, and his mother, which accounted for reduced IDUA activity in these individuals. They also had the *R468W* mutation, common in iduronate-2-sulfatase deficiency, which leads to the Hunter syndrome (1).

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Mucopolysaccharidosis I-S (Scheie syndrome). Sibs with mucopolysaccharidosis I-S (MPS I-S) were described in 1962 by Scheie et al (8). Patients referred to in the older European literature as having "late Hurler disease" may have had the same condition (9,10).

The disease is rarely recognized in childhood. It is characterized by normal stature, corneal opacities, deformity of the hands (clawhands), involvement of the aortic valve, normal intelligence, and biochemical evidence of lysosomal storage of HS and DS and their excessive urinary excretion.

The disorder has autosomal recessive inheritance. Its frequency has been estimated at 1/500,000 (5) to 1/600,000 (4) live births. Abnormal intracellular accumulation of DS and HS results from the deficient activity of α-L-iduronidase, the same enzyme deficiency responsible for MPS I-H (1). It is now clear that MPS I-H and I-S are caused by allelic mutations (6). The milder forms of MPS I, the Scheie and Hurler-Scheie syndromes, are likely to have at least one mutant allele that permits some residual enzyme activity. In MPS I-S, various mutations have been described (12,13).

Facies. No major abnormalities are noted in early childhood: symptoms usually become apparent by 5–15 years of age. In adults, the face is somewhat coarse, but not Hurler-like. It is broad with increased midfacial height and with mandibular prognathism. In most cases, the corners of the mouth are turned downward. Macroglossia may be present. Occasionally, the nose is broad and the nares are wide. Corneal clouding starts in early life and is initially peripheral, but by the third or fourth decade the corneal dystrophy can severely curtail vision (Fig. 5–6).

Skeletal system. Patients are normal or near-normal in height. The neck may be short. In some, the trunk is relatively shorter than the extremities. Hands and feet are broad and short, and fingers and toes are fixed in a clawlike position (Fig. 5–7). The range of mobility is limited in all joints. Genua valga and pes cavus are common (3).

The most prominent radiographic changes are small carpal bones and claw deformity of the fingers. Cystic changes are frequent in the carpals and metacarpals.

The carpal tunnel syndrome, complicated by median nerve entrapment, is common. In addition, there are widened ribs and sometimes mild hypoplasia of the basilar portion of the iliac bones.

Other findings. Intelligence is usually normal. Liver and spleen may be enlarged. Rarely, peripheral corneal clouding has been found (11). Inguinal and/or umbilical hernias are frequently present. Most adult patients show signs of aortic stenosis and/or regurgitation. The murmurs are detected in childhood, but are not clinically significant until maturity. Valve replacement has been reported, although experience is limited (2). Compression of the cervical cord by thickened dura, pachymeningitis cervicalis, with resulting myelopathy can occur in MPS I-S, though less commonly than in MPS I-H/S (7). Life span is normal or may be reduced because of cardiac disease.

Oral manifestations. The oral changes are similar to those seen in MPS I-H, MPS II, and MPS VI—i.e., cystic changes around unerupted first permanent molars. The mandibular condyles are underdeveloped.

Laboratory aids. As is true in MPS I-H, diagnosis may be readily accomplished by direct assay for α-L-iduronidase activity in isolated leukocytes or cultured skin fibroblasts (7). In childhood and late adolescence, pseudo-Hurler polydystrophy should be excluded, since the body habitus of young patients with this condition may be similar to that in MPS I-S. However, in pseudo-Hurler polydystrophy the GAG excretion is normal, the corneae are usually clear, and there is mental retardation.

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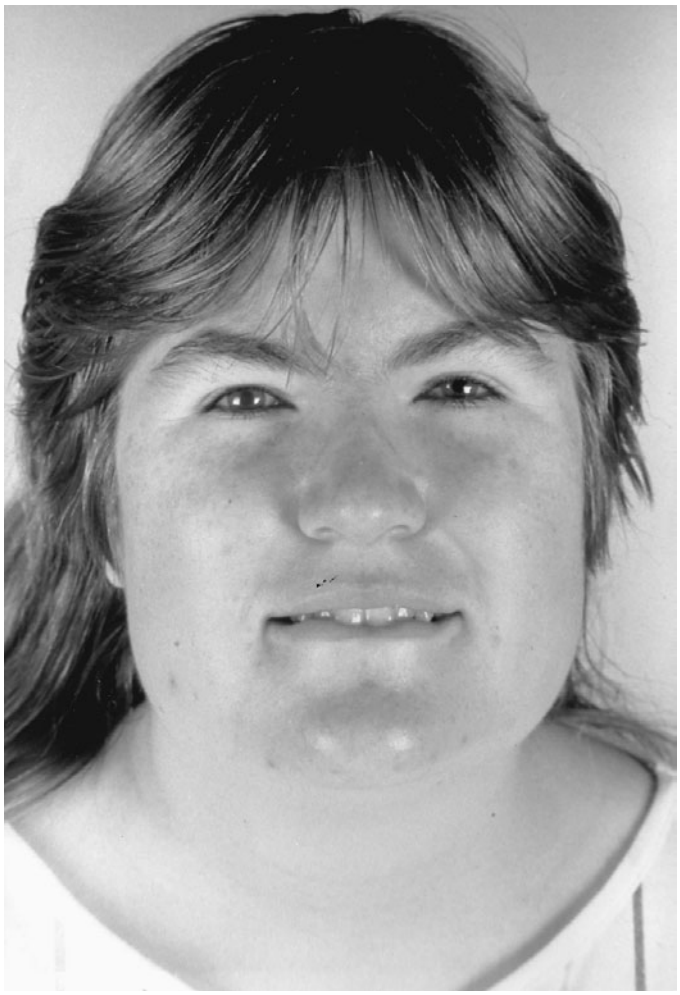

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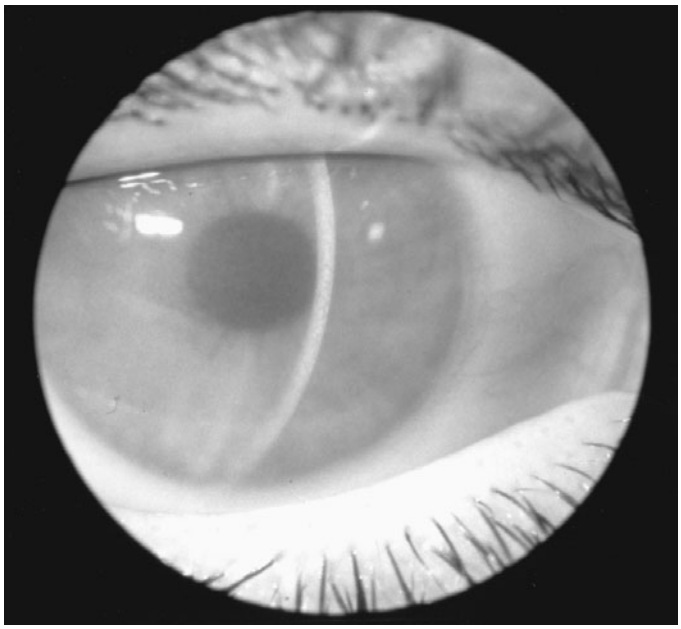

B

Fig. 5–6. *Scheie syndrome*. (A) Round face, downturned mouth, and relatively coarse facial features. (B) Cloudy cornea. (Courtesy of C Whitley, Minneapolis, Minnesota.)

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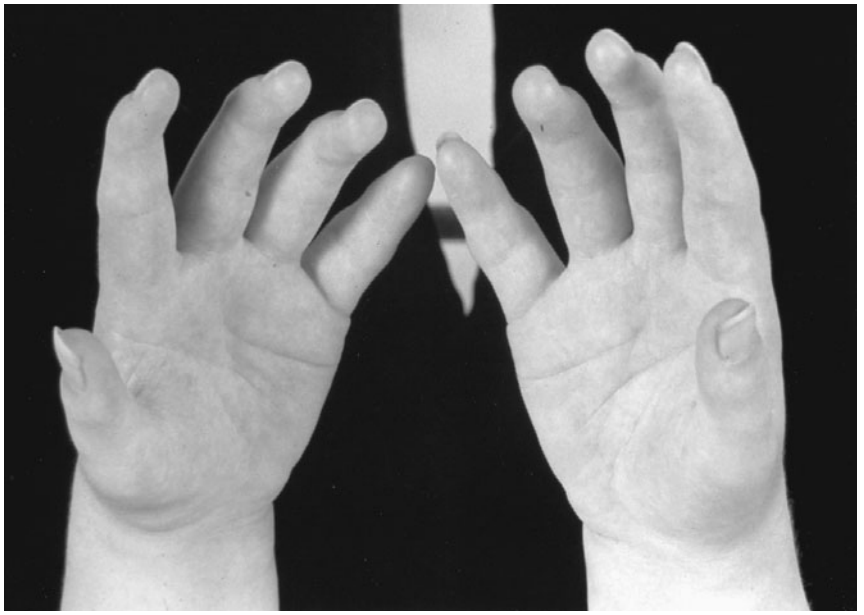
Mucopolysaccharidosis I-H/S (Hurler-Scheie syndrome). McKusick et al (7) described a third disorder having a phenotype intermediate between Hurler syndrome and Scheie syndrome, designated Hurler-Scheie disease (MPS IH/S). This disorder is also caused by a deficiency of α-L-iduronidase that results in lysosomal accumulation of DS and HS. The fact that MPS I-H/S patients have milder phenotypes than MPS I-H individuals and more severe manifestations than MPS I-S patients suggests that MPS I-H/S patients have the genetic compound of MPS I-H and I-S alleles (3,7,8). Earlier reports of MPS I-H/S patients from consanguineous parents indicated that these patients did represent the expression of other mutant alleles at the α-L-iduronidase locus (4). Molecular genetic studies have supported this supposition and have provided additional information for genotype-phenotype correlations (17). The incidence in Northern Ireland has been estimated at 1/280,000 (9).

Clinical manifestations of the disease are usually evident between 3 and 8 years of age (1,5,10) and survival to adulthood is common. Affected individuals have certain features in common with MPS I-H patients, including marked short stature, dysostosis multiplex, hepatosplenomegaly, umbilical and/or inguinal hernias, and corneal clouding (Fig. 5–8) (1,13,16,19). However, the symptoms present later and are milder than those seen in MPS I-H patients at the same age. The disease is progressive, particularly with regard to cardiopulmonary disease, and death usually occurs by age 25 years (18) due to cardiac involvement and upper airway obstruction. Nearly all patients are mentally normal (1). Psychotic symptoms have been observed in older patients (2). Other anomalies include hearing loss (12%), thickened skin (25%), hirsutism (20%), and carpal tunnel syndrome (10%) (1). In a 5-year-old boy with MPS I-H/S, diffuse thickening of the skin and clustered, skin-colored papules on the upper portions of thighs, scapular area, and sides of the arms were reported (14). Earlier, these papules were supposed to be unique findings in MPS II (12). Pachymeningitis cervicalis, compression of the cervical cord due to mucopolysaccharide accumulation in the dura, occurs in MPS I-H/S, but communicating hydrocephalus appears to be uncommon in patients with normal intelligence (10). Severe nasal polyps have been documented (6).

Oral findings. Oral findings are similar to those found in MPS I-H patients. Some patients with MPS I-H/S have micrognathism that creates a characteristic facies (10). Particular care must be taken in the induction of anesthesia (11). Airway obstruction and sleep apnea have been reported, as in both Hurler and Hunter syndromes.

Laboratory aids. The diagnosis of MPS IH/S can be confirmed by demonstration of deficient α-L-iduronidase activity in isolated leukocytes or cultured fibroblasts, or by the massive urinary excretion of DS and HS. Residual α-L-iduronidase activity has been detected in all three MPS I subtypes. By characterization of the allelic mutations at the molecular level, classification of patients with MPS I-H, I-S, and I-H/S has become possible (15,17). Finally, it is anticipated that the explanation for the



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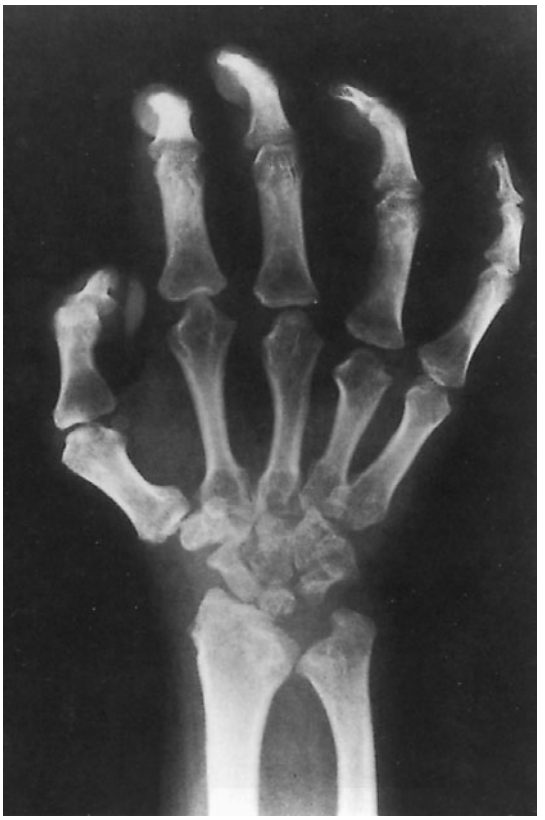

B

Fig. 5–7. *Scheie syndrome*. (A) Contractures. (B) Clawing deformities of fingers, and small carpal bones with reduced carpal space. (A courtesy of C Whitley, Minneapolis, Minnesota. B from CG Summers et al, Ophthalmology 96:977, 1989.)

presence of severe neurologic manifestations in MPS I-H and I-H/S and their absence in MPS I-S patients will provide further insight into the pathogenesis of α-L-iduronidase deficiency.

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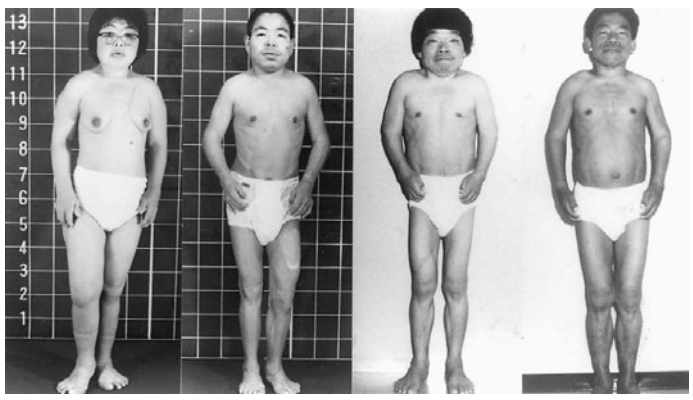
Fig. 5–8. *Hurler-Scheie syndrome*. Four patients from two families. Note similarity of phenotype. (From N Kaibara et al, Hum Genet 53:37, 1979.)



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Mucopolysaccharidosis II (Hunter syndrome). The first patients manifesting the X-linked form of MPS were reported by Hunter in 1917 (18). These two brothers were mildly affected at ages 8 and 10 years, respectively, with clear corneas and apparently normal intelligence. Although they died at 11 and 16 years, they probably suffered from the mild form of the disease (MPS II–mild), which is compatible with survival to adulthood (41,49,55). In the severe form (MPS II–severe), which occurs three to four times more frequently than the mild form, rapid motor deterioration and progression of physical deformities may be observed after the third year of life, with death usually occurring between 4 and 14 years of age (41,56).

A deficiency of the enzyme iduronate-2-sulfatase (IDS) is the cause of both forms of Hunter syndrome (MPS II) (1), resulting in progressive accumulation of DS and HS. Approximately 20% of the patients have deletions of the whole gene or major structural alterations (7,16,21,29). An IDS-related region (IDS2) has been found which is located on the telomeric side of the *IDS* gene at Xq28 within 80 kb (4).

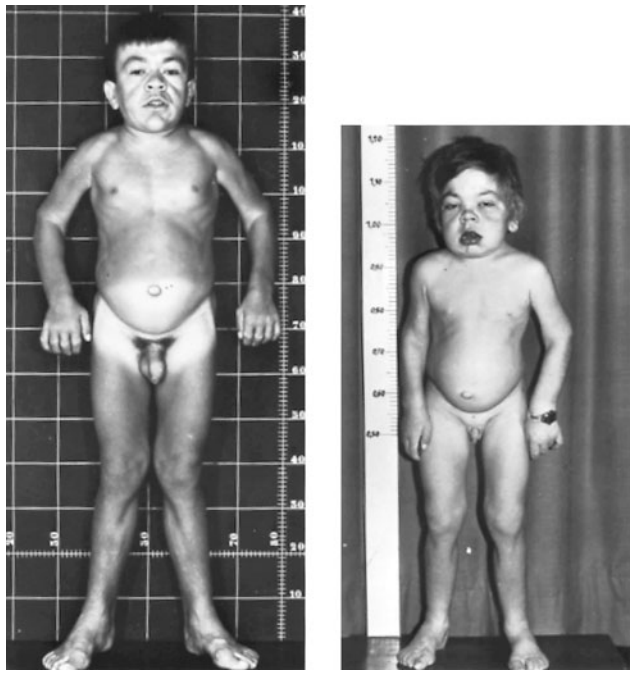
In patients with the severe Hunter syndrome, molecular and phenotypic variation is great (47,51). Missense or nonsense point mutations as well as deletions of various numbers of base pairs have been described (6,17a,19,20a,21a,22,44). Mutation "hot spots" have been noted (31). In two patients with Hunter syndrome who had a complete deletion of the *IDS* gene, features were seen that were uncommon in this syndrome (53)—e.g., early onset of seizures and ptosis. Contiguous gene syndromes were postulated (53). Truncation of the last 108 amino acids of iduronate sulfatase permitted an intermediate clinical phenotype of Hunter syndrome and a trace of residual enzyme activity (43). Recently, it was demonstrated in a patient with features of moderate to severe Hunter syndrome that a complete lack of expression of IDS is consistent with the moderate to severe phenotype (48). There is certainly molecular and phenotypic variation (47).

Incidence of MPS II has been estimated at 1/78,000 to 1/111,000 male births in British Columbia (23). In Northern Ireland, the incidence has been estimated 1/72,000 male live births (26). It may be more common among Jews (34,57).

Data about the number of new mutations vary from 25% (8) to 100% (20). MPS II in female patients is a rare occurrence that requires nonfunctionality of the *IDS* gene on both X chromosomes (27). Interestingly, full expression of the MPS phenotype has been observed in two females, one with an X/5 translocation breakpoint presumably involving the region Xq26 (33), the other with a small X chromosome deletion involving band Xq25 (5). Tools for the genetic analysis of similar patients have been developed (12). Hunter syndrome has also been reported in karyotypically normal females (9,45).

Facies. Macrocephaly is present, with all measurements being enlarged. The facies, although similar to that observed in MPS I-H, is sufficiently different as to be distinguishable. Although all MPS I-H facies are very similar as a whole, the facies of any MPS II patient bears a coarse resemblance to the facies of family members. The facies of patients with the more common MPS II–severe form is usually more striking than that of the milder form (41,55) (Figs. 5–9 and 5–10).

Skeletal system. The neck is short, the chest is broad, and the abdomen protrudes with umbilical hernias. Moderate thoracolumbar kyphosis may be present. The trunk is relatively shorter than the extremities. Joint mobility is restricted, with clawlike deformities of the fingers. The gait is stiff, with the trunk bent forward. Typically, there is shortness of stature only from about 3 years of age; however some patients are not dwarfed until 5 or 6 years of age. Patients with the severe form of MPS II grow as fast or faster than healthy children during the first 2–3 years of life. Adults with a mild type reach a height of between 120 and 140 cm (55), whereas patients with the severe form reach a height of between 105 and 115 cm.



A B

Fig. 5–9. *Hunter syndrome*. (A) Sixteen-year-old male with mild MPS II. He has mild coarseness of facies with broad face, low nasal bridge, joint contractures, and genua valga, as well as mixed hearing loss and normal intelligence. (B) Thirteen-year-old patient with severe MPS II. Growth retardation is evident, and he has abundant and coarse scalp hair, coarse facies, low nasal bridge, and open mouth. (A from UN Wiesmann and S Rampini, Helv Paediatr Acta 29:73, 1974).

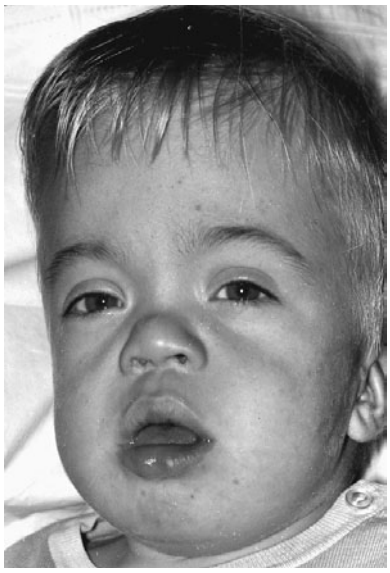
Radiographic changes are qualitatively similar to, but quantitatively less pronounced than, those observed in MPS I-H when compared at identical ages (41).

Other findings. Intelligence is only slightly impaired in the mild form. In the severe type, there is progressive loss of intellectual function after the age of 2–3 years. In retrospect, it can be seen that intellectual function of these patients never was normal. At 3 years of age, patients may be brought to a physician because of lack of speech. Patients become restless, hyperactive, and destructive (2,56). Diarrhea due to autonomic nervous system involvement and perhaps also to mucosal dysfunction is common (56). Hepatosplenomegaly, inguinal, and/or umbilical hernia, and cardiovascular defects are often found (32).

Eye findings. Corneal clouding does not occur in either the mild or severe forms with rare exception (42). Optic nerve head swelling and optic atrophy have been described (10). Vision may be impaired because of retinitis pigmentosa or chronic papilledema associated with chronic hydrocephalus. Two brothers were reported with bilateral epiretinal membranes (25).

Central nervous system. The central nervous system deterioration is probably exacerbated by moderate to severe communicating hydrocephalus with increased intracranial pressure after the age of 7 to 10 years (27,39). In a 44-year-old Japanese male with a mild type of Hunter syndrome, cranial magnetic resonance imaging (MRI) revealed patchy areas of increased and decreased signals in the thalamus and basal ganglia giving rise to a honey comb–like appearance as a whole (40). Thickening of soft tissue posterior to the odontoid peg was present with associated canal stenosis in five cases studied, resulting in compression of the cervical cord in four (28).

In both forms of the disease, progressive hearing loss occurs in most patients. It is often of the mixed type but may be predominantly conductive or sensorineural (35).



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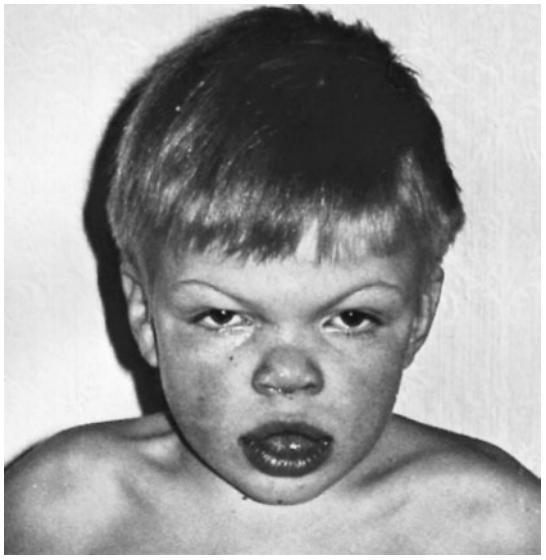

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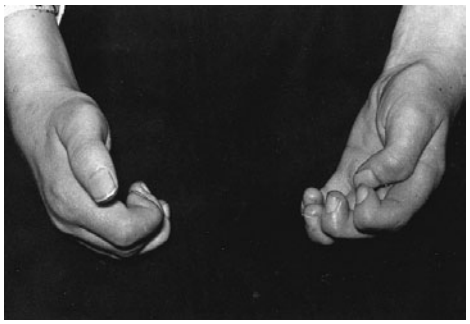

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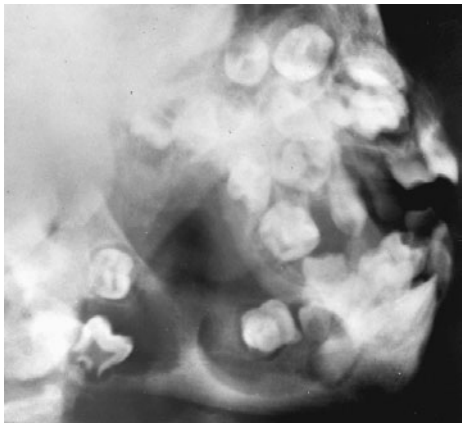

D

Fig. 5–10. *Hunter syndrome*. (A) Coarse facies, low nasal bridge, and open mouth. (B) Compare facies with patient in A. (C) Clawhands. (D) Radiograph showing cysts around crowns of malaligned teeth. (B,C from E Passarge et al, Dtsch Med Wochenschr 99:144, 1974. D from HM Worth, Oral Surg 22:21, 1966.)

Skin findings. Skin changes, present in a minority of patients, consist of hard, nontender, irregularly shaped papules (pebbling of skin) varying in size from a few millimeters to a centimeter in diameter located over the scapulae and deltoid areas (30,46). These papules are also found in MPS I-H/S (36).

Oral findings. Oral characteristics are the same as those in Hurler syndrome (14).

Complications. Patients with the severe form usually die by 15 years of age; death is preceded by complications of progressive neurologic deterioration. Cardiopulmonary disease, primarily resulting from infiltrative valvular disease, is a common cause of death. In contrast, patients with the mild form typically live into the sixth and seventh decades of life. Disease complications in these adult patients include carpal tunnel syndrome with medial nerve entrapment, degenerative disease of the hips, compromised respiratory function, and sleep apnea (38).

Laboratory findings. Most patients with MPS II excrete approximately equal amounts of DS and HS in the urine, which is readily determined by routine screening tests. Alder-Reilly granules may be present in peripheral granulocytes and bone marrow cells. Lymphocytes show metachromatic granules within vacuoles following toluidine blue staining. Ultrastructural studies show single membrane-bound structures that are even evident on conjunctival biopsy (24).

Hemizygotes with both forms of MPS II can be enzymatically diagnosed by the demonstration of iduronate sulfatase deficiency in serum, isolated leukocytes, and cultured fibroblasts (13,50). Carrier detection is more difficult because of random X-inactivation, but has been accomplished by enzymatic and DNA techniques (3,37,52,54). Germline mosaicism has been reported in MPS II (3,17). Prenatal diagnosis has been carried out in hemizygotic males and heterozygous female fetuses as well (11,15).

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Mucopolysaccharidosis III (Sanfilippo A, B, C and D syndrome). Mucopolysaccharidosis III (MPS III) was first recognized in 1958 by Meyer et al (23) and later described by Meyer et al (24) and Sanfilippo (30). The disease is characterized by severe mental and neurologic degeneration associated with relatively mild MPS features resulting from the progressive lysosomal accumulation of HS (7).

Four enzymatic steps are required for the normal degradation of HS, and deficiency of each enzyme in the pathway has been found in patients with MPS III (see Table 5–1). MPS IIIA results from deficient heparan-*N*-sulfate activity (22,33), MPS IIIB from defective α-*N*-acetylglucosaminidase activity (28,40), MPS IIIC from deficient α-*N*-acetyltransferase activity (16), and MPS IIID from deficient α-*N*-acetylglucosamine-6-sulfate sulfatase activity (5). An animal model of MPS IIID has been reported (36). Most notably, all four enzymatic defects result in the lysosomal accumulation of HS and cannot be differentiated phenotypically. All four subtypes have autosomal recessive inheritance. Taken together, the MPS III subtypes represent the most common type of mucopolysaccharide disorders, their frequency having been estimated at about 1/24,000 in The Netherlands (28a,38) and 1/280,000 in Northern Ireland (25). Because of the mild somatic phenotype of MPS III subtypes, the frequency estimate may be lower than the actual incidence of the disease. MPS IIIA is found most often in the United States and the United Kingdom while MPS IIIB is more common in Greece (2,37).

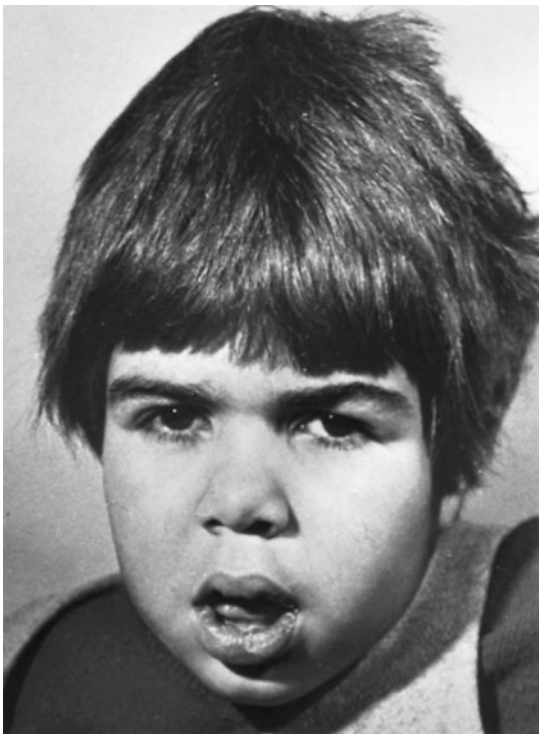

Fig. 5–11. *Sanfilippo syndrome*. Seven-year-old girl with MPS III. Note coarse features and thick abundant scalp hair. (From E Passarge et al, Dtsch Med Wochenschr 99:144, 1974.)

The isolation, sequence, and expression of cDNA clones encoding the enzyme deficient in MPS IIIA has been reported. The gene has been mapped to 17q25.3 (14,33). Mutational analyses have been reported from various ethnic groups, thus facilitating molecular diagnosis of MPS IIIA and allowing heterozygote testing in these populations (3,4). A late onset type has been described (1b).

The gene for α-*N*-acetylglucosaminidase, the enzyme involved in MPS IIIB, has been cloned, mapped to 17q21, and symbolized as *NAGLU* (43,44). Subtype IIIC has been mapped to chromosome 14 and IIID to 12q14. Additional mutations have been reported (32) and attempts at genotype–phenotype correlation have been made (1a,40a,45).

Facies. No abnormalities are noted in the young child. Older children may develop mild facial coarsening resembling that of patients with the MPS I-H phenotype, but the facial features never become as strikingly abnormal as in MPS I-H. Approximately 80% of children with MPS III have a dull appearance with a slightly sunken nasal bridge and abundant, coarse scalp hair (29). The latter finding is the most consistent clinical feature even in children without other morphologic alterations. Hairs have been described as triangular (6) or as having marked variability in shape and pigment in cross section (35). Corneal clouding is absent (Fig. 5–11).

Skeletal system. Height may be slightly reduced or normal. Joint mobility may be mildly restricted in elbows and knees. Radiographically, thickening of the posterior calvaria, sclerotic mastoids, ovoid-shaped vertebral bodies, and minimal hypoplasia of the supra-acetabular portions of the ilia are the most consistent abnormalities (10,18) (Fig. 5–12). Otherwise, dysostosis multiplex develops slowly and is very mild. For example, the hands in MPS III are normal.

Other findings. Early development is usually normal. In the second to fifth year of life, development ceases, and behavioral problems, such as restlessness, aggressiveness, diminished attention span, and sleep disturbances, become manifest. Aggressive hyperactivity is frequently the parents' reason for seeking medical help. Subsequent to this hyperactivity

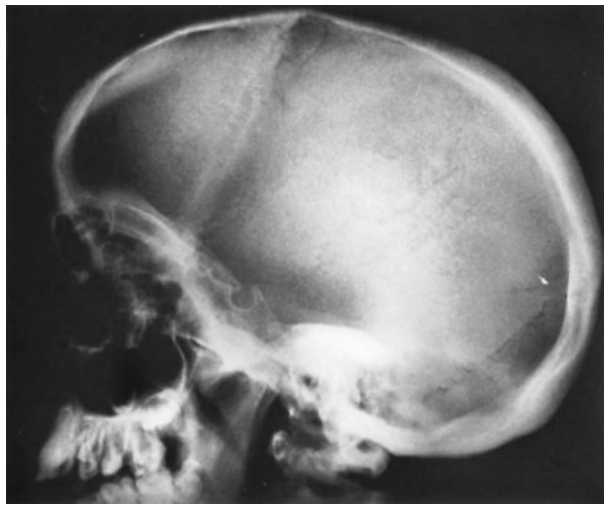

Fig. 5–12. *Sanfilippo syndrome*. Thickening of parietal and occipital portions of cranial vault in 11-year-old girl with MPS III.

is a progressive loss of mental and motor skills. Loss of environmental contact is evident prior to a "vegetative" state, with spastic diplegia and death occurring between the ages of 10 and 20 years (26). A comparison of the clinical course of patients with MPS IIIA, B and C indicates that patients with MPS IIIA are generally more severely affected than those with B or C subtypes (1,19,38,39,42). Subtype A has earlier onset, is more marked, and results in earlier death. In addition, intrafamilial variation in the clinical expression of each of the subtypes has been noted (22,38), consistent with different allelic mutations causing genetic heterogeneity in each subtype. The clinical manifestations of only 10 patients with MPS IIID have been reported to date (13).

Pathologic study of the brain has revealed marked deposition of HS as well as ceramide polyhexoside and G_{M1} ganglioside in the cerebrum (11,17). Hearing loss is frequently suspected but difficult to prove. Hepatosplenomegaly is present in more than 80% of patients. Histochemical and ultrastructural studies of MPS III have been reported (8,12,34).

Oral manifestations. There seem to be no remarkable oral manifestations, but tooth abscesses are of major concern during the late stage of the disorder. Obliteration of pulp chambers has been reported in one child (41). The tongue is not large but may protrude later in the disorder.

Laboratory findings. Clusters of coarse granulations are seen in the cytoplasm of about 35% of peripheral lymphocytes and in plasmacellular and reticulohistiocytic cells of the bone marrow. The granulations are frequently surrounded by areas of diminished stainability. The inclusions stain metachromatically with toluidine blue. Excessive amounts of HS (in the absence of DS) are excreted in the urine. It should be noted that the diagnosis of this disorder by demonstration of increased urinary excretion of HS may be missed by using certain procedures, such as the toluidine blue filter paper test.

Definitive diagnosis of each of the subtypes of MPS III, carrier detection, and prenatal diagnosis in chorionic villi or cultured amniocytes are feasible by demonstration of deficient enzyme activity (9,15,21,27,37).

A dog model was reported by Aronovich et al (1).

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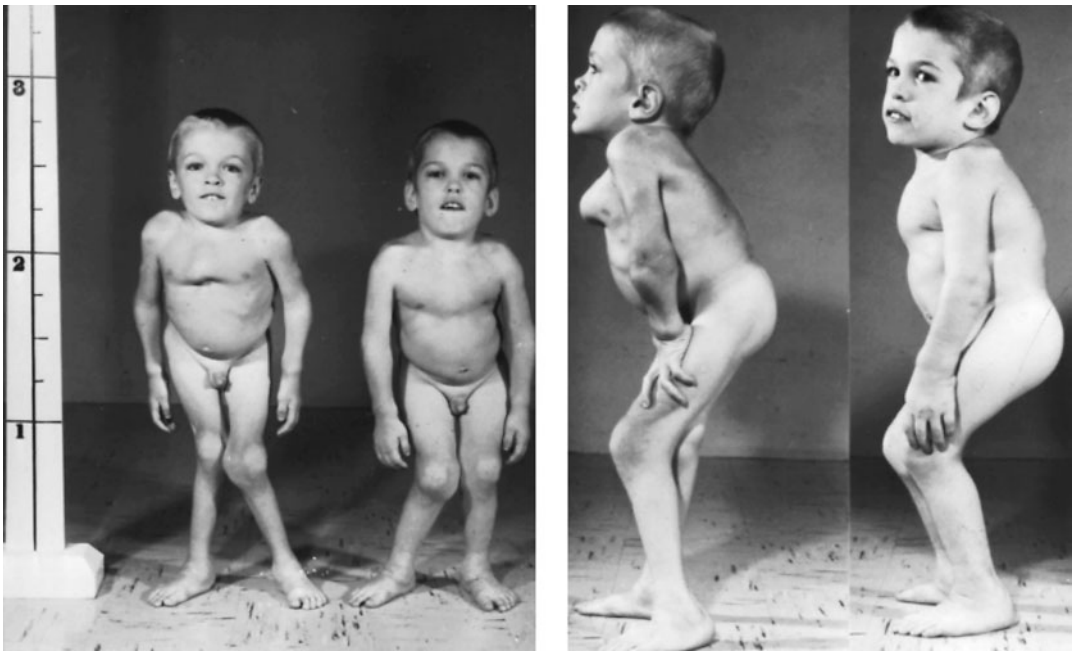
Mucopolysaccharidosis IVA and IVB (Morquio syndrome). In 1929, Morquio (29) and Brailsford (4) independently reported cases of a disorder characterized by short trunk dwarfism, progressive spinal deformity, short neck, pectus carinatum, genua valga, pes planus, odontoid hypoplasia, and normal intelligence (Figs. 5–13 to 5–15). Clinical and, later, biochemical and molecular heterogeneity was demonstrated by Dale (8) as early as 1931 and later by others (15,16,34). About 1960, the disorder was recognized as a MPS, caused by lysosomal accumulation and urinary excretion of the glycosaminoglycan KS.

Matalon et al (27) discovered the more common severe form (MPS IVA), caused by a deficiency of galactosamine-6-sulfate sulfatase, an enzyme that degrades KS (41). Arbisser et al (1) described a patient with normal *N*-acetylgalactosamine-6-sulfate sulfatase but deficient lysosomal β-galactosidase. This generally milder condition, known as MPS IVB, has been reported in several patients (1,12,13,17,21,46). However, not all examples have been mild (17,48). That β-galactosidase was indeed the primary defect was indicated by the absence of an endogenous inhibitor and by the intermediate enzyme levels in the parents (13,42). Maroteaux et al (26) described two patients with a clinical picture consistent with Morquio syndrome, but with normal *N*-acetylgalactosamine-6-sulfate sulfatase and β-galactosidase activities. Through fluorescence in situ hybridization, galactosamine-6-sulfate sulfatase was mapped to chromosome 16q24.3 (2,44).

MPS IVA has subsequently been shown to have severe, intermediate and even mild forms (7,16,32–34,46), implying different alleles. Difference in severity may also be explained by the associated finding of reduced neuraminidase activity in some cases (12). On the molecular level, allelic heterogeneity was proved and appeared to be marked (5,43a,45). A great number of different mutations (e.g., missense, nonsense, splice site alteration, cryptic site alteration, premature termination) have been reported from different populations (19,23,45). All forms of Morquio syndrome have autosomal recessive inheritance. The frequency of MPS IVA has been estimated to be about 1 in 76,000 (31) to 1 in 216,400 (25). The frequency of MPS IVB has not been estimated, but it is rarer than MPS IVA.



A B

Fig. 5–13. *Morquio syndrome*. (A,B) Brothers, ages 10 1/2 and 9 1/2 with dwarfism, kyphosis, genua valga, flexed knees, abnormally short neck, sternal protrusion, and large joints. (From H Zellweger et al, J Pediatr 59:549, 1961.)

MPS IVA. Type IVA has three grades of severity, and dental findings are present in all grades (11,32–34).

Facies. The facies is not specific, but the lower half of the face is often outstanding because of shortness and hyperextension of the neck.

Musculoskeletal system. There is reduced height because of shortened neck and trunk and, to a lesser extent, shortened extremities. Adult height rarely exceeds 100 cm (range 80–120 cm). The head is essentially normal, but mild scaphocephaly may be present because of premature closure of sutures. The head seems to rest directly on the shoulders. The neck is greatly shortened, with exaggerated cervical curvature and restricted movement (8,39,43).

Cervical myelopathy is an important complication (28,36). Cervical MRI studies have shown that the degree of cord compression may be more marked than that suggested by symptoms and signs (20). After the second year of life, the thorax exhibits marked kyphosis or kyphoscoliosis, with general flattening of vertebrae and a characteristic pectus carinatum, the sternum extending almost horizontally from its clavicular junction, then angling downward in midsection. The lumbar region of the spine frequently exhibits a gibbus-like kyphosis or, less often, lordosis in the region of the first lumbar vertebra (Fig. 5–13). Spinal cord compression may occur in the upper cervical segment as a complication from either atlantoaxial dislocation or subluxation at the thoracolumbar gibbus (3) and may result in death.

Extremities appear disproportionately long. There may be excessive joint mobility, and the wrists are usually enlarged. Genua valga, thickened knee joints, and pes planus are nearly constant findings (Fig. 5–13). The stance is semi-crouching. Usually there is a prominent potbelly.

Radiographically, generalized platyspondyly with hypoplasia of the last thoracic and first lumbar vertebrae, coxa valga, flared ilia, and progressive femoral head flattening and fragmentation are found. In the young child, the vertebral bodies are ovoid and the superior acetabulae are deficiently ossified. The odontoid process is hypoplastic or absent. The bases of the second to fifth metacarpals are conical, but their shafts are normally constricted (24), (Fig. 5–14). The distal ends of the radius and ulna are inclined toward each other. All the bones become markedly osteoporotic.

Other findings. The corneas become slowly but diffusely opacified in the form of a filmy haze; this is rarely obvious to the unaided eye before the tenth year of life. Glaucoma may develop (6,48), as well as cataracts (38). Progressive hearing loss usually begins in adolescence.

Intelligence is nearly always normal. Mitral and aortic regurgitation have been reported (49).

MPS IVB. In contrast to patients with MPS IVA, affected individuals with MPS IVB have a significantly milder phenotype. They have normal intelligence, milder dysostosis multiplex, mild pectus carinatum, corneal clouding, odontoid hypoplasia, moderate lumbar kyphosis, and minimal genua valga. Radiographs show platyspondyly and tongue-like protrusions of the lumbar spine. C2–C3 subluxation has been noted. Typically, the patients have normal hearing and no cardiac murmurs. Corneal clouding may be obvious or a slit- lamp examination may be required to observe fine corneal deposits. Often the clinical onset of the disease is characterized by an unstable, waddling gait.

Oral manifestations. In patients with MPS IVA, both the deciduous and permanent teeth have dull, gray crowns with pitted enamel that is very thin and has a tendency to flake off, causing small diastemas between the teeth (32,39a). The cusps are small, flattened, and poorly formed, and caries is frequent (11,40) (Fig. 5–15). The mandibular condyles may be flat or concave (39a). In contrast, in MPS IVB, the enamel appears normal and provides a means through which to clinically distinguish between the two types. Patients with MPS IVB tend to have a wide palate and widely spaced teeth.

Differential diagnosis. Practically all types of short-spine dwarfism have been confused with Morquio syndrome. In contrast to Morquio syndrome, *achondroplasia* is usually apparent at birth, with skeletal changes entirely different from those in MPS IVA. *MPS I-H* has radiographic similarities to Morquio syndrome during the first few years of life, but mentality is reduced and the gross physical appearance is strikingly characteristic. Although corneal clouding and hearing loss were thought to be the distinguishing factors, they are also features of Morquio syndrome (48). Multiple epiphyseal dysplasia, a dominantly inherited disorder, may also simulate Morquio syndrome, but spinal involvement, if present, is of a lesser degree.

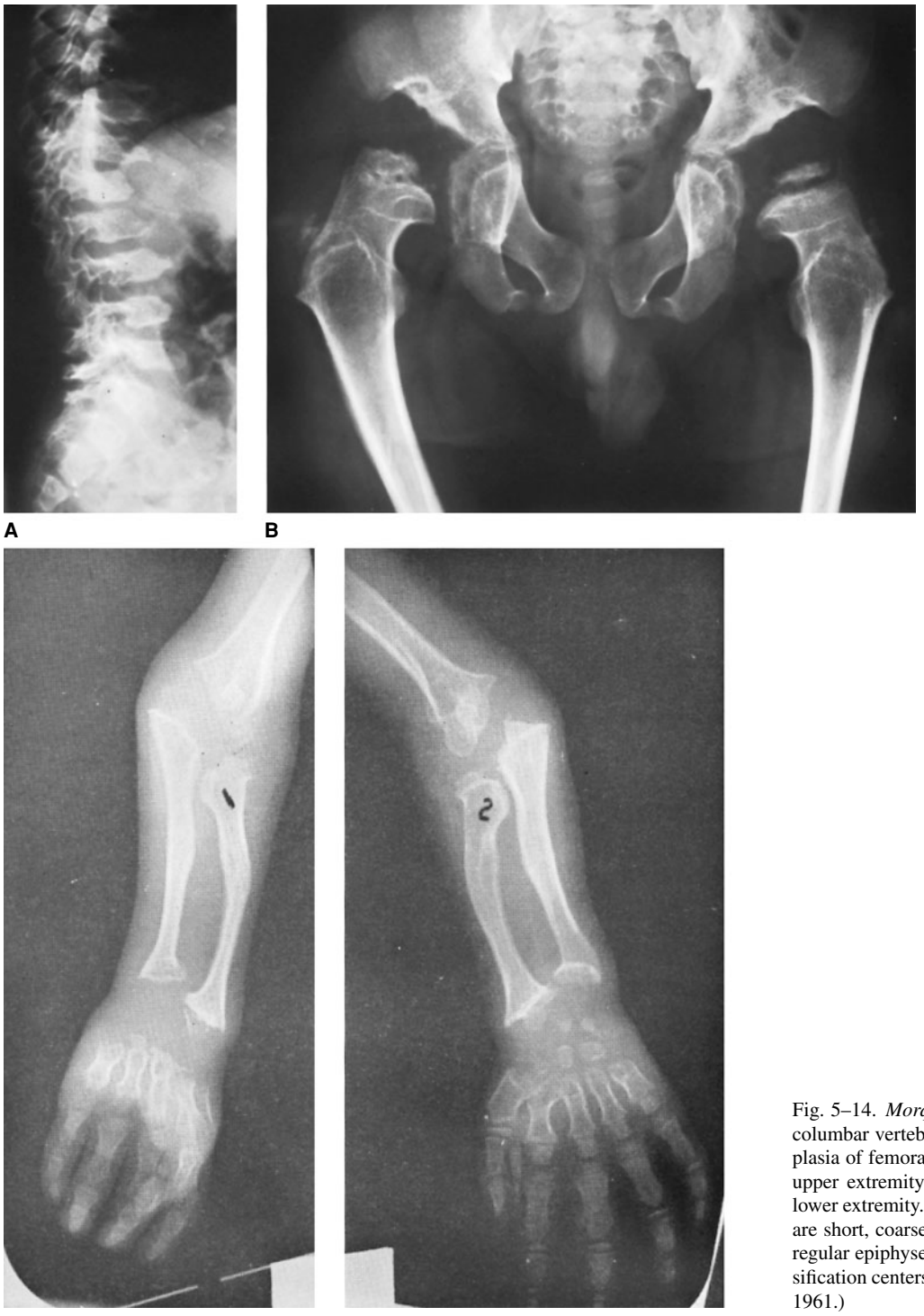


Fig. 5–14. *Morquio syndrome*. (A) Platyspondyly of thoracolumbar vertebrae. (B) Deficiently ossified acetabula, dysplasia of femoral heads, and coxa valga. (C) Long bones of upper extremity are more severely involved than those of lower extremity. The humerus, radius, ulna, and metacarpals are short, coarse, curved, and irregularly tubulated, with irregular epiphyseal plates. Also note deficiency of carpal ossification centers. (From H Zellweger et al, J Pediatr 59:549, 1961.)

Diastrophic dysplasia is characterized by progressive kyphoscoliosis, but normal vertebral body height, micromelia, clubfoot, widening of metaphyses and epiphyses of long bones, some limitation of joint motion, and thickened pinnae easily distinguish Morquio syndrome.

Children with metatropic dysplasia at first exhibit a long-trunked and later a short-trunked dwarfism. The disorder is characterized by progressive kyphoscoliosis and anisospondyly without hypoplasia of the last thoracic and first lumbar vertebral bodies.

Spondyloepiphyseal dysplasia congenita, a type II collagen defect, inherited as a dominant trait, is a short-trunk dwarfism. There is platyspondyly but little or no involvement of the hands and feet, no corneal clouding, and no keratansulfaturia. Myopia is often severe. Rickets and *hypophosphatasia* should also be considered.

Individuals with *Dyggve-Melchior-Clausen syndrome* somewhat resemble those with Morquio disease in skeletal alterations but do not have corneal clouding, do not excrete KS in the urine, and are usually mentally retarded. They do not have enamel deficiency. Pointing of the proximal metacarpals does not occur. There is neither hypoplasia of the odontoid process nor of the inferior thoracic and lumbar vertebrae. The iliac crest has a lacy border. The disorder has autosomal recessive inheritance. Since several patients have had normal intelligence (Smith-McCort dysplasia), this disorder has genetic heterogeneity (30).

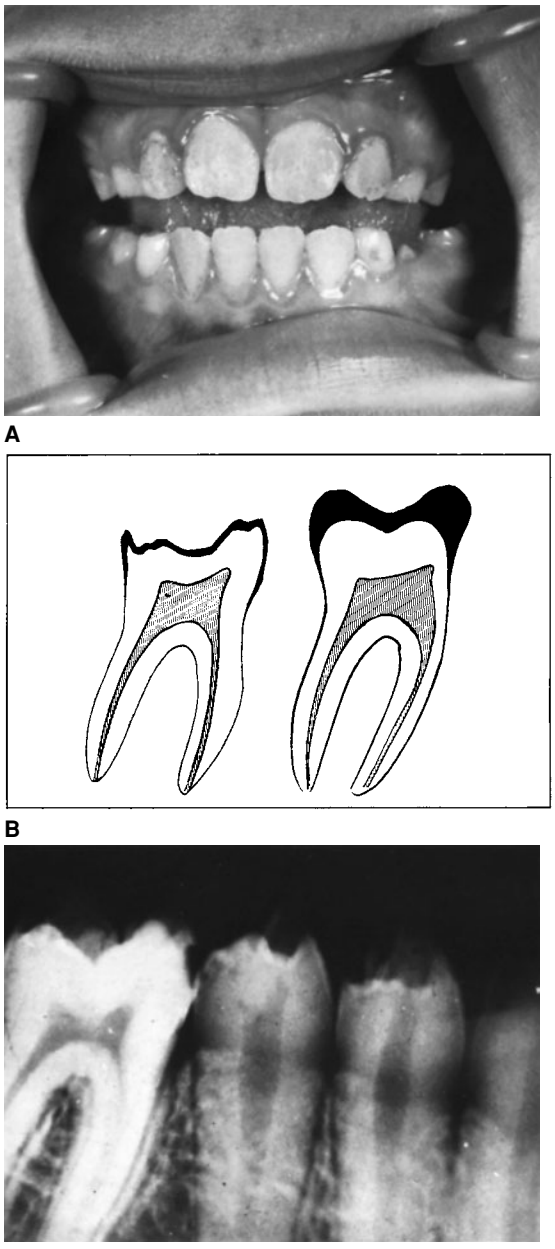


Fig. 5–15. *Morquio syndrome*. (A) Hypoplasia of enamel. (B) Diagram of lower molar showing reduced thickness of enamel layer in affected tooth (left) compared with corresponding tooth in normal sibling. (C) Dental radiograph showing reduced enamel thickness. (B,C from SM Garn and VO Hurme, Br Dent J 93:210, 1952.)

Congenital dysplasia of the odontoid process with atlantoaxial dislocation can be seen in a number of disorders: Morquio syndrome, *Aarskog syndrome, Dyggve-Melchior-Clausen syndrome,* pseudoachondroplasia, *cartilage-hair hypoplasia, spondyloepiphyseal dysplasia congenita*, and spondylometaphyseal dysplasia.

Laboratory findings. Marked excretion of KS in the urine in childhood is a constant feature but excretion diminishes markedly by the teenage years in MPS IVA. Some younger patients with MPS IVB do not excrete KS (10,22,35). *N*-acetylgalactosamine-6-sulfatase may be determined in cultured fibroblasts, isolated leukocytes, cultured amniotic cells, and chorionic villi (50). The same applies to mutational analyses (18,37,47), postnatally as well as prenatally. β-Galactosidase may be assayed using a *p*-nitrophenyl or 4-methylumbelliferyl β-galactoside (1).

Marked excretion of KS in the urine, in childhood, is a constant feature of MPS type IVA (12). It slowly decreases, reaching normal levels in adults. Usually coarse granular inclusions may be found in peripheral neutrophilic granulocytes and fibroblasts exhibit metachromasia. Ultrastructural studies of epiphyseal plates (22) and brain (23) have been described. Prenatal diagnosis has been carried out (23a,51).

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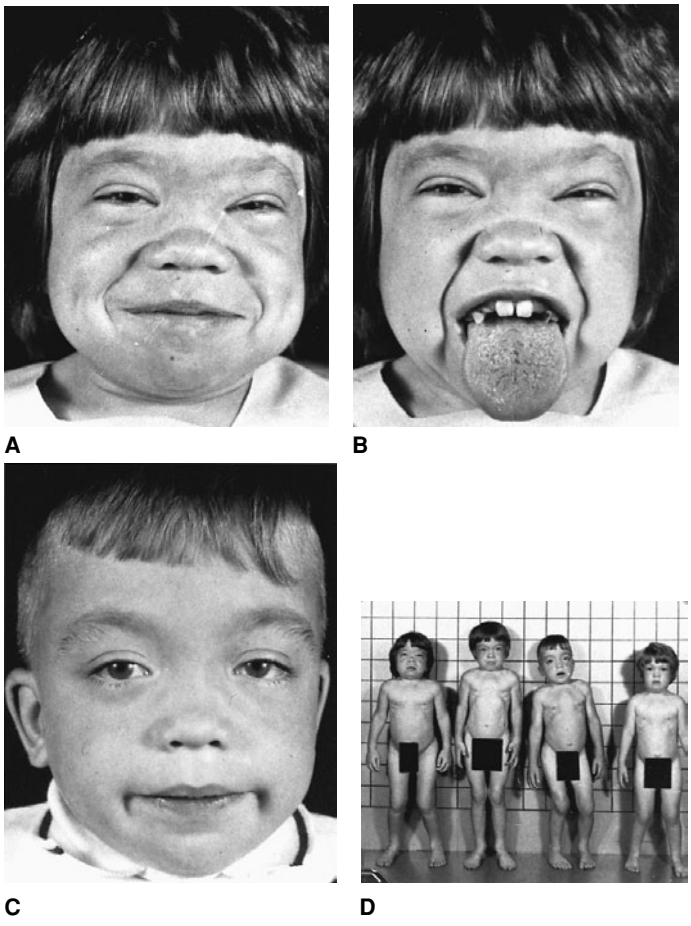


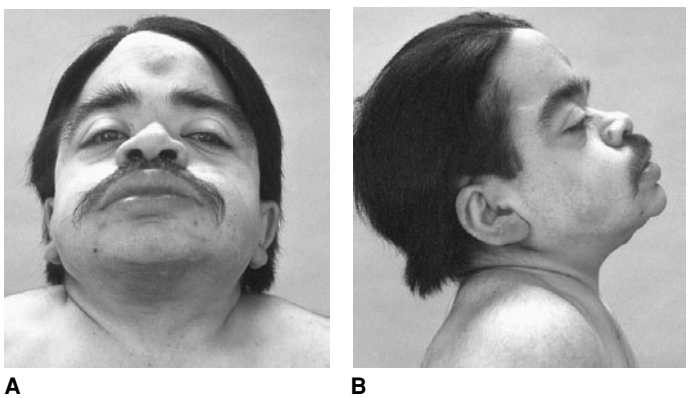
Fig. 5–16. *Maroteaux-Lamy syndrome*. (A–D) Note coarse facies, large head, hypertelorism, flat nasal bridge with arched nostrils, fissured tongue, anterior sternal protrusion, genua valga, protruding abdomen, and growth retardation. (Courtesy of VA McKusick, Baltimore, Maryland.)

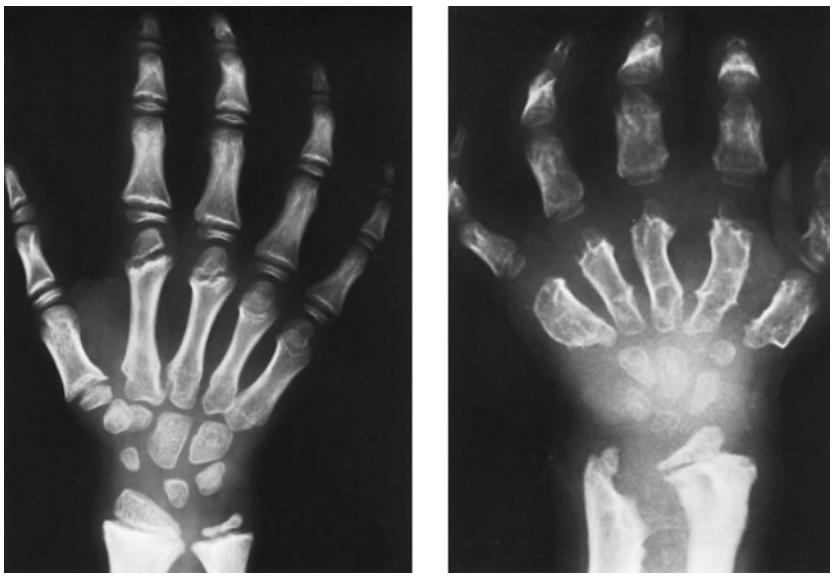
Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome). In 1963, Maroteaux et al (16) described a patient with a moderately severe Hurler-like phenotype but normal intelligence and high urinary excretion of DS.

Three forms of mucopolysaccharidosis VI (MPS VI) exist: mild type (21,24), intermediate type, and severe type (25,32,33). There may even be a very mild form (29). Mutational studies in variable phenotypes have been performed (6). Children with the mild type develop reasonably well until about 6 years of age when short stature, corneal clouding and spinal deformities are noted. Legg-Perthes–like disease of the hips and aortic stenosis become apparent. The patients usually survive to adulthood (21). In patients with severe type, morphologic changes are noted in early childhood and the disease progresses more rapidly to a state of severe disability with strikingly short stature, coarse facial appearance, hyperextended head, musculoskeletal abnormalities, severe corneal clouding, markedly reduced hearing, and prominent cardiac defects that frequently lead to death in adolescence (Figs. 5–16 and 5–17).

MPS VI has autosomal recessive inheritance, the three types being the results of allelic mutations in the structural gene encoding arylsulfatase B. The gene has been mapped to chromosome 5q13–q14 (12) by in situ hybridization. The Maroteaux-Lamy syndrome was found to occur in

Fig. 5–17. *Maroteaux-Lamy syndrome*. (A,B) Severe form. Note head hyperextension. (Courtesy of S Rampini, Zürich, Switzerland.)





A B

Fig. 5–18. *Maroteaux-Lamy syndrome*. Radiographs. (A) Mild involvement of short tubular bones in 11-year-old. (B) Severe shortening and distortion of short tubular bones with marked epiphyseal and metaphyseal dysplasia in 14-year-old.

1/216,000 births in British Columbia (14). An animal model of MPS VI in Siamese and other cats has been extensively described and characterized (2,8,18). The clinical and biochemical features are caused by abnormal intracellular accumulation of DS in mesenchymal cells and, secondarily, in parenchymal cells of internal organs, such as the liver. Although *N*-acetylgalactosamine-4-sulfate residues are also present in chondroitin-4-sulfate, there is no evidence for the accumulation of this GAG in MPS VI individuals.

Facies. A prominent forehead may be noted at birth. The facies, similar to that in Hurler syndrome, with apparent hypertelorism, depressed nasal bridge, full cheek and lips, relatively broad jaws, large cranium, and abundant eyebrows and scalp hair, becomes evident at the sixth year of life, occasionally earlier (33,36). Marked corneal opacity is present in some patients (20) as well as glaucoma (1) (Figs. 5–16 and 5–17).

Musculoskeletal system. Adult height is usually 110–140 cm but those having the mild form may near 168 cm (23). The chest is deformed, with a prominent sternum. Multiple joint contractures and clawhand deformity secondary to flexion contractures of the fingers begin after the first year of life.

Genua valga, lumbar kyphosis, and sternal protrusion are common. The radiographic changes in the severe type are similar to those of MPS I-H and are striking examples of dysostosis multiplex (20). Ossification of the superior portion of the femoral capital epiphysis may be markedly defective. In the mild type, there are cranial changes, wide ribs, and pelvic dysplasia but few changes in spine and tubular bones (33) (Fig. 5–18). Hernias are common in the severe form.

Other findings. Hepatomegaly is almost invariably present in the severe form. The spleen is enlarged in about half of the cases. Cardiovascular involvement is common, with aortic stenosis, mitral valve regurgitation, cardiomyopathy (as a presenting feature), endocardial fibroelastosis, and narrowing of the coronary and other arteries (3,5,17,30,34).

Hearing defects, both conductive and sensorineural, may be detected audiometrically. Mentation is nearly always normal, with rare exception (35,38); when there is mental retardation, it is not always clear that it was caused by the MPS. However, impaired vision and hearing, restricted mobility, and secondary psychologic reaction may impede intellectual performance (32,33). Neurologic deficits most frequently include hydrocephalus, peripheral nerve compression (e.g., carpal tunnel syndrome), or hypoplasia of the odontoid process associated with atlantoaxial subluxation. Myelopathy and radiculopathy have also been reported (4,22,26). Marked tracheal stenosis has been documented (26).

Oral manifestations. The tongue becomes large with the full development of all clinical features. The teeth are frequently widely spaced. Eruption of primary and permanent dentition is retarded (19,31). Some are deeply buried, being angulated in the mandible, and are surrounded by radiolucent bony defects that presumably represent the accumulation of dermatan sulfate in hyperplastic follicles as seen in MPS I-H, MPS I-H/S, and in MPS II-B. The follicular fluid in MPS VI is composed of hyaluronic acid (27). The mandibular condyle is hypoplastic.

Differential diagnosis. For differential diagnosis of MPS VI, see Table 5–1.

Laboratory findings. There is an abundance of coarse, dense inclusions in granulocytes and monocytes and in a large proportion of lymphocytes in peripheral blood smears. Bone marrow preparations exhibit coarse inclusions in reticulohistiocytes, granulocytes, and their precursors (15). Biopsy may be easily done on the conjunctiva (11). Electron microscopic studies have shown numerous electrolucent vacuoles in cells from brain, liver, lung, and skin (10,11). Large quantities of DS are excreted in the urine, but the level decreases with age. Heterozygote testing has been difficult through enzymatic methods, but a method has been reported in which ratios of arylsulfatase B to another lysosomal sulfatase, arylsulfatase A, are used to minimize the overlap between normal and heterozygote populations.

The condition has been diagnosed prenatally (37). Diagnosis from chorionic villi through enzyme determination may not be accurate (28). Through molecular genetic studies, progress has been made toward determining various mutations in the arylsulfatase B gene, providing molecular evidence for genetic heterogeneity (7,9). Attempts to relate molecular findings and clinical phenotype have been made (13). In several patients with an intermediate form of MPS VI, novel mutant alleles have been found (39,40).

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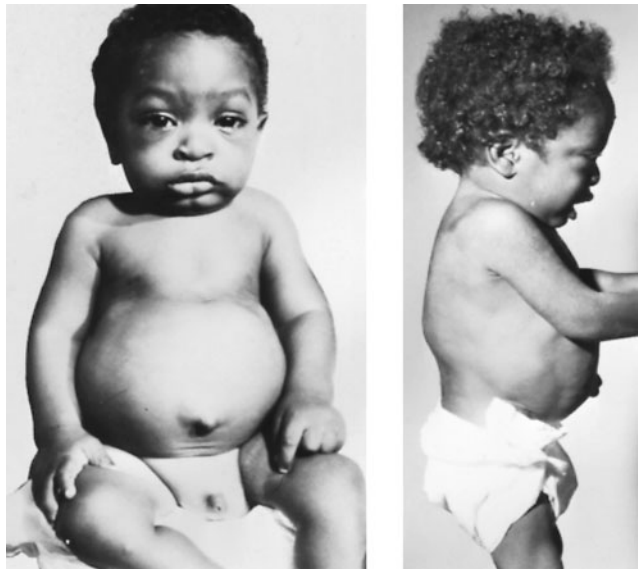
Mucopolysaccharidosis VII (Sly syndrome, β-glucuronidase deficiency). Mucopolysaccharidosis VII (MPS VII) which results from β-glucuronidase deficiency, was first described by Sly et al (20) in 1973. The disease is characterized by short stature, hepatosplenomegaly, progressive dysostosis multiplex, and progressive mental retardation after the age of 2 years. Clinical heterogeneity exists in the approximately 25 patients described so far (10,18): there are rather severely affected patients, and others who are moderately or mildly affected (2). There may also be a chronic variant (5). The severe type has its onset at birth or even prenatally. The severe neonatal form of β-glucuronidase deficiency is one of the few lysosomal storage diseases that may be recognized in utero or at birth (14,24,25). The milder types have symptoms from 3 to 4 years of age on, or sometimes at adolescence (Figs. 5–19 and 5–20). Inheritance is autosomal recessive for each type. The gene for MPS VII, at 7q21.1–q22 (1), encodes β-glucuronidase (GUSB), is 21 kb long, and is subdivided into 12 exons (12). The architecture is the same in the mouse gene (4). The human gene includes multiple unprocessed pseudogenes and/or closely related genes (21).

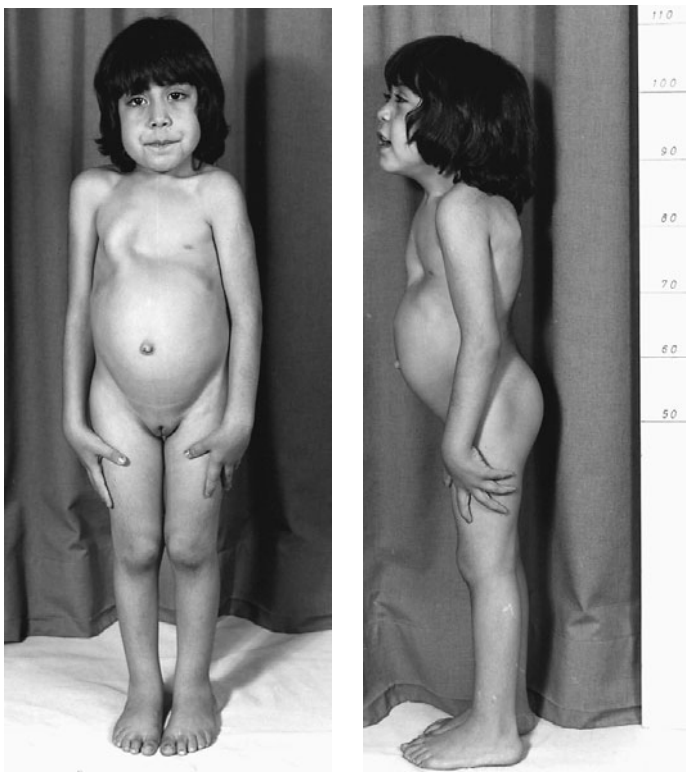
Murine (3), canine (7), and feline (6) models have been described. Deficiency of lysosomal β-glucuronidase activity in fibroblasts, leukocytes, and most tissues leads to an inability to degrade DS and HS, the predominant GAGs containing β-linked glucuronic acid residues, and results in their lysosomal accumulation and urinary excretion. Autopsy findings in a 19-year-old man (26) included dysostosis multiplex and extensive cardiovascular lesions, including arterial stenosis and marked fibrous thickening of the atrioventricular and aortic valves. In the brain, storage was localized to specific regions, primarily intraneuronal ones, and appeared ultrastructurally as delicate whorled filamentous accumulations in lysosomes.

Facies. In the severe form, the disorder may present a nonimmune hydrops fetalis (9,13,22,25). The severe type and, to some degree, the

Fig. 5–19. *Sly syndrome*, *β-glucuronidase deficiency*. (A,B) Coarse facies, pot belly, gibbus. (From WS Sly et al, J Pediatr 82:249, 1973.)



A **B**



A B

Fig. 5–20. *Sly syndrome*, *β-glucuronidase deficiency*. (A,B) Six-year-old showing disproportionate growth retardation. There is right-sided sternal protrusion with resultant pectus excavatum, and mild kyphoscoliosis. (From AC Sewell et al, Clin Genet 21:366, 1982).

moderate type have moderate Hurler-like changes, with hypertelorism, depressed nasal bridge, prominent alveolar processes, and anteverted nostrils (2,8). The corneas appear cloudy in the severe type, but are clear in the milder types (5).

Skeletal system. In the severe type and, to some degree, in the milder type, short stature becomes apparent in the second year of life, with height falling below the third centile. The head is large, with frontal prominence and premature closure of the sagittal and lambdoidal sutures. Pectus excavatum or carinatum and thoracolumbar gibbus, already noted in infancy, increase with age in the severe and milder types (5). Talipes and hernia also occur.

Radiographically, in both severe and mild types there are moderately severe changes of dysostosis multiplex with premature closure of cranial sutures, J-shaped sella, oar-shaped ribs, hook-like deformities of the lower thoracic and upper lumbar vertebrae, underdevelopment of the basilar portions of the ilia, aseptic necrosis of femoral heads, shortening of tubular bones, and proximal pointing of metacarpals II–V.

Other findings. Hepatosplenomegaly, inguinal and/or umbilical hernia, and developmental retardation are present after the age of 2 years, but psychomotor retardation is evident only in the severe-type patients. Recurrent pulmonary infections are common.

Oral manifestations. Widened alveolar ridges have been described.

Differential diagnosis. For differential diagnosis of MPS VII, see Table 5–1.

Laboratory findings. Coarse metachromatic inclusions are present in peripheral granulocytes, granulocyte precursors in bone marrow, and in cultured fibroblasts. Ultrastructurally, there are clear vacuoles and granular inclusions in nearly all granulocytes and mononuclear cells in MPS VII (15).

The definitive diagnosis can be made by demonstration of markedly deficient β-glucuronidase activity in serum, leukocytes, and cultured skin fibroblasts. Prenatal diagnosis can be accomplished by demonstrating β-glucuronidase deficiency in chorionic villi or cultured amniocytes (11). Increased nuchal translucency has been reported as well (5a). Molecular analyses will become available in the near future for pre- and postnatal diagnosis (23,25,27). Studies on gene therapy are ongoing; however these are mainly in animal models (16,17,19).

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Mucopolysaccharidosis IX. Triggs-Raine et al (1) recently reported mucopolysaccharidosis IX (MPS IX). The patient exhibited a deficiency of serum hyaluronidase and a surprisingly mild clinical phenotype, including notable periarticular soft tissue masses, mild short stature, and absence of neurological and visceral involvement and histological and ultrastructural evidence of a lysosomal storage disease. MPS IX maps to 3p21.3.

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Oligosaccharidoses and related disorders

This section deals with various oligosaccharidoses and related conditions.

G_{M1} gangliosidosis, type 1. G_{M1} gangliosidosis is an oligosaccharidosis caused by the lysosomal accumulation of G_{M1} ganglioside, asialo-G_{M1} ganglioside, and galactose-containing oligosaccharides (16,21). The disease was first recognized in 1964 by Landing et al (11). There are three major forms of G_{M1} gangliosidosis: infantile (type 1), late infantile/juvenile (type 2), and chronic/adult (type 3). Since mainly the infantile form is dysmorphic, the latter two types will not be discussed here.

The infantile form is manifest at or shortly after birth. In its full expression, it is characterized by progressive cerebral deterioration, with death usually occurring between 6 months and 2 years of age from bronchopneumonia. The other clinical and radiographic features resemble either I-cell disease or MPS I-H. Neonatal ascites (23) and transient hydrops fetalis (7) have been described as a presenting symptoms in the infantile form. Cardiomyopathy at 4 months of age leading to heart failure was described in a child that deteriorated neurologically and died at the age of 9 months (4). There were no bony changes, and β-galactosidase was almost undetectable.

G_{M1} gangliosidosis of all types is the consequence of the homozygous state of the mutant gene that produces a functionally deficient acid β-D-galactosidase. The β-galactosidase gene is located in the 3p21-3pter region (*GLB1*) (24). A second beta-galactosidase locus (*GLB2*) has been assigned to 20q13.1 and codes for protective protein (14,21). A mouse model has been reported (13).

Gene mutations in G_{M1} gangliosidosis have been found to be heterogeneous among Japanese patients with infantile G_{M1} gangliosidosis (17,20). The disorder is seen mostly in compound heterozygotes without parental consanguinity (21). The number of reports on Caucasian patients is relatively small (3,15)

Inheritance is autosomal recessive. Patients of various ethnic origins have been reported (21), and the incidence is high in the Maltese Islands (12).

Facies. The facial features are coarse at birth, in contrast to the face in MPS I-H, which is normal for the first 6 months of life. Mild macrocephaly with frontal bossing is found in about 60% of patients. The nasal bridge is depressed, the philtrum is prominent, the cheeks are full, and the eyelids puffy (Fig. 5–21). In mild cases, these facial changes are present only in later infancy. Corneal opacities are rarely found, but cherry-red macular spots are detected in most cases (8).

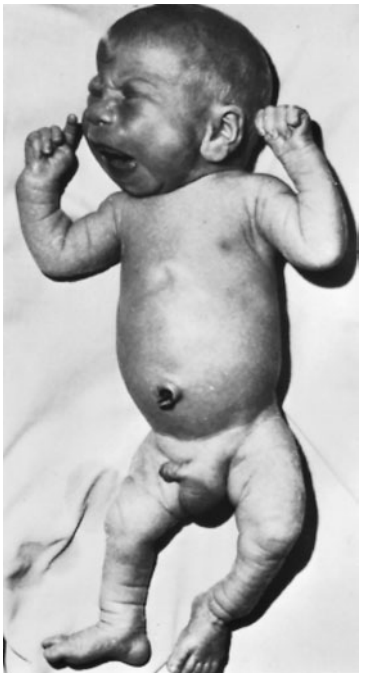

Fig. 5–21. *G_{M1} gangliosidosis, type I.* Coarse facial features, widened alveolar processes, and large ears. Wrist and ankle deformities were apparent at 2 weeks of age. (From CR Scott et al, J Pediatr 71:357, 1967).

Skeletal system. Kyphoscoliosis is an early finding. The hands are short and stubby. There are multiple flexion contractures of the joints.

The radiographic changes are those of dysostosis multiplex which appear earlier and are more severe than in MPS I-H. The ribs are wide, and the vertebral bodies are short in their anteroposterior diameter, with convex endplates and hook-shaped deformities at the thoracolumbar junction.

The basilar portions of the ilia are hypoplastic. In young infants, there is periosteal cloaking of the shafts of the long tubular bones. This is not observed in MPS I-H, but is a well-known early finding in patients with I-cell disease. In older infants and in young children, the shafts of the long bones are overtubulated, with irregular contours. The short tubular bones appear swollen, with proximal pointing of the second to fourth metacarpals. Bone trabeculation is coarse (5,9).

Central nervous system. The infants are hypotonic. They suck and swallow poorly, fail to thrive, and never learn to crawl or sit. In addition to gross motor delay, they exhibit seizures, blindness, hearing loss, and often spastic quadriplegia within the first year after birth. Cranial computed tomography (CT) and MRI show diffuse atrophy of the central nervous system in early-onset patients, generalized cortical atrophy, enlargement of the ventricular system, and features of myelin loss in the cerebral white matter (6,7a,10,21). A CT scan revealed increasing white matter involvement in one case (13), with generalized areas of reduced density early in the course of the disease.

Other findings. Hepatosplenomegaly is present; hydrocele is frequent (5). Ectopic mongolian spots when present may aid in diagnosis (22).

Oral manifestations. The tongue and alveolar processes are enlarged (Fig. 5–22) (11).

Differential diagnosis. Cherry-red macular spots can also be found in Tay-Sachs disease, Sandhoff disease (AB variant), metachromatic leukodystrophy, infantile Niemann-Pick disease, the *sialidoses*, and Farber lipogranulomatosis. Similar, but not typical, changes have been described in cases of other lysosomal diseases such as metachromatic leukodystrophy, globoid-cell leukodystrophy, and Gaucher disease.

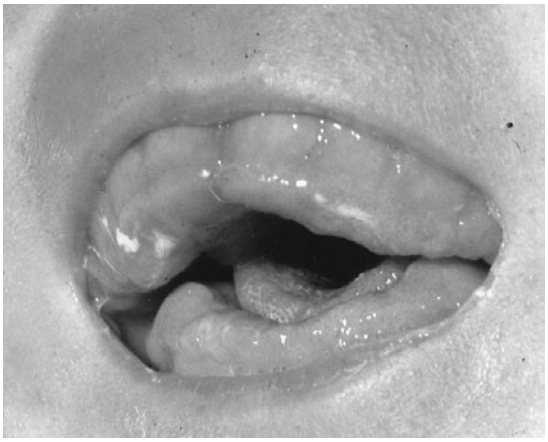

Fig. 5–22. *G_{M1} gangliosidosis, type I.* Gingival enlargement. (Courtesy of CR Scott, Seattle, Washington.)

Marked dysostosis multiplex-like skeletal anomalies in an infant are more compatible with G_{M1} gangliosidosis or I-cell disease than with a mucopolysaccharidosis.

Laboratory findings. Between 10% and 80% of peripheral lymphocytes are vacuolated. Foam cells are found in the bone marrow and in the viscera. Glomerular epithelial cells are vacuolated. The neurons of the central nervous system and retina have a granular appearance because of G_{M1} ganglioside–loaded lysosomes. Under electron microscopy these appear as whorled and striped "zebra bodies," identical to those seen in Tay-Sachs disease (19). Urinary excretion of GAGs is usually normal, although galactose-containing oligosaccharides are markedly elevated. The activity of acid β-galactosidase is deficient in tissues and body fluids, including lymphocytes and cultured fibroblasts; assay of urine is not recommended anymore (21). It is also important to determine other enzyme activities including neuraminidase for differential diagnosis of disorders with secondary β-galactosidase deficiency, such as *galactosialidosis, I-cell disease*, *mucolipidosis III*, and MPS other than *Morquio B disease* (21). Prenatal and heterozygote detection are possible, either with enzymatic or with molecular genetic techniques.

Animal models of G_{M1} gangliosidosis have been reported for cats (2), dogs (1), and sheep (18).

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Fucosidosis. Fucosidosis is an oligosaccharidosis caused by a deficiency of α-L-fucosidase, leading to accumulation and excretion of glycoproteins, glycolipids, and oligosaccharides containing fucoside moieties (20). It was first described by Durand et al (4) in 1966.

Fucosidosis has autosomal recessive inheritance. It appears to be more common in Southern Italians and in people from the southwestern part of the United States—e.g., New Mexican Spanish-Americans, and Navajo (5,23). In a review (23), 40% of the 45 families reported were consanguineous.

Through in situ hybridization studies, the α-fucosidase 1 gene (*FUCA1*) was assigned to chromosome 1p34 (7). Using similar techniques, a pseudogene, *FUCA1P*, has been mapped to 2q31–q32 (2). The gene structure for human fucosidase includes eight exons spanning 23 kb, and the sequence of the pseudogene is 80% identical to the cDNA (10). Most mutations have been found in isolated families, suggesting that fucosidosis is due to a large number of different mutations (16,17,21,24).

Traditionally, two phenotypes have been identified: a more severe infantile form referred to as type I, and a milder form, described as type II. In a review of 77 cases (23), it was suggested that this is an arbitrary separation of a continuum of severity (20). In addition, mild and severe cases occur within sibships (22) and among patients who are homozygous for the common Gln to stop mutation at codon 422 (Q422X) (4). The major distinguishing features of the milder phenotype are the presence of angiokeratomas, longer survival, and a more normal sodium chloride content of sweat, as compared with the severe form (20).

Facies. Patients with a more severe phenotype typically have a progressively coarse facies in the first year of life with large lips, periorbital puffiness, and frontal bossing. There is some resemblance to patients with MPS III. The hair, however, is not as coarse. The tongue may be large. The corneas are clear and the fundi are unremarkable.

Skeletal system. Patients exhibit growth retardation and dysostosis multiplex. The vertebral bodies are initially ovoid with subsequent flattening, marginal irregularity, and beaking in lateral projection (1,11,15). There is mild hypoplasia of the supraacetabular portions of the ilia. Bone trabeculation is coarse.

Central nervous system. Progressive neurologic deterioration has been reported (15). Cranial CT and MRI have shown density and signal

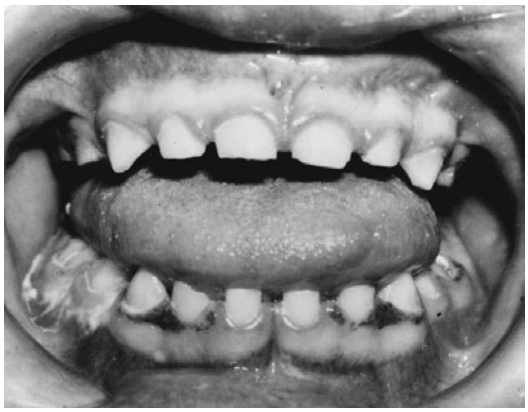

Fig. 5–23. *Fucosidosis*. Telangiectatic lesions of gingiva. (From DE Prindiville and D Stern, J Oral Surg 34:603, 1967.)

abnormalities within the globus pallidus, internal capsules, and periventricular white matter (15,19). Spasticity, hyperreflexia, and dystonia may be present (9).

Other findings. Psychomotor retardation, hepatosplenomegaly, cardiomegaly, seizures, and respiratory infections occur frequently but are variable. Tortuous conjunctival vessels and bull's eye retinopathy have been reported (18). Kivlin (*Peters plus*) syndrome has been diagnosed in a single patient (18). Angiokeratomas may be present (6,9). Hernias have also been reported.

Oral findings. Gingival and labial telangiectasias (Fig. 5–23) have been reported (14).

Laboratory findings. Peripheral lymphocytes are vacuolated. Skin biopsy shows deposits of homogeneous eosinophilic material between the dermis and epidermis. Electron microscopic studies reveal numerous membrane-bound vacuoles in all tissues (8). Urinary excretion of MPS is normal, but there is excess excretion of fucosyl-containing oligosaccharides. There is a suggestion that fucosidosis types I and II can be distinguished by the pattern of urinary excretion (12). There is deficient activity of the lysosomal enzyme, α-L-fucosidase in tissues, cultured fibroblasts, leukocytes, serum, and urine (3). Sweat chlorides are markedly increased in the severe form and to a lesser extent in the milder form.

Prenatal diagnosis has been accomplished (13). If the molecular lesion in a specific family has been identified, prenatal diagnosis through DNA analysis can be considered.

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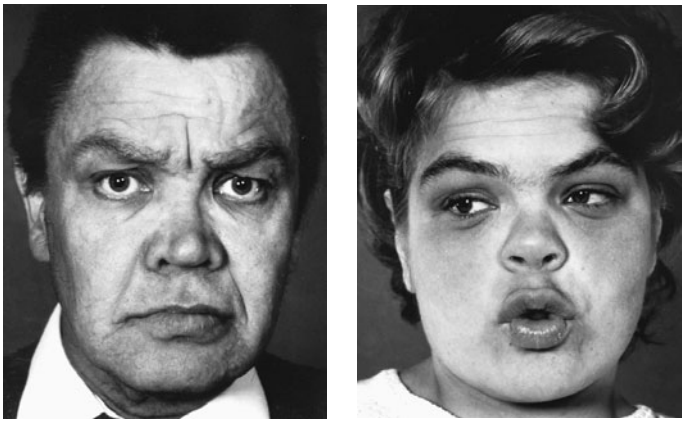
Aspartylglucosaminuria. Aspartylglucosaminuria, an oligosaccharidosis in which glycoprotein-derived aspartylglucosamine accumulates in various tissues and fluids, was first identified in England by Jenner and Pollit (20). Most of the identified patients have come from Finland (7,9,10). Aspartylglucosaminuria is in Finland what phenylketonuria (PKU) is in many other populations. Its frequency was estimated at 1/26,000 in Finland (11), but recalculated to be at least 1/18,500 (1). Mononen et al (22) found a frequency of 1 in 3643 in a study of children in eastern Finland. Aspartylglucosaminuria has also been observed in Finns living in Norway (26). A few cases have been reported from other ethnic groups, e.g., Puerto Rican (13), Italian (15), Dutch (14), Mauritian (23), Palestinian Arabs (27), and others.

Inheritance is autosomal recessive. The basic defect is deficiency of aspartylglucosaminidase (1-aspartamido-α-*N*-acetylglucosaminine amidohydrolase). Heterozygotes may be identified (16,22) and prenatal diagnosis is possible (8). The gene is located at 4q32–q33 (6) and consists of 9 exons spanning a total of 13 kb. A high degree of homogeneity in disease alleles is suggested in the Finnish population. In 115 aspartylglucosaminuria patients from 109 families, not only were the *C163S* and *R161Q* mutations always associated, but they were found in 98% of the aspartylglucosaminuria chromosomes analyzed (25). Moreover, the two mutations were not found in 120 unrelated control individuals. Aspartylglucosaminuria outside Finland appears to result from a large variety of mutations of the gene (18). A mouse model has been reported (19).

Infancy and childhood are usually characterized by recurrent diarrhea, umbilical and inguinal hernia, and frequent respiratory and ear infections, all of which diminish after six years of age (1). Early onset of splenomegaly occurs with abdominal protrusion. Lifespan is usually under 45 years.

Facies. A remarkable resemblance is noted among affected individuals. The skull is frequently asymmetric. The features gradually become coarse during childhood; the nasal bridge is broad and low. The nostrils are anteverted and the lips thickened. Mild hypertelorism, epicanthic folds, and crystal-like lens opacities have been present in about half the cases. The facial skin, particularly that of the eyelids and cheeks, has a tendency to sag with age (Fig. 5–24). Seborrheic and erythematous facial skin begins in adolescence (4). Acne, particularly of the face, has been noted in several patients (25).



A B

Fig. 5–24. *Aspartylglucosaminuria*. (A,B) Remarkable resemblance between affected individuals. Coarse facial features include furrowed brow, broad low nasal bridge, mild hypertelorism, epicanthal folds, sagging of facial skin, and thick lips. (Courtesy of S Autio, Helsinki, Finland.)

Skeletal manifestations. Inguinal and/or, more often, umbilical hernia has been found in over one-third of patients before the age of 3 months. Muscular hypotonia has been present in about 20% of patients, and genua valga is seen in at least 75%. Clubfoot needing surgical treatment has been reported. The long bones, metacarpals, and phalanges have thin cortices. Spondylolisthesis and spondylolysis have been described (13). Kyphosis or scoliosis and protuberant abdomen have also been frequently reported. There is excessive infantile growth and an early pubertal growth spurt (5). Growth retardation is seen only after 15 years of age.

The calvaria are characteristically thickened and brachycephalic. The frontal and maxillary sinuses are absent or poorly developed (Fig. 5–25A). Mild dysostosis multiplex in the spine is common. The ulna is somewhat shortened (24).

Nervous system. Progressive mental retardation to an IQ value of 40 or less in the second decade is a constant feature. It usually first becomes evident around 5 years of age. Speech is severely delayed. In about one-third of patients, the voice becomes raspy in adult life. Periodic hyperactivity, hyperirritability, and/or aggressive reactions have been noted in about 50% of patients.

Mild to moderate hearing loss has been found in about 20% of adults with this disorder. Clumsy gait and poor coordination of the hands are noted early in life. In 12 patients, MRI studies (11) showed that aspartylglucosaminuria is primarily a gray-matter disease, also affecting white matter by delaying myelination.

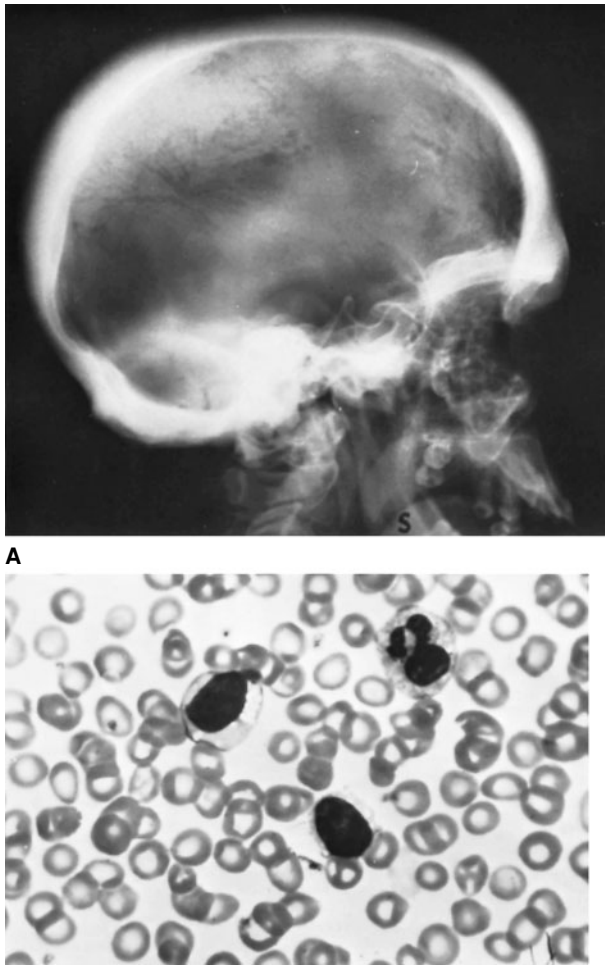
Skin. About 20% of affected individuals have angiokeratomata of the face (24).

Other findings. Macroorchidism has been documented (13). Amenorrhea and oligomenorrhea in females and scant beard and pubic hair have been noted (9).

Oral manifestations. The teeth have often been noted to be spaced. Tooth crown size and crown shape are normal, but dental malocclusions are common. In a study of 81 cases, an abnormally large tongue was reported in almost all cases (2), causing anterior openbite. Fibroepithelial hyperplasia of the gingiva and leukedema of the buccal mucosa are common (4). Diagnosis has been made on gingival biopsy (12).

Laboratory findings. From 5% to 20% of the blood lymphocytes are vacuolated in 75% of the patients (Fig. 5–25B) and about one-half of patients exhibit mild neutropenia and decreased prothrombin time.

The definitive diagnosis is made by finding large amounts of aspartylglucosamine in the urine by thin-layer chromatography, paper chromatography, or electrophoresis (25). Final diagnosis of aspartylglucosaminuria is usually based on the measurement of aspartylglucosaminidase activity in white blood cells or fibroblasts. Prenatal diagnosis using cultured amniotic cells or direct chorionic villi biopsy material has been accomplished (8).



A B

Fig. 5–25. *Aspartylglucosaminuria*. (A) Radiograph showing thickened calvaria. (B) Vacuolated lymphoctyes in peripheral blood smear. (A from RB Foundation, Proc R Soc Med 67:878, 1974. B from JN Isenberg and HL Sharp, J Pediatr 86:713, 1975.)

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α-Mannosidosis. α-Mannosidosis, a type of oligosaccharidosis, was first characterized in 1967 by Öckermann (17). At least 60 cases have been reported to date (2,3). Inheritance is autosomal recessive with parental consanguinity in 25% (22). Genetic heterogeneity is evidenced by a more severe infantile form (type I) and a milder juvenile–adult form (type II) (6), and there may be considerable variability among affected family members (14,15). The gene encoding acid α-mannosidase is located at chromosome 19p13.2–q12 (12). The lysosomal α-mannosidase cDNA has been cloned and many mutations have been reported (5,10,16).

Affected children are essentially normal for the first months to 1 year of life but about 60% exhibit a propensity toward recurrent respiratory infections (6,13a). Expression has varied from death in childhood to few clinical signs (3,4). Adults have stunted growth (3).

Facies. The coarse facies (prominent supraorbital ridges, hypertelorism, broad based nose, prominent jaw) noted after the first few years of life becomes progressive but not to the degree noted in MPS I-H or as early as in I-cell disease (15). The nasal bridge tends to be depressed; the forehead and mandible are prominent. The neck is somewhat short (Fig. 5–26A,B).

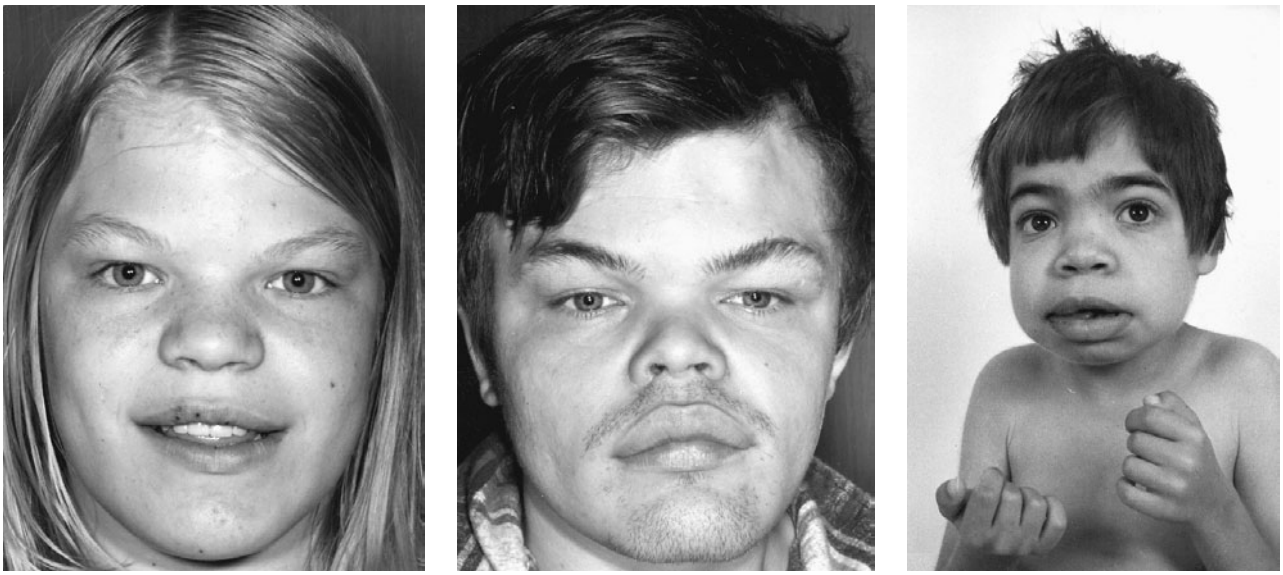
Central nervous system. There is delayed early motor development, which manifests as clumsy motor function and ataxia. Mental retardation is present in both type I and type II patients, but there is rapid progression of mental deterioration in type I patients. Speech is delayed. Tendon reflexes are brisk. In three patients, MRI findings in the head showed bony changes, verticalization of the chiasmatic sulcus, cerebellar atrophy, and white-matter signal changes (7).

Eyes and ears. Spoke-wheel posterior lenticular or superficial corneal opacities have been noted in 25% of cases (1,13); cherry-red spots have also been reported. Severe high-frequency sensorineural hearing loss is a common, if not constant, feature of type II patients (16).

Musculoskeletal system. There is general mild hypotonia, and the abdomen is protuberant. Umbilical hernia is found in 60% of cases.

All affected individuals have mild dysostosis multiplex, which becomes more severe in some and improves in others (5a,8,20,24).

Fig. 5–26. (A,B) *α-Mannosidosis*. Note gradual coarsening of features with age in 11-year-old and 18-year-old sibs. (C) *β-Mannosidosis*. Severely mentally retarded female with coarse facies and short neck. (C courtesy of E Seemanová, Prague, Czechslovakia.)



A B C

The calvaria is thick with hypoplastic to absent paranasal sinuses in at least 60% of cases. The long bones are osteoporotic. The ulna and radius are broad with curved diaphyses and a thin cortex. Joint mobility is remarkably variable in severity (22). The vertebrae are ovoid, flattened, and beaked in some cases, with gibbus formation (15,25). Mild bony deformity at the hip is common.

Other findings. Hepatosplenomegaly has been noted in 50% of patients (22) but this may disappear in childhood.

Oral findings. Macroglossia and widely spaced teeth have been noted (17). Transmission electron microscopy studies in gingival and oral hyperplastic mucosa have revealed histiocytic cells containing storage vacuoles with fine reticulogranular material (11).

Laboratory aids. The peripheral and bone marrow lymphocytes are vacuolated in as many as 90% of the cells counted (3). Coarse dark granules are present in the neutrophils, and there is a defect in neutrophil chemotaxis. Pancytopenia has been found (19), and decreased serum IgG has been noted. The condition is diagnosed by finding markedly reduced acid α-D-mannosidase in leukocytes and cultured fibroblasts (21). Mannose-rich oligosaccharides can be readily detected in the urine of affected individuals. Heterozygote detection is possible and prenatal diagnosis can be accomplished by finding acid α-D-mannosidase deficiency in chorionic villi (18). α-Mannosidase activity, however, has been found to be less than one-third of that found in cultured amniotic fluid cells (9); this finding emphasizes the need for good control data.

Bone marrow therapy (BMT) in cats with α-mannosidosis has been reported (23). The disease in cats shows clinical, morphologic, and biochemical features that closely resemble those of human disease. The BMT-treated animals showed little or no progression of neurologic signs 1 to 2 years after BMT, whereas untreated cats became severely impaired.

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β-Mannosidosis. Deficiency of β-mannosidase was well known in goats and cattle (6) as a severe neurologic disease associated with dysmyelination of the central nervous system and early death before the first human patient was reported in 1986 (3). The first mutation associated with human β-mannosidosis was reported in a study (1) of 2 sibs with different manifestations of β-mannosidosis described by Kleijer et al (7). The gene for β-mannosidase was mapped to 4q22–q25 by study of a panel of rodent/human somatic cell hybrid lines (1). There appears to be homozygosity for an A-to-G transition 2 bp upstream of a splice acceptor site. Lysosomal β-mannosidase has been cloned (2). Inheritance of β-mannosidosis is autosomal recessive; the frequency is not yet known. Patients of different ethnic backgrounds have been reported— e.g., Hindu (3) and Turkish (5) patients. A goat model has been described (6).

Upper and lower respiratory tract infections are frequent.

Facies. There is a coarsening of facial features (Fig. 5–26C).

Central nervous system. Most patients are normal in the first few months of life; eventually all have mental retardation. In the most severe phenotype, status epilepticus at age 12 months with quadriplegia and death at 15 months have been reported (4). Speech is impaired (10). Aggressive or unstable behavior has been described. Brain atrophy has been demonstrated by CT scan in a severely affected patient (4).

Peripheral neuropathy has been documented in a number of patients (9).

Eyes and ear. Hearing loss and ear infections are common.

Musculoskeletal system. Skeletal abnormalities occur but are not usual (7).

Other findings. Hepatosplenomegaly has not been described, but angiokeratomas have been reported (3,11).

Laboratory aids. Cytoplasmic vacuoles have been noted on skin biopsy but not in lymphocytes or bone marrow cells. Slight vacuolization and granulation of bone marrow cells were reported in another patient (4).

A disaccharidase containing mannose and *N*-acetylglucosamine is the major abnormal component found in the urine of β-mannosidosis patients (12). Definitive diagnosis of β-mannosidosis is made by measuring the activity of β-mannosidase in leukocytes or cultured fibroblasts (12). Prenatal diagnosis can be carried out (8).

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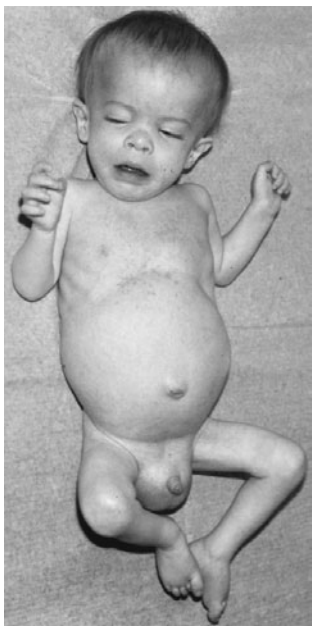
Sialidosis (neuraminidase/sialidase deficiency). Delineation of the clinical features of the various forms of sialidosis is complicated by the existence of both an isolated neuraminidase deficiency ("sialidosis") and a combined neuraminidase and β-galactosidase deficiency (galactosialidosis) (14). Patients with type I, the normosomatic sialidosis, present with symptoms between 8 and 25 years of age, have normal stature and intelligence, severe myoclonus, and macular cherry-red spots with visual loss. Since the facies is normal and there is no dysostosis multiplex, this type is not discussed further here. The reader is referred to reviews by Spranger (13), O'Brien (8), and Young et al (16).

Type II sialidosis consists of three forms with dysmorphic phenotype and more or less coarse facies (Figs. 5–27 to 5–29): (*a*) a congenital lethal variety, presenting with hydrops fetalis; (*b*) an infantile form (nephrosialidosis) initially presenting from birth to the end of the first year of life; and (*c*) a juvenile form, with onset at between 8 and 20 years that becomes progressively worse.

Fig. 5–27. *Sialidosis*. Note prominent scalp veins, mildly coarse features with broad hypoplastic nasal bridge, abdominal distension and large hydroceles. (From AS Aylsworth et al, J Pediatr 96:662, 1980.)



All types have autosomal recessive inheritance. Although the genetic relationships of the various clinical forms of the sialidosis remain uncertain, ethnic predilections of at least some forms appear to differ (14). Most reported type I patients have been Italian. The expression of the glycoprotein-specific neuraminidase, absent in sialidosis patients, requires the presence of at least two genes for normal expression (7). The lysosomal sialidase gene was mapped to 6p21.3, which is consistent with the previous chromosomal assignment of this gene in proximity to the HLA locus (10). The neuraminidase deficiency in a sialidosis type II patient is caused by a mutation in a structural protein encoded by a gene at 10pter–q23 (7). In contrast, the neuraminidase deficiency found in a galactosialidosis patient was shown to be caused by a mutation in a gene located at 20q13.1 (7). These findings indicate that sialidosis patients and individuals with the combined deficiencies suffer from two distinct and separate genetic disorders (14). The specific mutation affects the severity (1a).

Of those individuals with type II, the juvenile form has the mildest course, the life span usually being somewhat reduced, but most patients have survived to the fourth and fifth decades. There is variable coarsening of features ranging from thick lips, flat nasal bridge, and mild hypertelorism to a facies resembling MPS I-H, short trunk, relatively long limbs, and moderately severe dysostosis multiplex. Myoclonus, similar to that in the normosomatic type, is noted in 75% of patients. Neuromuscular findings have commonly included ataxic gait, tremor, myoclonic jerks, generalized seizures, impaired hearing, hypotonia, wasting, and peripheral neuropathy. Mental function is essentially normal until adolescence, when it tapers off to an IQ of 60–70. Eye findings include progressive visual loss, cherry-red macular spots, punctate lenticular opacities, and occasional corneal opacities (Fig. 5–30). Angiokeratomas similar to those found in Fabry disease and fucosidosis have been reported (6).

The infantile form (nephrosialidosis) is characterized by more severe dysostosis multiplex, hepatosplenomegaly, glomerular nephropathy, hearing loss, seizures, pyramidal tract signs, and severe mental retardation (1,5). Survival to the second decade is frequent. As in the juvenile form, visual loss, cherry-red spots, myoclonus, and ataxia are seen in older children (15,16).

In the so-called congenital or fetal form, infants are frequently stillborn with hydrops fetalis. Those not stillborn usually die within a few months. In addition to ascites with pericardial effusion, corneal opacities, hepatosplenomegaly, inguinal hernia, stippled epiphyses, and periosteal cloaking of long bones are seen (Fig. 5–28). Renal involvement with proteinuria also occurs in the congenital form (1,4,12) (Fig. 5–27).

A strain of mice (SM/J) has been shown to have a deficiency of neuraminidase in some tissues (9).

Differential diagnosis. Neuraminidase deficiency with β-galactosidase deficiency has been classified as a separate entity (see Galactosialidosis, below).

Laboratory findings. Vacuolated lymphocytes and bone marrow and placental foam cells are lacking in the normosomatic form but are prominent in the other types. Other findings include tissue storage of sialyloligosaccharides, increased urinary excretion of oligosaccharides, and sialylglycopeptides derived from glycoproteins. The definitive diagnosis of sialidosis is based on the direct measurement of sialidase activity in isolated leukocytes, fibroblasts, or cultured amniotic fluid cells (14). Prenatal diagnosis has been reported (3), using cultured amniotic fluid cells or chorionic villi samples (2). Recently, a point mutation in the neu-1 locus has been identified (11).

Hydrops fetalis may occur (13a).

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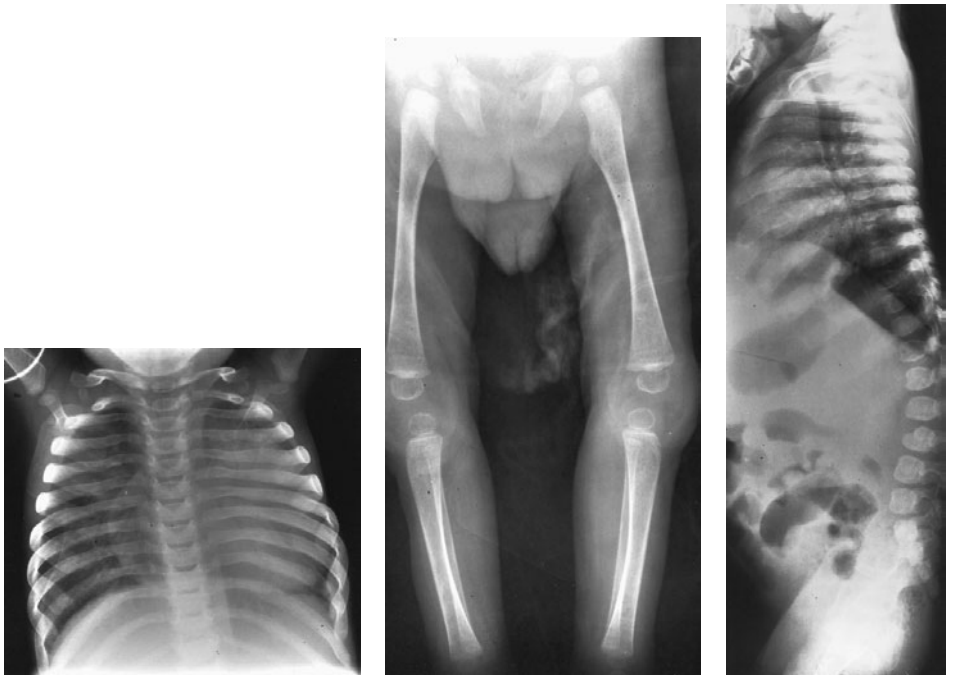

A B C

Fig. 5–28. *Sialidosis*. (A–C) Mild dysostosis multiplex at 15 1/2 months showing broad irregular ribs, broad femoral and tibial diaphyses with poor modeling, broad femoral neck with coxa valga, and hook-shaped lumbar vertebral body. (From AS Aylsworth et al, J Pediatr 96:662, 1980).

Fig. 5–29. *Sialidosis*, type *2*. Two affected Pakistani sibs, aged 13 and 12 years, with mother and normal 15-year-old sib. (From *M King et al*, J Inherit Metabol Dis 7:91, 1984.)

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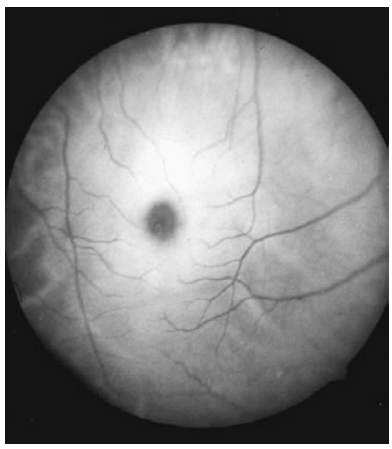
Fig. 5–30. *Sialidosis*. Cherry-red spot. (From T Miyatake et al, Ann Neurol 6:232, 1979.)



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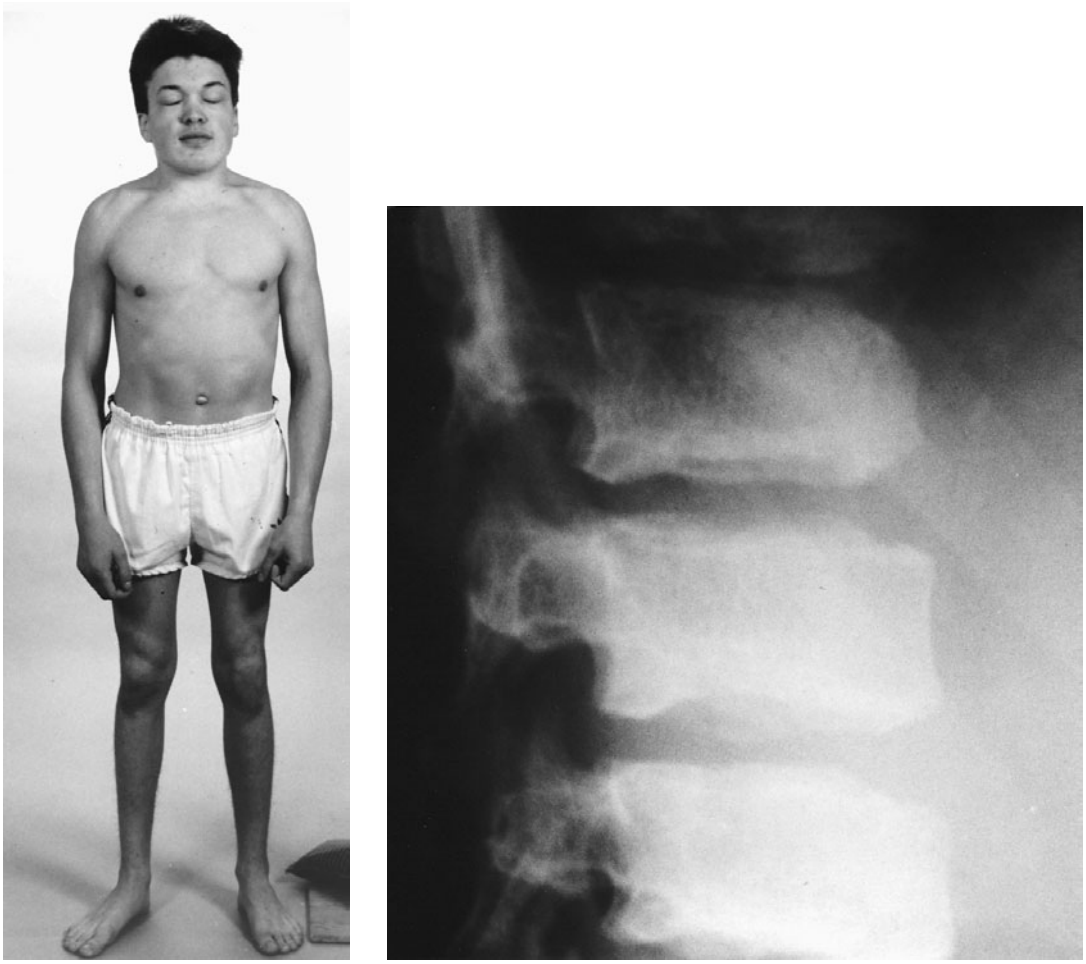
Galactosialidosis. Galactosialidosis, an oligosaccharidosis, was originally described by Okada and O'Brien in 1968 (8). The disorder occurs in three clinical forms: (*a*) early infantile, (*b*) late infantile, and (*c*) juvenile/adult. Most of the patients belong to the juvenile/adult group and are mainly of Japanese origin.

The disorder has autosomal recessive inheritance. Galactosialidosis is associated with a combined deficiency of β-galactosidase and neuraminidase, secondary to a defect of another lysosomal protein, the protective protein (1). The gene encoding human protective protein (PPBG) is located at 20q13.1 (18). The protective protein forms a complex with β-galactosidase and neuraminidase and protects these enzymes against excessive proteolytic degradation (1). The human protective protein appears to be identical to lysosomal cathepsin A and has catalytic and protective functions as well (1,4,6). Its deamidase/carboxypeptidase activity has been found to be deficient in all patients with galactosidosis (11). Studies of the relation between protective protein/cathepsin A mutations and clinical severity (10,20) have shown that the main factor determining the clinical course in galactosialidosis patients is the lysosomal level of mutant *PPCA* (20). A mouse model has been reported (19).

Early-infantile type. The severe infantile form presents between birth and 3 months of age with fetal hydrops (7,9), neonatal edema, kidney involvement, coarse facies, inguinal hernias, and telangiectasias (9,16), the latter symptom being rare in the late-infantile and juvenile/adult types (1). Patients develop visceromegaly, psychomotor delay, and skeletal abnormalities, though to a lesser degree than in the other two types (1). Optic disc abnormalities and cherry-red spot have been described, as have cardiomegaly, thickened septum, and cardiac failure (16).

Late-infantile type. In this form, coarse facies develops in the first months of life, as well as hepatosplenomegaly and dysostosis multiplex, especially of the spine (13) (Fig. 5–31A). Cherry-red spots, cloudy corneas, and retinal and optic nerve abnormalities may be present (17). Mild or very mild mental retardation may be a feature (13). Mitral and aortic heart valve disease is a common feature, as well as conductive or mixed type hearing loss (13).

Fig. 5–31. *Galactosialidosis*. (A) Mild coarseness of facial features and muscular upper body. (B) Mild irregularities in vertebral bodies. (From D Chitayat et al, Am J Med Genet 31:887, 1988.)



A B

Juvenile/adult type. The clinical course is variable and there is a broad spectrum of severity and age of onset (2,14,15). Coarse facies is a constant finding, though less marked than in other lysosomal storage diseases (1). Visceromegaly is absent. Platyspondyly of thoracic and lumbar vertebrae is common (Fig. 5–31B). Major neurologic findings include myoclonus, cerebellar ataxia, generalized seizures, and mental retardation with deterioration (1). Cherry-red spots, corneal clouding and lens opacities have been reported. Angiokeratoma is present in this type of galactosialidosis only (3,16).

Laboratory findings. In all types of galactosialidosis, foam cells in the bone marrow and vacuolated lymphocytes in blood smears are seen. Excessive amounts of sialyloligosaccharides are excreted in the urine. Combined deficiencies of β-galactosidase and neuraminidase in white blood cells or cultured skin fibroblasts are found. Demonstration of a cathepsin A deficiency, the primary defect, may aid in diagnosis (6). However, the catalytic activity of the protein is distinct from its protective function (1). Prenatal diagnosis is possible by enzyme analysis in cultured amniotic fluid cells or chorionic villus tissue (5,7).

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I-cell disease (mucolipidosis II). I-cell disease, formerly known as mucolipidosis II, was originally described in 1967 by Leroy and DeMars

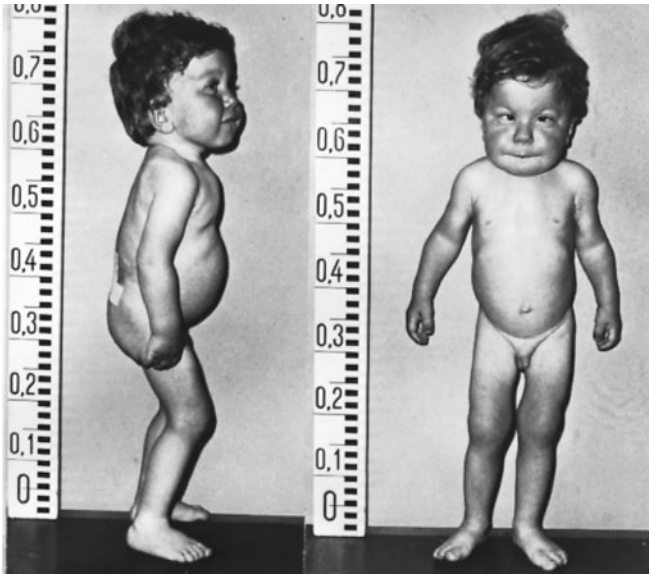


Fig. 5–32. *I-cell disease*. Hurleroid features are evident from early infancy. (From U Wiesmann et al, Acta Paediatr Scand 63:9, 1974.)

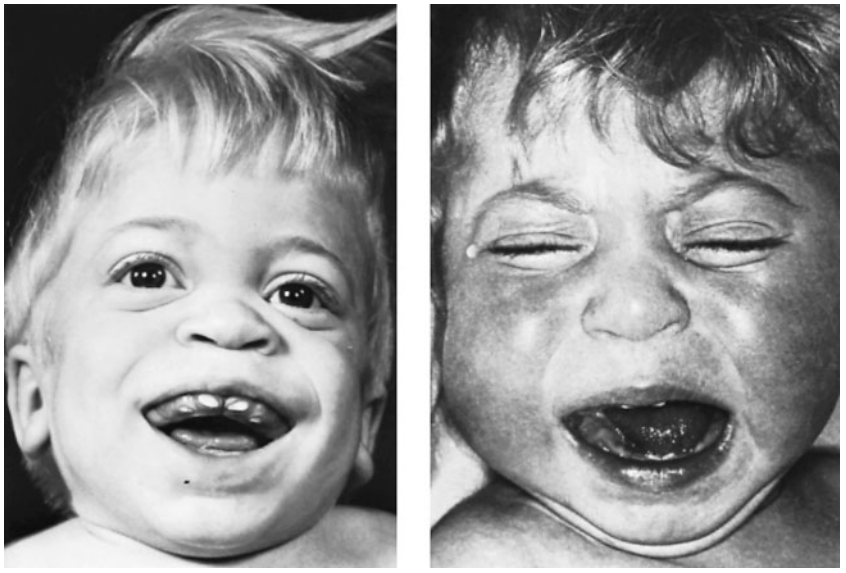
(6,12–15). It is characterized by severe psychomotor retardation, marked shortness of stature, facial features reminiscent of MPS I-H, impressive gingival enlargement, a rapid deteriorating course, and death from heart failure (hypertrophic cardiomyopathy), bronchopneumonia, or pulmonary atelectasis, usually by the age of 5 years (1,10) (Figs. 5–32 to 5–34). However, survival of patients with I-cell disease into their teens has been described (20). In a French-Canadian population, a prevalence at birth of 1/6184, has been found for mucolipidosis II, giving a carrier frequency of 1/39 (5). This disorder, like Hurler polydystrophy, is the result of a deficiency in recognition marker phosphotransferase. Inheritance is autosomal recessive, and consanguinity is high (20). The disease may be somewhat more frequent in Japan and there is probably genetic heterogeneity (19,24). The gene locus has been identified at 4q21–q23 (18). Important negative signs and symptoms are absent splenomegaly, equivocal or absent corneal cloudiness, and normal urinary excretion of MPS (7,25).

This disorder received the name of I-cell disease because of the numerous granular inclusions in the cytoplasm of cultured fibroblasts and amniotic fluid cells observed under phase-contrast microscopy (6,13). The inclusions are large lysosomes containing heterogeneous undegraded material (7).

At birth, the infants are small (<10th centile) and have coarse facies, muscular hypotonia, and dislocated hips. Inguinal hernias occur in males, and both genders may have tight and thickened skin that becomes more pliable with age (1,4,22) (Fig. 5–33). Hirsutism has been noted in about 60% of cases. During the first year, infants have a history of recurrent upper respiratory tract infections (rhinitis, otitis media), failure to thrive, and marked lack of psychomotor development. The full clinical picture is reached by 1 year of age (1). There is severe shortness of stature, with most never reaching the average height of a 1-year-old child and growth ceasing by the third year. This phenomenon differs markedly from MPS I-H, where excessive growth from 6 to 18 months of age has been frequently documented.

Motor retardation is more severe than mental retardation. Many patients do not accomplish unaided ambulation, but several older patients can walk without support. Most patients over 4 years of age can speak two-word sentences and are toilet trained.

Facies. Some patients have exhibited premature lightening of hair color. Head circumference remains normal with respect to stature. The facies is reminiscent of that in MPS I-H patients, with small orbits, flat supraorbital ridges, puffy eyelids, a slight degree of exophthalmos, and a pattern of tortuous veins around the orbits and temporal areas (1)



A B

Fig. 5–33. *I-cell disease*. (A,B) Characteristic facial appearance. (A courtesy of CI Scott, Wilmington, Delaware. B from NS Gordon, Postgrad Med J 49:359, 1973.)

(Fig. 5–33). The cheeks are full and pink, partly because of multiple fine telangiectasias. The gingiva shows marked enlargement (Fig. 5–34).

Intermittent copious nasal discharge has been noted, but to a lesser degree than in MPS I-H patients. Hearing impairment has been reported (9).

Mild corneal clouding has been documented as a late sign in about 40% of cases, but vision is not impaired. However, on slit lamp examination, all patients have some degree of corneal opacification. Glaucoma and megalocornea have been occasionally noted (16).

Musculoskeletal system. Shortness of the neck and a deformed thoracic cage are common. Umbilical and/or inguinal hernias are found in up to 75% of cases. Despite hypotonia, there is considerable restriction of joint mobility, particularly in the shoulders and wrists. The hands and fingers are stubby and the wrists broadened. Restriction of motion is less impaired in the lower limbs, which appear hypotrophic. Thoracolumbar kyphosis with gibbus formation may be present, but is not observed in any patient who can stand upright. The costochondral junctions are knob-like. Pes valgus has been noted in 25% of neonates.

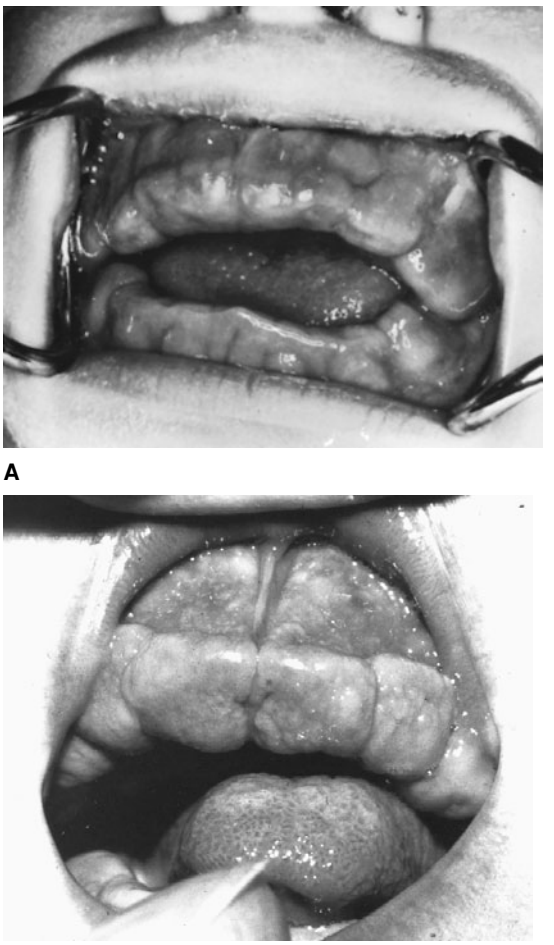
Radiographically, generalized demineralization, a coarse trabecular pattern, and extensive periosteal cloaking of all long bones are seen in early infancy (21). This phenomenon is also observed in newborns with G_{M1} gangliosidosis type I and the disorders cannot be differentiated radiographically at this stage. Congenital fractures have been reported (17). Periosteal new bone formation can be observed until 4–6 months of age. Subsequently, this overgrowth becomes confluent with the underlying cortex and disappears entirely at between 8 and 12 months of age. From that point on, dysostosis multiplex is observed as in MPS I-H, the bony abnormalities being more severe in I-cell disease patients than in MPS-I-H patients at comparable ages. Other differences are minor involvement of the calvaria and minor to moderate diaphyseal widening in long bones, particularly of the lower limbs in I-cell disease (4,26).

Stippled epiphyses, particularly of the calcaneus and knees, and pathologic fractures have been documented (11,12), as have dysharmonic epiphyseal ossification and butterfly vertebral bodies (8). Premature synostosis of skull sutures has also been reported (27). No lamina dura is found around the teeth. The metacarpals are proximally pointed, with the distal phalanges being poorly modeled (11).

Other findings. Minimal to moderate hepatomegaly, evident at birth, occurs in 40% of cases.

Oral manifestations. Enlargement of the gingiva and anterior alveolar process is present as early as 4 months of age and is slowly progressive.

Fig. 5–34. *I-cell disease*. (A,B) Marked thickening of gingiva. Note anterior open bite in A. (A from D Galili et al, Oral Surg 37:533, 1974. B from DT Whelan et al, Clin Genet 24:90, 1983.)



A

B

In some patients, it reaches grotesque proportions (14) and together with a thick tongue prevents proper closure of the mouth (Fig. 5–34). Usually the teeth are deeply buried in the hypertrophic tissue or do not erupt at all. Radiographic examination of the teeth reveals that the enamel is quite hypocalcified and that there is accumulation of storage material about the crowns of unerupted first molar teeth.

Laboratory findings. Peripheral lymphocytes contain large lysosomal cytoplasmic inclusions. The urinary excretion of GAGs is normal. All cultured fibroblasts contain an abundance of coarse cytoplasmic inclusions (hence I-cell disease), with a characteristic inclusion-free perinuclear zone (13).

Most lysosomal acid hydrolase activities, such as hexosaminidase, iduronate sulfatase, and arylsulfatase A, are considerably increased (up to 10- to 20-fold) in the serum but are decreased (10% to 20% of normal) in cultured fibroblasts. The ratio of extracellular to intracellular enzyme activities can also be used (15).

The enzymatic defect is UDP-*N*-acetylglucosamine:lysosomal enzyme *N*-acetylglucosamine-1-phosphotransferase (10). This enzyme is defective in both mucolipidosis II and III. The enzyme catalyzes the first step in the synthesis of the recognition marker, necessary for targeting the lysosomal enzymes to lysosomes (10). Heterozygotes have intermediate levels of phosphotransferase activity in cultured fibroblasts and isolated white blood cells (10). Measuring the activity of acid hydrolases in amniotic fluid and cultured amniotic cells is reliable for prenatal diagnosis (3,23). This has also been accomplished by assay of *N*-acetylglucosamine-1-phosphotransferase assay of chorionic villi (2).

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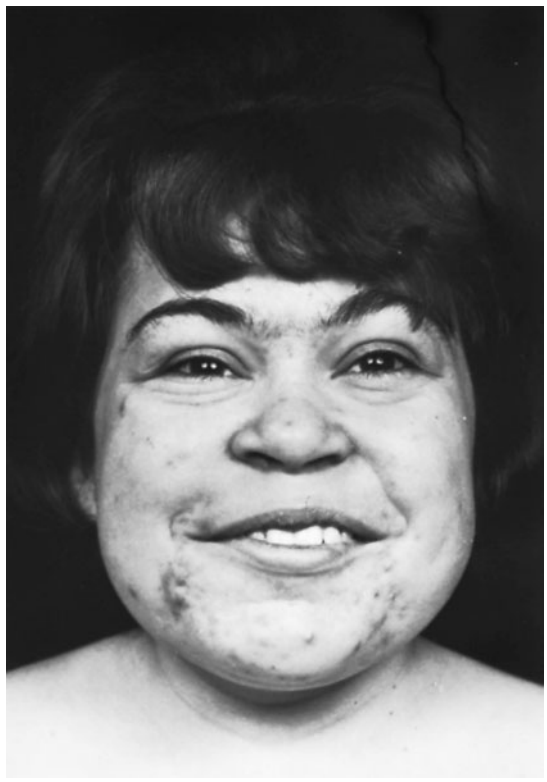
Mucolipidosis III (pseudo-Hurler polydystrophy). Reported initially by Maroteaux and Lamy (8) in 1966, pseudo-Hurler polydystrophy is characterized by mild mental retardation or learning disabilities in about 50%, early restriction of joint mobility, dysostosis multiplex, and normal mucopolysaccharidurıa. At least 90 patients have been described (Figs. 5–35 to 5–37) (1,3,5,17).

Like I-cell disease, pseudo-Hurler polydystrophy results from a deficiency in recognition marker phosphotransferase (6). The disorder has autosomal recessive inheritance. The gene for *N*-acetylglucosaminyl phosphotransferase has been mapped to 4q21–q23 (10), and there is genetic heterogeneity (4,11a).

Typically, in the second or third year of life, restricted joint mobility, small stature, short neck, tight indurated skin, scoliosis, and hip dysplasia, often leading to a waddling gait, are noted. Mild nonprogressive mental retardation (IQ 65–85) has been found in most patients (5,12). A relatively benign clinical course has been reported in at least three adult patients (16).

Fig. 5–35. *Pseudo-Hurler polydystrophy*. Mildly Hurleroid facies.



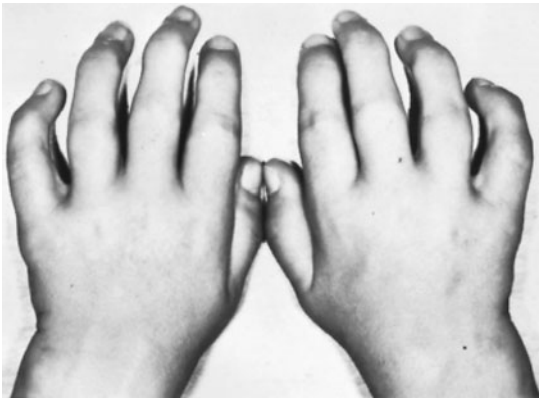


Fig. 5–36. *Pseudo-Hurler polydystrophy*. Fingers cannot be flexed or extended. (Courtesy of J Sensenbrenner, Baltimore, Maryland.)

Facies. The facies has been variable, but most patients exhibit some coarsening of features (Fig. 5–35). The mandible becomes progressively prognathic.

Eyes. Under slit-lamp examination nearly all patients have corneal clouding, often occurring together with mild retinopathy and hyperopic astigmatism (5,15).

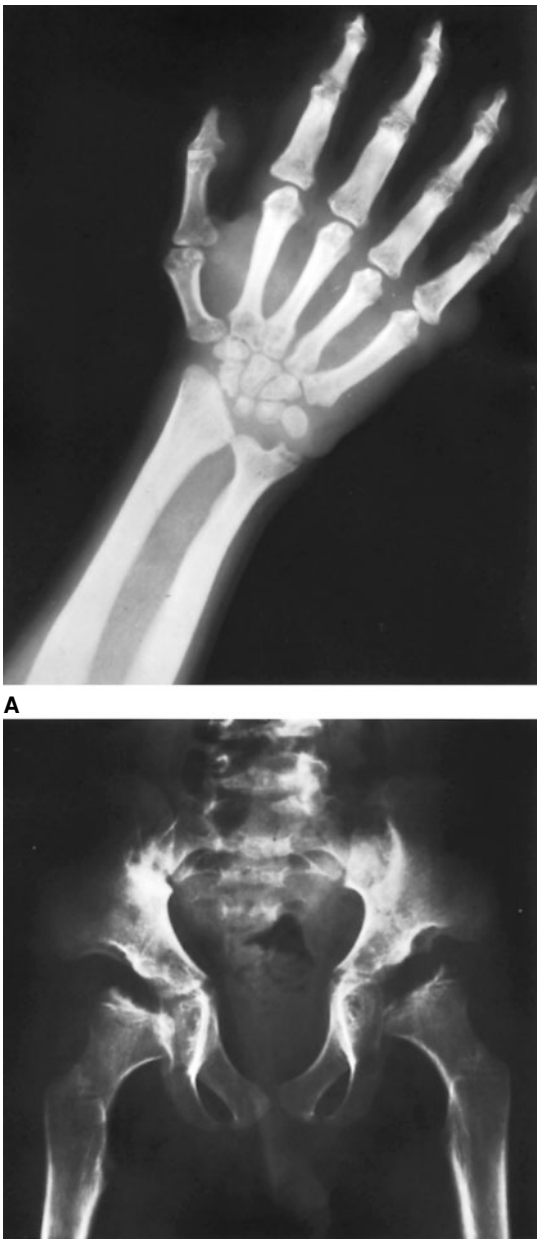
Musculoskeletal system. Short stature, decreased upper-to-lower segment ratio, and shortened arm span are present in all patients. Joint stiffness, suggestive of rheumatoid arthritis, begins about the age of 3 years (2) and progresses slowly until puberty (Fig. 5–36).

Premature closure of cranial sutures is frequent, but the skull is normal in shape. The foramen magnum is small. The clavicles are short and thick, with the midportions bowed superiorly. Vertebral body alterations seen within the first year of life are quite variable but generally are mild (1,11). There is flaring of the iliac wings with constriction of the iliac bones and prominent anterior superior iliac spines. The acetabula are shallow with oblique roofs. Progressive destruction of the capital femoral epiphyses is a striking feature in most patients (Fig. 5–37B). The metacarpals are pointed proximally. The carpal bones are small and irregular. Bone age is considerably retarded (Fig. 5–37A) (1,7,9).

Skin findings. A huge connective tissue nevus of the skin of the back has been described in an adult male patient (13).

Laboratory findings. Peripheral leukocytes are normal. Vacuolated plasma cells are often found in the bone marrow. Finely granulated intracytoplasmic material with staining characteristics of MPS has been found in bone marrow cells. Ultrastructural studies of cultured fibroblasts reveal lysosomal vacuoles containing abnormally accumulated lipids, glycoproteins, and MPS storage (14). Urinary excretion of MPS is normal but that of sialyloligosaccharides is excessive. The activities of most lysosomal enzymes are low in fibroblasts, but high levels (5–50 times normal) are found in serum, findings similar to those demonstrated in I-cell disease (6).

The enzymatic defect is UDP-*N*-acetylglucosamine-1-phosphotransferase (6), the same as that found in I-cell disease. Heterozygotes can be identified by measuring the activity of phosphotransferase in cultured fibroblasts or isolated white blood cells (6). Obligate heterozygotes also have somewhat elevated levels of serum β-hexosaminidase (6).



A

B

Fig. 5–37. *Pseudo-Hurler polydystrophy*. (A) Hand bones are coarsely trabeculated, with small proximal carpal bones and irregular distal radius and ulna. (B) Hypoplastic iliac bodies and femoral heads and necks. (A courtesy of M Robinow, Charlottesville, Virginia. B courtesy of J Dorst, Baltimore, Maryland.)

References [Mucolipidosis III (pseudo-hurler polydystrophy)]

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Sialic acid storage diseases (includes Salla disease). The sialic acid storage disorders include Salla disease and the more severe infantile free sialic acid storage disease (ISSD). Intermediate forms may also exist. Salla disease and ISSD are most likely allelic disorders (18). Salla disease, characterized by early onset of developmental delay, ataxia, and minor dysmorphic features without signs of visceral or ocular involvement (1), was named after the geographical area in which the original Finnish kindred was found. Among the 92 cases reported so far, 87 come from Finland. It may be genuinely rare outside Finland or underdiagnosed (17,21). Infantile free sialic acid storage disease is more severe, is rare (less than 30 cases), and has no ethnic or geographic predilection. The mode of inheritance of Salla disease and ISSD is autosomal recessive. Both disorders are allelic and map to chromosome 6q14–q15 (10). The gene is involved in anion transport (23). There is some genotype-phenotype correlation (1a).

The clinical picture may vary (7) from the hypotonic, nephrotic syndrome or neonatal ascites (60%) of a newborn baby to the severely disabled adult with a nearly normal life span (4,6,11,15). Somatic growth is often retarded (6). Death ensues in early infancy (mean age at death, 13 months).

Facies. The facial features are usually normal in Salla disease but are often abnormal in ISSD. They may be coarse at later stages of the disease but to a much lesser extent than in other lysosomal storage disorders (6). Gingival enlargement at birth is common (25).

Eye findings. Ocular horizontal nystagmus may be an early presenting sign, even before muscular hypotonia and ataxia. Eye findings such as those found in other lysosomal storage disorders, e.g., corneal clouding, are absent in Salla disease (6).

Organomegaly. In Salla disease, there is no organomegaly. In ISSD, nephrosis has been reported (22), cardiomegaly was found in 9 of 21 cases, and hepatosplenomegaly and ascites with inguinal hernia in the first months of life are seen in roughly 60% (3,9). Especially good reviews of the pathology are those of Hale et al (8) and Lemyre et al (9).

Neurologic findings. A low-voltage-type electroencephalographic recording is a constant finding in Salla disease patients over 10 years of age. Cranial CT has revealed cortical and basal atrophy which is more pronounced in older than in younger patients (6). Brain atrophy has also been reported in MRI studies of ISSD (12). Neuropathological findings in Salla disease include reduction of cerebral white matter and degenerative features in the cerebellum (2,22a).

Differential diagnosis. There are four clinical entities (a-d) that present with intracellular accumulation and urinary excretion of sialic acid. Distinction between Salla disease and (*a*) ISSD is easy in typical cases, as a relatively severe phenotype points to the latter disorder. Hydrops/ascites (65%), prematurity (60%), psychomotor retardation (100%), failure to thrive (100%), visceromegaly (100%), dysmorphic features (100%), and hypopigmentation of the skin(100%) also characterize ISSD (6,9). Sialuria (*b*), originally described in 1968, is a rare disorder of free sialic acid metabolism (5,24). It is probably allelic to Salla disease and is due to mutations in UDP-*N*-acetylglucosamine 2-epimerase (20). The clinical presentation is characterized by varying degrees of developmental delay, hepatosplenomegaly, and coarse facies (6). The accumulation of sialic acid is in the cytosol and not in the lysosomal fraction as in Salla disease and ISSD. In patients with (*c*) sialidosis caused by a deficiency of neuraminidase, lysosomal accumulation of storage material is found in the urine, but not free sialic acid (6). The clinical findings in (*d*) galactosialidosis may look similar to those of ISSD but can be differentiated by assaying urinary oligosaccharides and enzyme activities in leukocytes.

Laboratory findings. There is increased urinary excretion of free sialic acid in Salla disease and ISSD (14). Vacuolated lymphocytes or enlarged lysosomes on electron microscopic examination of skin or on conjunctival biopsy can be found (16). Prenatal diagnosis has been accomplished (13,14) and is now possible by using markers linked to chromosome 6q (19) and mutational analysis. Heterozygote detection is also possible by analysis of markers linked to 6q (10).

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Mucolipidosis IV (Berman syndrome). Berman et al (5) first described in 1974 a rare lysosomal storage disease characterized by bilateral corneal opacities in infancy, full facial features with puffy eyelids, hypotonia, and progressive psychomotor retardation (7,10). Storage of intralysosomal phospholipids and glycoconjugates in tissues occurs as a result of deficiency of soluble ganglioside sialidase (2,3). Electron microscopic studies of skin biopsies can be used as a diagnostic tool (18).

Mucolipidosis IV has autosomal recessive inheritance, with about 80% of the patients being Jews of Ashkenazi origin, probably from Poland-Lithuania (18a,20). There may be genetic heterogeneity in this disorder (6,9). The gene mapped to 19p13.2-p13.3 has been linked to mucolipidosis IV (3,21). The gene encodes a novel membrane protein, mucolipidin (3).

Facies. The face is full, but unlike that of other mucolipidoses, it is not truly coarse. Some patients have a somewhat bulbous nose and full lower lip (7,8,15).

Eyes. Strabismus, amblyopia, myopia, photophobia, increased lacrimation, and bilateral moderate to severe corneal clouding are seen in infancy (5,14,15,20). Corneal involvement is congenital in about one-half of the cases (1). The latter improves with time but tapetoretinal changes and marked pallor of the optic discs become enhanced in older children (20). Recurrent episodes of severe ocular pain have been reported (16).

Organomegaly. Organomegaly is absent.

Skeletal anomalies. No skeletal changes or restricted joint movements are observed.

Neurologic. Mild to severe mental and motor retardation appears during the first year of life. Initially, hypotonia with normal or decreased reflexes is followed in time by athetosis and spasticity with hyperreflexia and clonus (15,22).

Differential diagnosis. The severely affected corneal epithelium with an intact Bowman's membrane distinguishes mucolipidosis IV from MPS and G_{M1} *gangliosidosis*. Lack of identifiable enzyme changes in serum and tissues rules out *sialidosis, I-cell disease*, and *pseudo-Hurler polydystrophy*.

Laboratory findings. There is no increase in urinary MPS. Phase contrast examination reveals numerous 1×2 mm inclusions in cultured fibroblasts similar to those in I-cell disease.

Diagnosis is confirmed by electron microscopic observation of characteristic storage bodies (single membrane, limited vesicles), filled with fibrillogranular material (MPS) and lamellar cytoplasmic bodies (phospholipids) in biopsied tissues (cornea, conjunctiva, skin, fibroblasts) (9,11,18). Fibroblasts have reduced (but not absent) ganglioside β-neuraminidase levels (4). The disorder has been diagnosed prenatally by ultrastructural examination of cultured amniotic fluid cells and chorionic villi for inclusions (12,17). Prenatal diagnosis is now possible with molecular markers (21).

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Mucosulfatidosis (Austin syndrome, multiple sulfatase deficiency). The clinical features of mucosulfatidosis, a disorder described by Austin (3) in 1973, are those found in (*a*) steroid sulfatase deficiency (ichthyosis); (*b*) mucopolysaccharidoses [dysostosis multiplex, psychomotor delay, coarse facial features (Fig. 5–38), stiff joints, hearing loss, hepatosplenomegaly]; and (*c*) late infantile metachromatic leukodystrophy (motor weakness, psychomotor delay, demyelinization, and gliosis of white matter of the brain) (5). Corneal opacification does not occur. Oral changes are similar to those of MPS I-H, MPS II, and MPS VI. More than 50 cases have been reported (1,3,4,6,7,8,12,14,15). The eye findings have included skew deviation, optic atrophy, retinal degeneration, and cherry-red macula (7,9).

Children presenting with symptoms during the first 2 years of life then gradually lapse into a vegetative state and succumb during the late first or early second decade. Speech and locomotion are not achieved. However, survival into the third decade has occurred (9). Cervical cord compression and severe hydrocephalus have been reported (10).

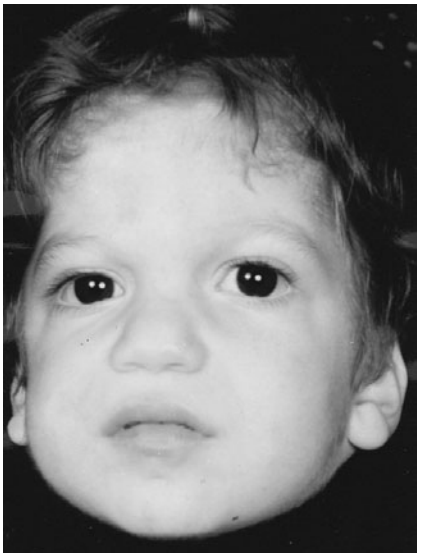

Fig. 5–38. *Mucosulfatidosis*. Coarse facial features. (Courtesy of RD Burck, New York, New York.)

The decrease in arylsulfatase A, B, and C activities is caused either by impaired enzyme production or excessive degradation. Mucopolysaccharidurias and sulfatiduria occur. Schmidt et al (13) showed that a conserved cysteine residue in sulfatases is replaced by a 2-amino-3-oxopropionic acid residue normally, but not in sulfatases derived from multiple sulfatase deficiency cells. It has been proposed that this defect in post-translational conversion is the basic defect in mucosulfatidosis.

Inheritance is autosomal recessive. Prenatal diagnosis using chorionic villi is possible (11).

There is a Saudi variant (1,2) that differs from classic multiple sulfatase deficiency by the presence of macrocephaly, corneal cloudiness, severe dysostosis multiplex, and gibbus and the absence of ichthyosis, retinal degeneration, severe deafness, severe mental retardation, and dementia. The chief neurologic presentation is cervical cord compression due to axis abnormalities.

Laboratory findings. An increase in cerebrospinal fluid protein has been demonstrated. Nerve conduction velocity is slowed. Alder-Reilly granules are found in bone marrow and peripheral blood leukocytes. Besides the arylsulfatase A deficiency, there is a loss of activity of arylsulfatases B and C and four other sulfatases that help to degrade mucopolysaccharides (3).

The disorder is most often confused with *MPS II (Hunter syndrome)*.

References [Mucosulfatidosis (Austin syndrome, multiple sulfatase deficiency)]

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Other metabolic disorders with dysmorphic features

Fabry syndrome (angiokeratoma corporis diffusum universale). The clinical syndrome was described independently in 1898 by two dermatologists, Anderson (2) in England and Fabry (25) in Germany. The characteristic cutaneous lesions led Fabry to call this disease "angiokeratoma corporis diffusum universale." The disorder results from the deficient activity of α-galactosidase A (9,19), a lysosomal enzyme encoded by a gene located at Xq22 and containing seven exons (14,17,23,24,45). The enzymatic defect leads to the systemic accumulation of the glycolipid globotriaosylceramide, particularly in the lysosomes of endothelial, perithelial, and smooth muscle cells of blood vessels and, to a lesser degree, in histiocytic and reticular cells of connective tissue (21). The progressive endothelial glycolipid deposition in affected males results in ischemia and infarction, and leads to the major clinical manifestations (16,56). The disease is inherited as an X-linked recessive trait with complete penetrance and variable clinical expressivity in hemizygous males (34,41,42,53). Disease expression in most heterozygous females is limited to keratopathy; however, a few have been described with manifestations as severe as those of affected males (6,10)

Onset of the disease in affected males usually occurs during childhood or adolescence. Early manifestations include periodic crises of severe pain in the extremities (acroparesthesias), the appearance of angiokeratomas, hypohidrosis, and characteristic corneal and lenticular opacities (21,48). With advancing age, progressive vascular involvement causes ischemia and infarction leading to cardiac, cerebral, and renal vascular disease with death typically occurring in the fourth or fifth decade of life (32,35,40,56). Affected individuals who are blood group B or AB have a more severe course since the blood group B substance also accumulates due to the deficient α-galactosidase A activity (21).

There is no pathognomonic facies; however, frontal bossing and prominent lower jaw and lips have been reported in several male patients. Many patients appear young for their chronological age (55).

Skin. The cutaneous vascular lesions (angiokeratomas) are telangiectases, which usually appear as clusters of individual punctate, dark red to blue angiectases in the superficial layers of the skin. The lesions may be flat or slightly raised and do not blanch with pressure (54). There may be a slight hyperkeratosis over these lesions. They usually appear during childhood and, with age, progressively increase in size and number. Characteristically, these lesions are most dense between the umbilicus and the knees (over the iliosacral area, scrotum, posterior thorax, thighs, buttocks, and umbilicus) and have a tendency toward bilateral symmetry (21) (Fig. 5–39). The face, with the exception of the submental area, may be involved.

Variants, without the characteristic skin lesions, have been described (1,4,53). Hypohidrosis is a common symptom, and atrophic or sparse sweat and sebaceous glands have been reported (50,52). Males shave infrequently and body hair may be slight.

Eyes. Ocular manifestations include aneurysmal dilatation and tortuosity of conjunctival and retinal vessels as well as characteristic corneal and lenticular changes (50). The conjunctival and retinal vascular lesions are common and part of the diffuse systemic vascular involvement. The keratopathy is characterized by diffuse haziness and whorled streaks extending from a central vortex in the corneal epithelium. The corneal

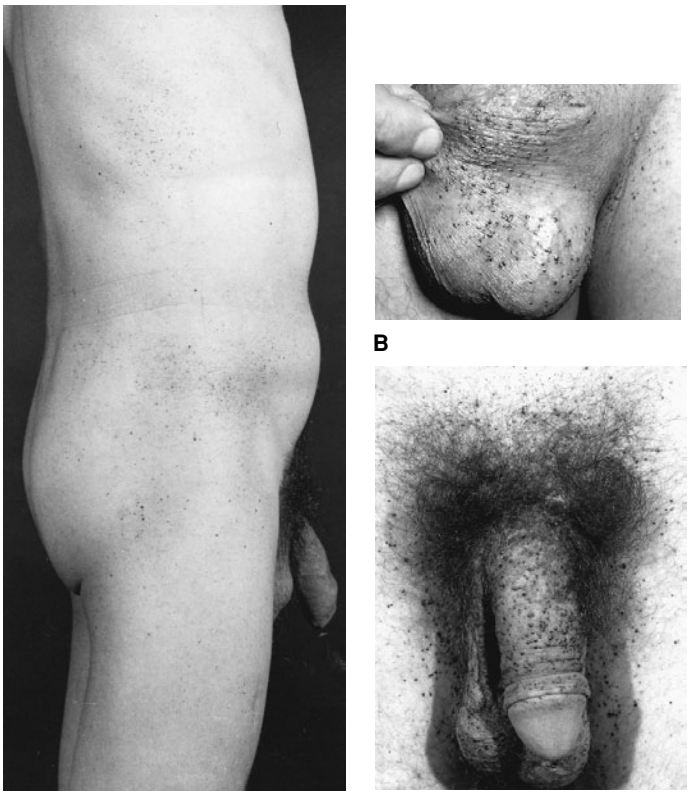

Fig. 5–39. *Fabry syndrome*. (A) Note distribution of skin lesions in 27-year-old man. (B,C) Small, somewhat raised, vascular lesions on scrotum and penis of patients. (A,B from A Rahmen, Trans Assoc Am Physician 75:371, 1961.)

lesions resemble the changes seen in chloroquine intoxication and must be observed by slit lamp microscopy (21). They occur in all hemizygous males and in about 80% of heterozygous females (38,50). The lenticular changes include a granular anterior capsular or subcapsular deposit seen in about 30% of males and a unique linear opacity (termed the "Fabry cataract") in hemizygous males and some heterozygous females that is best observed by retroillumination. The opacity appears as a whitish, spoke-like deposit of fine granular material near the posterior capsule (50). These lesions do not impair vision.

Cardiac, cerebral, and renal vascular manifestations. With increasing age, the major morbid symptoms result from the progressive involvement of the vascular system. Early in the course of the disease, casts, red cells, and lipid inclusions with characteristic birefringent "Maltese crosses" appear in the urinary sediment. Proteinuria, isosthenuria, and gradual deterioration of renal function and development of azotemia occur in the second to fourth decades of life (21). Cardiovascular findings may include hypertension, left ventricular hypertrophy, anginal chest pain, myocardial ischemia or infarction, cardiomyopathy, and congestive heart failure (10,14,20,22,29,35,57). Mitral insufficiency is the most common valvular lesion (20,47). Abnormal electrocardiographic and echocardiographic findings are common (28,57). Cerebrovascular manifestations result primarily from multifocal small vessel involvement. Death most often eventuates from uremia or vascular disease of the heart or brain (39).

Microscopic examination of various tissues demonstrates the accumulation of the glycolipid, predominantly in endothelial, perithelial, and smooth muscle cells of blood vessels, epithelial cells of the cornea and of glomeruli and tubules of the kidney, muscle fibers of the heart, ganglion cells of the autonomic nervous system, and peripheral Schwann cells and dermal nerves (12,30,32). Foamy, lipid-laden macrophages are seen in the bone marrow and lymph nodes.

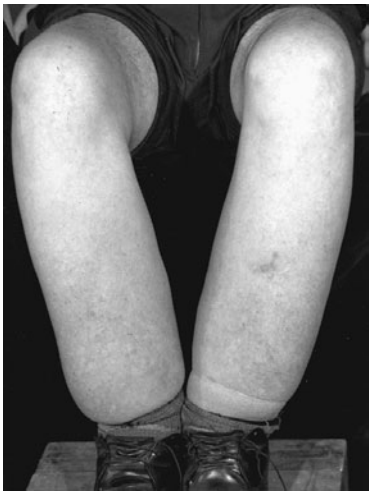

Fig. 5–40. *Fabry syndrome*. Extensively swollen lower legs.

Acroparesthesias. The single most debilitating symptom of this disease is pain. Typically, affected males experience episodic crises of excruciating burning pain in fingers and toes in childhood that may become more frequent and severe in adolescence (49). These painful acroparesthesias may last several days to a week and are associated with low-grade fever and elevation of the erythrocyte sedimentation rate; these symptoms have led to the misdiagnosis of rheumatic fever. During the second and third decades of life, these recurrent, painful episodes may occur only infrequently, usually associated with a fever. However, in some patients, they may become progressively more frequent and severe, and the pain may radiate to proximal extremities and occasionally persist for 1–2 weeks. Affected individuals may be incapacitated for prolonged periods of time with pain that is so unrelenting that suicide has been attempted. It has been suggested that the etiology of the acroparesthesias may be due to impaired autonomic function (13) and involvement of the peripheral nervous system (44). The frequency and severity of these episodes are decreased by use of phenylhydantoin and carbamazepine (36,37).

Other clinical findings. Nausea, vomiting, diarrhea, and abdominal or flank pain are common gastrointestinal symptoms (26,27,43). Other less frequent features include massive lymphedema of the legs (Fig. 5–40) and dyspnea (11,46). Musculoskeletal findings have included a permanent deformity of distal interphalangeal joints of the fingers and avascular necrosis of the head of the femur and talus. Mild normochromic, normocytic anemia, presumably caused by decreased red cell survival, has been observed. Many hemizygotes appear to have growth retardation or delayed puberty.

Oral manifestations. Most patients have symmetric, pinpoint, macular, purplish spots (angiokeratomas) on the lips, particularly on the lower lip near the skin-mucosal junction, on either side of the midline (55) (Fig. 5–41). The lesions are smaller than those on the skin. The buccal mucosa appears to be involved to a lesser degree (21,55). The gingiva, soft palate and uvula are only rarely involved (48,55). The tongue is not affected. Involvement of the nasal mucosa with resultant epistaxis has been reported (55). Hearing loss has been noted (48). Glycosphingolipid accumulation has been demonstrated in dental pulp from hemizygous males (18).

Differential diagnosis. The condition can be diagnosed in hemizygous males by determining a history of acroparesthesias, the presence of characteristic skin lesions, and corneal and/or lenticular changes. Heterozygotes usually are asymptomatic; however, about 80% of patients have corneal lesions that can be observed by slit-lamp microscopy.

The skin lesions are so characteristic in distribution that need for differential diagnosis is extremely limited. The lesions of *hereditary hemorrhagic telangiectasia* are larger, do not involve the lower trunk and

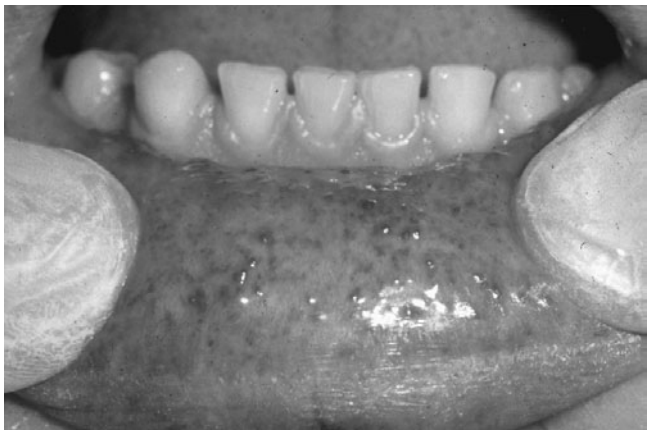

Fig. 5–41. *Fabry syndrome*. Pinpoint lesions on lower lip. Oral lesions are generally limited to the lips and do not involve the tongue.

thighs, and are less numerous and more irregular. The Fordyce type of angiokeratoma is usually limited to the scrotum, and the Mibelli type forms warty lesions on the extremities or ears (21,54).

Angiokeratomas are also found in *aspartylglycosaminuria*, *β-mannosidosis, fucosidosis*, and *galactosialidosis*.

Laboratory aids. Histological and ultrastructural examination of biopsied skin, kidney, or other tissues will show birefringent lipid inclusions and lamellar inclusions in lysosomes, respectively (21). All suspect cases should be confirmed enzymatically by demonstration of deficient α-galactosidase A activity in plasma, isolated leukocytes, tears, or cultured fibroblasts or lymphoblasts (19,21,51). Prenatal detection can be accomplished by demonstration of deficient α-galactosidase A activity in chorionic villi obtained in the first trimester or in cultured amniocytes retrieved by amniocentesis in the second trimester of pregnancy (33). If the causative mutation is known (v.i.), prenatal diagnosis can be achieved using molecular methods. Detection of female carriers is carried out by mutational analysis (3).

The cloning of the cDNA encoding α-galactosidase A (7) has allowed further characterization of the molecular nature of the mutations that led to the enzymatic defect (5,8,15,23). At-risk females can be examined clinically, biochemically, immunofluorescentally, and molecular genetically for heterozygote identification (31).

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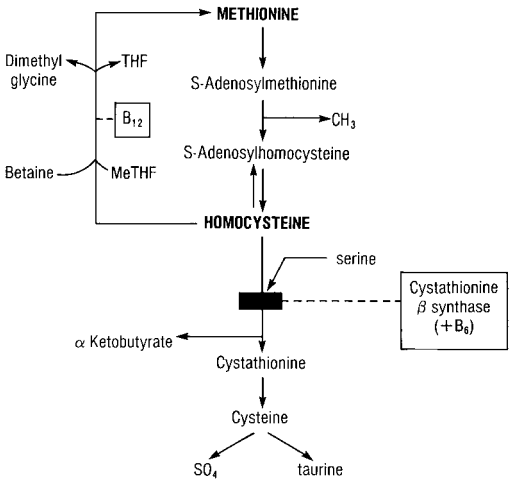
Homocystinuria (cystathionine synthase deficiency). Homocystinuria (cystathionine β-synthase deficiency) is accompanied by a distinctive clinical syndrome that includes ectopia lentis, arteriovenous thromboembolic episodes, dolichostenomelia, mental retardation, and osteoporosis (Figs. 5–42 to 5–45). It was first clearly distinguished from Marfan syndrome by Carson and Neill (6) and by Gerritsen and Waisman (21). Delineation of the biochemical defect followed soon after (19,20,39). The natural history of this condition has been expanded by a remarkable international survey of Mudd and others (42), who compiled the clinical findings for 629 affected individuals. Other excellent reviews are those by Przyrembel (47) and Fowler (16). A wide clinical spectrum of homocystinuria has been reported (12).

Fig. 5–42. *Homocystinuria*. Transsulfuration pathway. Cystathionine β-synthase is the key enzyme for conversion of sulfur-containing enzyme methionine to cysteine.



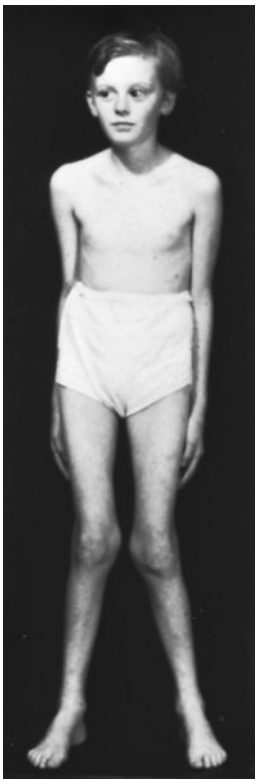
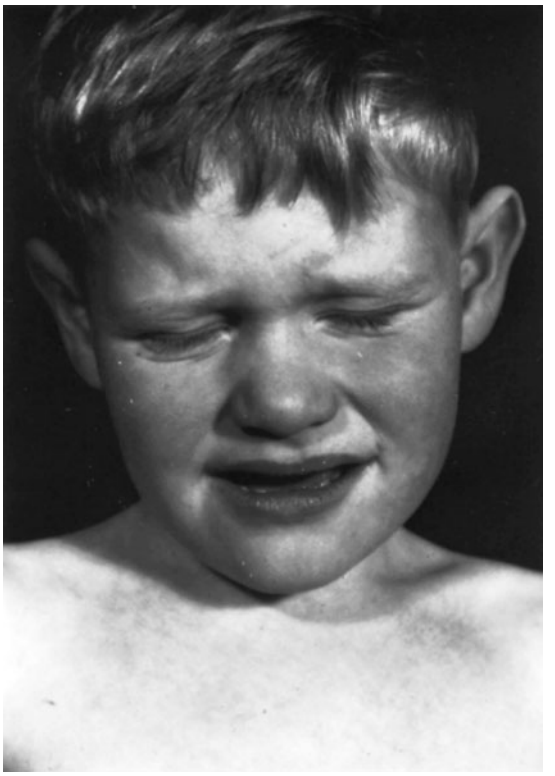


Fig. 5–43. *Homocystinuria*. Marfanoid habitus and genua valga.

Fig. 5–44. *Homocystinuria*. Note malar flushing. (From NAJ Carson and G Gaull, New York, New York.)



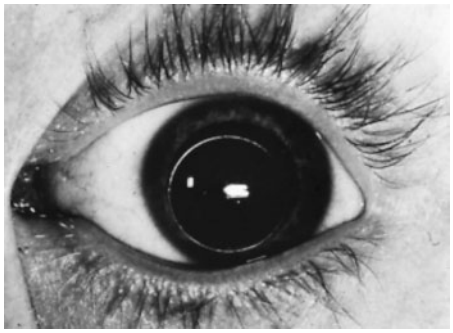


Fig. 5–45. *Homocystinuria*. Inferior dislocation of lens associated with acute glaucoma. (From MC Carey, Am J Med 45:7, 1968.)

Among 34 consecutively detected homocystinuria patients, the mean age at diagnosis was 24 years (range 1–61) (10). Cystathionine β-synthase is a heterodimeric enzyme whose size varies with the tissue of origin (43,55). Both subunits arise from the same parent polypeptide having a molecular weight of 63,000, but they are cleaved to fragments of 48,000 molecular weight in the process of enzyme activation. Thus, the size of the molecule and its activity are probably a function of tissue-specific proteolytic enzymes (55). The fetus probably directs a relatively larger proportion of available homocysteine through the 5-methyltetrahydrofolate-dependent methylation pathway than in the direction of cystathionine synthesis, with concomitant increases in methylneogenesis and conservation of the homocysteine moiety (43). Because fetal tissues and placenta lack γ-cystathionase activity, it has been suggested that cysteine may be an essential amino acid at this stage of life (60).

Cystathionine β-synthase is a key enzyme in the transsulfuration pathway that is responsible for the conversion of the sulfur-containing amino acid methionine to cysteine before it can be ultimately catabolized to its component parts—carbon dioxide, urea, and inorganic sulfate (Fig. 5–42). The enzyme normally requires pyridoxal-5′-phosphate, an active form of vitamin B6, as a cofactor and catalyses the replacement of the β-hydroxyl group of serine (another amino acid) by homocysteine to form cystathionine. In an important salvage pathway, homocysteine can also acquire a methyl group from an appropriate methyl donor, such as methylenetetrahydrofolate (MeH4F) or betaine (trimethylglycine), to regenerate methionine. A form of vitamin B12 known as methylcobalamin (MeCbl) is essential to this remethylation reaction (43). Homocysteine is the sum of the thio-containing amino acid homocysteine and the homocystinyl moiety of the disulfides cysteine-homocysteine, whether free or bound to proteins.

Cystathionine β-synthase deficiency is an autosomal recessive disorder with an estimated birth prevalence of about 1/200,000 to 1/335,000 (43). These figures are partly based on data from newborn screening programs that probably fail to recognize all patients. The much higher prevalence estimates in certain local surveys [e.g., New South Wales, Australia, (1/65,000–1/75,000); Northern Ireland (1/24,000)] further indicate an underestimate of the true frequency in populations with largely Irish ancestry (43,68). In contrast, the incidence is very low in other areas, e.g., Japan, where the rate is 1/900,000 (72).

In cystathionine β-synthase deficiency, both methionine and homocystine accumulate in various tissues, as well as in blood and urine. The deficiency has been studied in detail through the culture and biochemical or immunological characterization of mutant fibroblasts. There is a high concordance between the severity of the clinical syndrome and the extent of the enzyme defect (53).

The cDNA for human cystathionine β-synthase has been cloned and sequenced; alternative splicing during the formation of its mRNA and its expression in cultured cells have been reported (31).

Cystathionine β-synthase has been encoded by a gene located at 21q22.3 (36). There are two relatively common mutations, *I278T* and *G307S*, the former accounting for 15% and the latter for 58% of cases (51). To date, 16 different mutations have been identified (28,30), and a number of publications discuss the relation between genotype and phenotype (11,30,52,56). This allelic heterogeneity has clinical implications. Those individuals with no enzyme activity are essentially unresponsive to treatment with any amount of vitamin B6; those with residual activity in vitro are, as a rule, B6-responsive in proportion to that activity (24, 32,41,70,71). The degree of residual activity is relatively constant among family members, as are the clinical manifestations. There are also individuals, allelic compound heterozygotes, i.e., individuals with two different mutations for the cystathionine β-synthase gene, who may manifest a syndrome indistinguishable from that in apparently homozygous mutants.

Pathophysiology. Homocysteine, an amino acid with an active sulfhydryl side chain, readily forms disulfide bonds in place of its physiologic analog, cysteine. The proteins most susceptible to these abnormal reactions appear to be the collagens, although other structural peptides such as elastin may also be affected. Used as a drug, penicillamine is another sulfhydryl compound that can produce changes similar to those associated with cystathionine β-synthase deficiency via the same mechanism. The end result is weakened fibrous tissue, leading to altered bone formation, rupture of the ligaments of the lens, and abnormalities in joints, skin, and blood vessels (33,43).

Previously, the neurologic abnormalities were thought to arise from a deficiency of the enzyme product, cystathionine, which is a putative central nervous system neurotransmitter. Later, the mental deficit was attributed to high concentrations of a potentially toxic precursor, *S*-adenosylhomocysteine (Fig. 5–42). Adenosine itself is a known neurotoxin in vivo and *S*-adenosylmethionine accumulation leads to significant cytotoxic changes in cell culture. A third view—that the neurological changes are the result of multiple subclinic thromboembolic events—is not supported by autopsy examinations of the brain (43).

The relationship of homocystinuria to thrombosis and atherosclerosis has fascinated investigators since the disorder was first described (17,22,29). Much attention has been focused on abnormalities of platelet function, but the etiology of the thrombotic tendency associated with hyperhomocysteinemia has not been elucidated (57,69). Thromboxane biosynthesis was found to be enhanced in homocystinuria (14). This was thought to reflect, at least in part, in vivo platelet activation.

However, there are quite distinctive changes in the structure of the walls of large and small arteries, and vascular endothelial cell dysfunction has been described (17). Focal intimal and medial fibrosis together with perivascular connective tissue proliferation and widening of the internal elastic lamina have been linked to vascular damage initiated by high homocysteine concentrations. These lesions are also observed in animal studies with homocysteine loading and in homocystinuria as a result of 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency (Table 5–3) (29).

Clinical manifestations. Individuals with cystathionine β-synthase deficiency are normal at birth. Although the disorder is usually identified in childhood, more than 90% of patients reach their 16th birthday and more than 75% survive to the fifth decade (42).

Eyes. Ectopia lentis (Fig. 5–45) is a hallmark, being mentioned in 86% of the 472 case reports that gave an initial presenting sign (42). Dislocation results from disruption of the suspensory ligaments and occurs downward in most cases but may dislocate in any direction. Common secondary features include iridodonesis (particularly evident when the head is moved), marked myopia, and astigmatism. Anterior dislocation may cause pupillary block, glaucoma, and acute ocular pain (5). Cataract is usually the result of lens trauma (43).

Lens dislocation has occurred in more than 50% of patients by age 8 and in more than 90% by age 25 (42). Although B6 responders are less likely to dislocate regardless of treatment, early treatment appears to offer added protection to this group. Other reported ocular findings are optic atrophy, cystic degeneration of the retina, central retinal artery occlusion, and retinal detachment (5,9,20,65).

Musculoskeletal system. Affected individuals are tall and thin as children. True arachnodactyly and Marfanoid habitus with radiographic evidence of excessively long, thin bones (dolichostenomelia) are seen

Table 5–3. Causes of homocystinuria/hyperhomocyst(e)inemia

Underutilization of homocysteine due to impaired activity of CBS deficiency
Genetic CBS deficiency
6-azauridine triacetate administration
Isonicotinic acid hydrazide administration
Underutilization of homocysteine due to impaired activity of 5 methyl-tetrahydrofolate-homocysteine methyltransferase
Genetic MTHFR deficiency
Genetically determined failure to absorb vitamin B12—Immerslund syndrome
Failure of cellular uptake of B12—transcobalamin II deficiency
Failure to release B12 from lysosomes—cobalamin F disease
Failure to convert B12 to methyl- or adenosyl-B12—cobalamin C disease
Failure to convert B12 to methyl- or adenosyl-B12—cobalamin D disease
Failure to convert B12 to methyl-B12—cobalamin E disease
Failure to convert B12 to methyl-B12—cobalamin G disease
Methotrexate inhibition of dihydrofolate reductase
Nutritional B12 deficiency
Nutritional folate deficiency
Nitrous/oxide oxidation of methylcobalamin
Impaired excretion
Renal insufficiency
Artifactual
Bacterial metabolism of cystathionine to homocyst(e)ine
Mechanism uncertain
Colestipol plus niacin therapy

CBS, cystathione β-synthase; MTHFR, 5,10-methylenetetrahydrofolate reductase.

in one-third of cases (43). Other somatic manifestations include joint contractures, joint laxity, pes planus, pes cavus, pectus carinatum, pectus excavatum, kyphoscoliosis, widened metaphyses and epiphyses (most recognizable at the knee), genua valga, and increased carrying angle at the elbow (Fig. 5–43). Associated radiographic features include tibial growth arrest lines, metaphyseal spicules, enlarged carpal bones, short fourth metacarpals, elongated talus, and retarded calcification of the lunate bone in the hand (4,50,61). Of all the radiographic features, osteoporosis is the most frequent finding. Although present in less than 5% of patients under 4 years of age, it affects 70% of individuals over 20 (42). It appears to be less severe in the B6-responsive group. It is most often identified in the spine and is associated with biconcavity of the vertebral bodies. Some investigators have suggested that the latter finding is not a feature of osteoporosis per se but is of vascular origin, as the biconcavity is posteriorly placed—a feature typical of the osteopenia associated with chronic hemolytic diseases such as sickle cell anemia (43). However, vertebral wedging, kyphoscoliosis, and pathological fractures that heal slowly are all directly attributable to loss of bone mass (43). Although the progression of osteoporosis is less rapid in the B6 responders, the effect of B6 treatment is not clear (18,42).

Thromboembolic events. Thrombosis and embolism are life-threatening complications in this disorder. Large or small arteries and veins may be affected, and vascular occlusions can occur at any age (22,34,43). In an international survey of 629 patients, 253 events were reported in 29% of patients (42). Of these, 32% were cerebrovascular accidents, 51% involved peripheral veins (including 13% pulmonary embolism), 4% produced myocardial infarction, and 11% affected peripheral arteries or damaged major organs. In spite of a 4-year, event-free period in early infancy, there was a very sharp increase in thromboembolic events at puberty. By the age of 30, half of the reported patients had experienced at least one event. B6 responders were only marginally better off than nonresponders and the beneficial effect of B6 therapy was not clearly demonstrable. Surgery poses a significantly increased risk for thromboembolism (42). Many reports deal with the potential benefit for cardiovascular problems of a relatively low plasma homocysteine level (58,67). High plasma homocysteine is a risk factor for deep-vein thrombosis in the general population (22). Patients with a concurrent homocystinuria due to deficiency of cystathionine-β-synthase have an increased risk of thrombosis when they also have the factor V Leiden mutation (35). The growth-promoting effect of homocysteine on vascular smooth muscle cells, together with its inhibitory effect on endothelial cell growth, may explain homocysteine-induced atherosclerosis (63). It has been calculated that approximately 10% of the population's risk for coronary artery disease is attributable to elevated homocysteine levels (38).

Central nervous system. The degree of mental retardation associated with homocystinuria varies widely. Both profound retardation (IQ <30) and normal intelligence are described. In the international survey, the median IQ for B6 responders was 86 but for nonresponders was 64, a highly significant difference (42).

Seizures are characteristic, being reported at an earlier age in B6-nonresponsive patients. The great majority are of the grand mal type and affect about 20% of all patients (42). Also reported are nonspecific EEG changes (13,27), psychiatric disturbances (including schizophrenia) (1,25), dystonia (26), spasticity, and hyperreflexia (43). In some case, these latter two signs are related to a cerebrovascular thromboembolic event, but in others, they have been attributed to the disorder itself (8,42). In homocystinuria due to MTHFR reductase deficiency, stroke may occur (66).

Other findings. Other connective tissue findings include bilateral malar flush (Fig. 5–44) (50%), recurrent spontaneous pneumothorax (3), and livedo reticularis. Hepatomegaly caused by fatty liver is observed occasionally, and electromyographic abnormalities have been found in those patients with clinical myopathy. There is an increased incidence of bilateral inguinal hernia, and omphalocele has been described (43). Hypopigmentation is a feature of homocystinuria and can be shown to be reversible in patients with pyridoxine-responsive homocystinuria (48). Darkening of newly growing hair has been observed after initiation of pyridoxine therapy, creating a clear demarcation between the old, blond and the new, dark hair (48). Probably, DL-homocysteine inhibits tyrosinase by interaction with copper at the active site of tyrosinase. Recurrent early spontaneous abortion has been shown to be linked to hyperhomocystinemia (46,59,72). Homocysteine metabolism may play a role in the prevention by folic acid of neural tube defects (37).

Oral findings. The palate is often narrow and highly arched. The teeth have been reported to be crowded and irregularly aligned. Mandibular prognathism has been noted (42).

Diagnosis and laboratory aids. Mass neonatal screening programs detect some of the patients with homocystinuria (43,44). They are more likely to miss those with milder disease who, in turn, are more likely to respond effectively to pyridoxine (43). Infants and children at risk are usually screened by the cyanide-nitroprusside spot test for urine, but other disorders of sulfur amino metabolism will also produce a positive test (62). Moreover, false negatives have known to occur. Other investigators (2) recommend measuring plasma total homocysteine as the most reliable method for diagnosis. Diagnostic proof, particularly in individuals without clinical findings, rests with the demonstration of enzyme deficiency in fibroblast culture (53,54). Prenatal diagnosis is possible using this assay on cultured amniocytes (15).

The human cystathionine β-synthase gene spans over 30 kb and consists of 19 exons (7). At least 17 mutations in the cystathionine β-synthase gene have been identified on the basis of clinical homocystinuria (64). The most prevalent mutations are the gly307ser and ile278thr mutations.

Differential diagnosis. Other causes of homocystinuria are listed in Table 5–3. Inborn errors affecting the remethylation pathway from homocysteine to methionine (Fig. 5–42) constitute the majority of these.

Inherited deficiency of the MTHFR enzyme is an autosomal recessive condition characterized by mental retardation and sometimes early death (43). Enzyme activity is impaired if the B12 cofactor is deficient, a situation that can arise if there is dietary B12 deficiency, a B12 malabsorption syndrome, or defect in the conversion of B12 to the methylcobalamin form used by the remethylation enzyme (5,23,45,49). Because these patients are unable to resynthesize methionine, they have low plasma methionine, clearly distinguishing them from patients with cystathionine β-synthase deficiency. They may also have other abnormalities associated

with disturbed B12 mechanism, such as methylmalonic aciduria and/or megaloblastic anemia, but they do not have a Marfanoid somatotype or associated clinical features (40,49).

Lens subluxation is a feature of other disorders of sulfur amino acid metabolism, as well as Marfan syndrome and related disorders (43). The Marfanoid habitus is found in *Marfan syndrome*, congenital contractural arachnodactyly, *XXY syndrome*, *XYY syndrome*, sickle cell anemia, *nevoid basal cell carcinoma syndrome*, and *multiple endocrine neoplasia, type 2b*.

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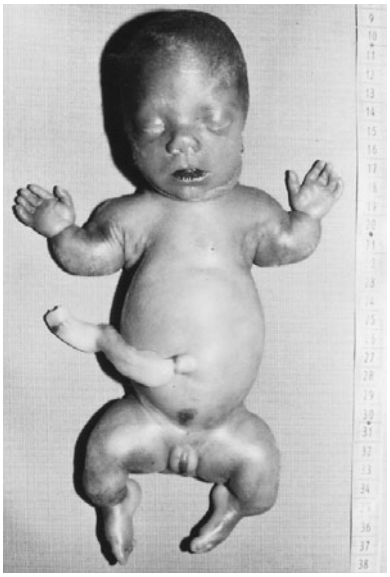
Hypophosphatasia. Hypophosphatasia is an inherited disorder of bone mineralization characterized by rhachitic changes in childhood or osteomalacia in adult life, absence of tooth cementum and premature loss of teeth, and decreased alkaline phosphatase enzyme activity (Figs. 5–46 to 5–50). Hypophosphatasia was first identified as a separate entity by

Fig. 5–46. *Hypophosphatasia*. Severe lethal hypophosphatasia. Note short limbs.



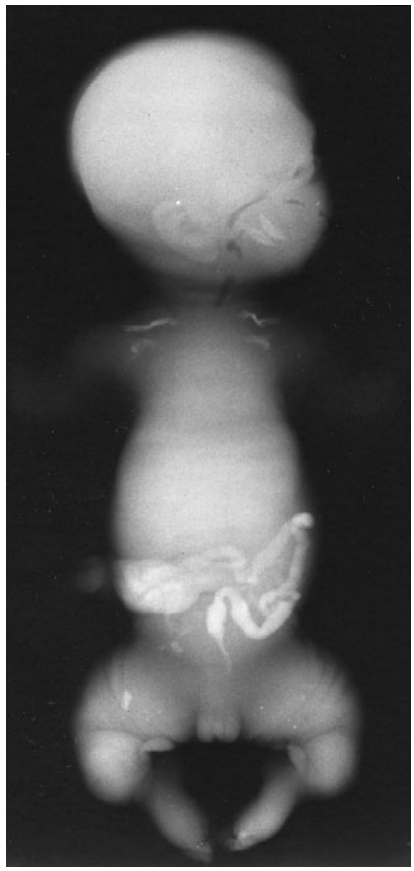
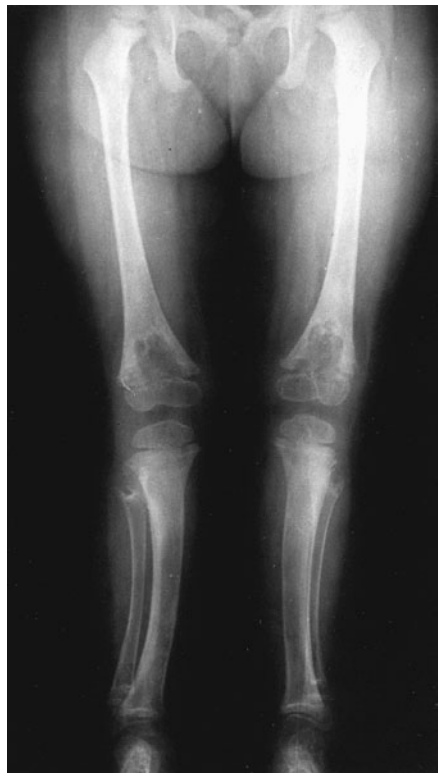


Fig. 5–47. *Hypophosphatasia*. Note markedly impaired mineralization and short extremities.

Fig. 5–48. *Hypophosphatasia*. Note large midmetaphyseal ossification defects and angulated tibias.



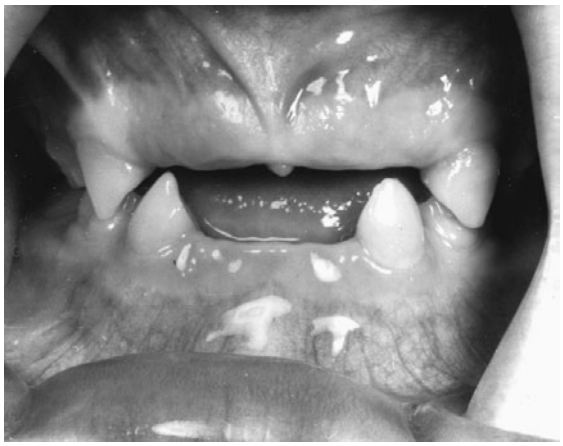
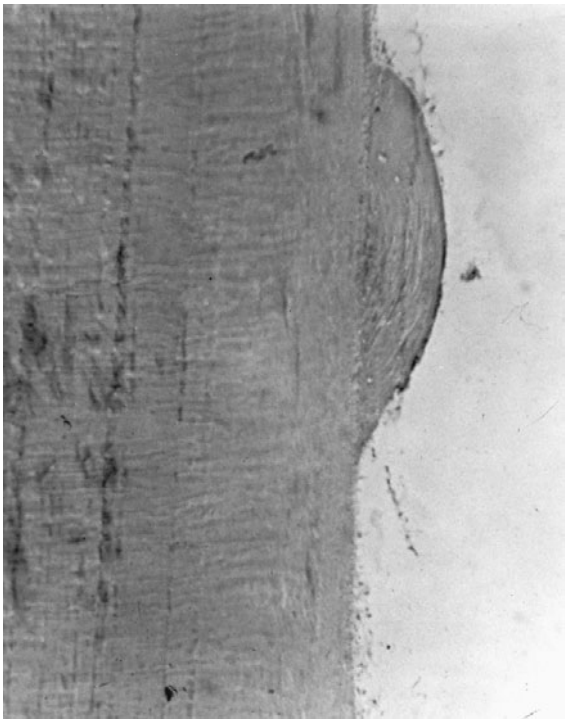


Fig. 5–49. *Hypophosphatasia*. Premature loss of deciduous teeth, most commonly affecting the anterior region.

Rathbun (43) in 1948, although there are earlier case reports (42). A wide range of presentations are described, but all patients have some deficit in serum and tissue alkaline phosphatase. From a clinical perspective, most individuals can be classified as having the perinatal (lethal), infantile, childhood, or adult form of the disorder (14,42). People who have only dental manifestations are regarded as having "odontohypophosphatasia." A very rare variant is called "pseudohypophosphatasia" (45) and resembles infantile hypophosphatasia, except that serum alkaline phosphatase activity is not reduced. A mild autosomal dominant form has been delineated. Prenatally it looks severe but has a benign course (32,40). Not all patients can be classified clinically. Some authors classify patients with hypophosphatasia into only two types: severe and mild (12,28,29). Others state that the levels of bone alkaline phosphatase immunoreactivity in serum reflect disease severity (65).

Fig. 5–50. *Hypophosphatasia*. Section of tooth in hypophosphatasia. Note almost complete absence of cementum.



Genetics and biochemistry. The human alkaline phosphatases share the property of hydrolyzing artificial phosphoester substrates at alkaline pH. They constitute a system of multiple molecular forms that originate from at least three different genes and multiple tissue-specific post-translational modifications (33). In hypophosphatasia, both the tissue-specific placental and intestinal isoenzymes localize to chromosome 2q34–37 (7) and are largely intact, but the so-called tissue-nonspecific or liver/kidney/bone group of isoenzymes is usually markedly deficient (33,52). A single gene localized to chromosome 1p34–p36 (17) codes for the protein precursor that is then modified to produce at least three electrophoretically and biochemically distinct isoenzymes found in bone, liver, and kidney, respectively (16,23). There are many mutations (50a). These isoenzymes are antigenically similar but have different developmental sequences (33,48). The bone isoenzyme is believed to play an important role in calcification, and its production varies with the rate of bone mineralization (44). Possible functions may include the supply of inorganic phosphate through phosphoester hydrolysis for mineralization, the clearing of pyrophosphate, a calcification inhibitor, and the binding and storage of inorganic phosphate (39,57).

Although pathologically similar to vitamin D-deficiency rickets, hypophosphatasia is clearly differentiated as a disorder of bone matrix rather than bone mineral, as secondary mineralization is intact (14,42). Moreover, vitamin D metabolism is normal in this disorder (60). Acid phosphatase activity, a marker of osteoclastic function, is also normal (14).

The deficit in the tissue alkaline phosphatase is reflected in decreased total serum activity, a composite of the various isoenzyme fractions (33). In serum, too, it is the tissue-nonspecific enzyme that is very low, but intestinal enzymes may also be depressed (57). Neutrophils and cultured skin fibroblasts are also deficient in alkaline phosphatase activity (7,49,52,55).

The birth prevalence of the severe form of hypophosphatasia in Toronto, Canada, has been estimated to be 1/100,000 live births (15). The disorder is especially prevalent in inbred Mennonite families from Manitoba, Canada, where 1 in 2500 newborns manifests severe disease and about 1 in 25 individuals is a carrier (18,57). Both recessive and dominant modes of inheritance have been observed in different hypophosphatasia kindreds (21,24,31,59). The frequency of consanguinity and the recurrence rates for infantile hypophosphatasia are clearly indicative of a recessive mode (18,30), but the suggestion that hypophosphatasia is an autosomal dominant condition with homozygous or compound heterozygous lethality is in keeping with the data on the adult form of the disorder (12,14,21,58). Subjects with childhood or adult hypophosphatasia can also be compound heterozygotes for tissue-nonspecific alkaline phosphatase missense mutations (57). It has now been demonstrated that all clinical forms of hypophosphatasia, with the possible exception of pseudohypophosphatasia, can result from tissue-nonspecific alkaline phosphatase missense mutations or, rarely, frameshift mutations (37). However, the precise genetic basis for most cases remains to be solved (57).

Clinical features. In the perinatal (lethal) form of hypophosphatasia, markedly impaired mineralization occurs in utero. The extremities are shortened, the long bones are deformed, and the cranial vault fails to mineralize (craniotabes) (Figs. 5–46 and 5–47). Polyhydramnios has been observed more frequently in hypophosphatasia pregnancies (46). Premature stillbirth deliveries are not uncommon (4,28). Radiographs show small, sclerotic bones at the base of the skull as well as a membranous calvaria. The ribs are small, thin, and deformed. The vertebrae are spottily involved; some are unossified, some dense, some rounded, and some flattened. Sclerotic patches are also observed in the ribs and other tubular bones. In some infants, almost no bone is formed. In others, the metaphyses are cupped and camptomelic changes are noted. The midshaft of the ulna and fibula may protrude through the skin. Spikes may be present at the elbows and knees (16b,35,47,51a,68). The clavicle is the least affected bone. In live births, the outcome depends on the extent of pulmonary and neurological compromise, but demise usually occurs within a few days (14,26).

Infantile. Those individuals with the infantile form commonly present some time after birth because of failure to thrive (14,57). This form is apparently difficult to recognize with radiographs; most newborns do well for a short period and then experience a wide variety of problems related to impaired bone growth. Hypercalcemia may be marked, explaining a history of irritability, poor feeding, anorexia, vomiting, hypotonia, polydipsia, polyuria, dehydration, and constipation. Episodes of unexplained fever, tender bones, and respiratory distress are also described. Renal function may be impaired by hypercalciuria and nephrocalcinosis. Traumatic fractures are frequently found (1,14,26). Mortality may be as high as 40% (50,51,67).

The anterior fontanel is often enlarged and may bulge. The membranous cranial sutures are also frequently widened, and some degree of ocular prominence resulting from shallow orbits may be apparent within the first few months of life. Head circumference also increases more slowly than expected as premature suture fusion sets in. Radiographs show widespread demineralization and rhachitic changes in the metaphyses (Fig. 5–48), but usually with less diaphyseal bowing than would be expected with severe metaphyseal disease (26). A rhachitic "rosary" is common. In infants who survive, there is often spontaneous improvement in mineralization and remission of clinical problems other than craniostenosis (64). Although the sutures appear widened and membranous, intense mineralization activity may be detectable by nuclear scintigraphy (50). Moderate short stature in adulthood and premature loss of deciduous teeth are also common. Skin dimples have been described (56). Carriers of the infantile form are stated to have less dense bones (8).

Childhood. Childhood hypophosphatasia is a milder condition that often presents as "rickets" in the second and third year of life (26). Signs of intracranial hypertension or failure to thrive are typical (14,26,57). Some long bone deformity is not unusual but tends to recede with time. The most serious treatable complication in this group is craniosynostosis. All sutures appear to be involved, but ocular prominence resulting from shallow orbits can be quite characteristic. Other ocular signs include keratopathy and conjunctival calcification caused by hypercalcemia (3). Spontaneous remission of bone disease is common. In at least one case, this has been accompanied by an increase in serum alkaline phosphatase activity (64).

Adult. The adult form is mild, but osteomalacia may produce significant pseudofractures, severe bone pain, and increased susceptibility to traumatic fracture (14,25,54,57,59). The proximal femur is a frequent site of pseudofractures that extend to complete transverse fractures and loss of mobility (9). In this group, a bone scan can be helpful in identifying and clarifying the sources of pain. There is also a predilection for chondrocalcinosis and marked osteoarthropathy later in life (61).

Oral manifestations. Delayed dentition, premature loss of deciduous teeth, and spontaneous loss of permanent teeth are characteristic of hypophosphatasia (Fig. 5–49) (2,6,13,36,41). These features may be the only clinical signs of disease, thus giving rise to the term "odontohypophosphatasia" for this variant condition (20,41). The anterior deciduous teeth are more likely to be affected and the most frequent loss involves the incisors. The process is that of relatively painless extrusion and does not invoke periodontal inflammation (2). Dental X-rays show reduced alveolar bone, enlarged pulp chambers and root canals, decreased cementum, but normal enamel (2,41). Findings in the permanent dentition may include large coronal pulp chambers, abnormal root cementum, and disturbances of the mineralization of the coronal dentin (36).

Pathology. In the infant, bone histomorphometry reveals a marked excess of osteoid volume and a osteomalacic pattern of tetracycline labeling in dynamic studies (14). Bone alkaline phosphatase is usually undetectable and electron microscopy shows otherwise normal subcellular architecture of osteoblasts and their associated matrix vesicles (14,39). Iliac crest biopsies in adults show less dramatic and more variable changes. The severity of the osteomalacia, as measured by relative osteoid volume, is inversely correlated with the amount of detectable alkaline phosphatase and with the concentration of serum alkaline phosphatase activity (12). In shed teeth, marked deficiency or absence of cementum (Fig. 5–50) is a striking characteristic, accounting for the ready loss of teeth (2,41,57). This appears to be the result of aplasia, since the resorption of cementum has never been observed. Dentin formation is delayed, thus less is formed. Interglobular dentin and osteodentin have also been seen (2,5,41).

Diagnosis and laboratory aids. Hypophosphatasia can be diagnosed on clinical grounds alone, but low serum concentrations of alkaline phosphatase will often help to rule out other disorders with similar findings. In general, the more severe the disease the lower the serum alkaline phosphatase activity level appropriate for age (57). In forms of rickets or osteomalacia other than hypophosphatasia, serum alkaline phosphatase activity is typically increased (57). In most cases, the detection of increased urinary phosphoethanolamine or pyrophosphate will serve to confirm the diagnosis, but is not pathognomonic (27). Measurements of the B6 vitamin pyridoxal-5′-phosphate in serum is a more sensitive test, as levels tend to be abnormally low in other bone diseases characterized by increased alkaline phosphatase activity (57). It may also be helpful in identifying mildly affected patients or detecting variants such as pseudohypophosphatasia (10,11). Alkaline phosphatase is also characteristically low in cultured fibroblasts from hypophosphatasia (60,62) but shows poor correlation with the severity of the disorder (60).

Neonatal hypophosphatasia can be distinguished from *osteogenesis imperfecta*, *achondrogenesis* of various types, *campomelic dysplasia*, and other congenital osteochondrodysplasias by radiographic and biochemical findings. Childhood and adult hypophosphatasia should be differentiated from treatable forms of rickets and osteomalacia and from other metaphyseal chondrodysplasias.

In the severe neonatal and infantile forms, prenatal diagnosis has been achieved using ultrasonic detection of the bony malformations (66). Monoclonal antibody testing of chorionic villus samples has been used successfully for first-trimester prenatal diagnosis (4,53). Successful prenatal diagnosis has also been reported with use of molecular techniques in chorionic villi samples, (22,34,38). High values of pyridoxal-5' phosphate have been found, and Gehring et al (16a) have suggested that during rapid growth, heterozygotes may be distinguished.

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Pseudohypoparathyroidism (Albright hereditary osteodystrophy, pseudopseudohypoparathyroidism)

Albright et al (2) first described pseudohypoparathyroidism (PHP), a hypocalcemic syndrome similar to hypoparathyroidism but with renal and skeletal resistance to parathyroid hormone (PTH). Ten years later, Albright and associates (3) defined a normocalcemic variant of PHP, calling it "pseudo-pseudohypoparathyroidism" (PPHP). Most authors now accept that PHP and PPHP are variants of the same condition. Clinical and biological heterogeneity in PHP may be great (18,33). Chase et al (8) delineated two different types of PHP on the basis of the biochemical response to exogenous PTH. An excellent minibiography is that of Kruse (26a).

In the more common type I defect, neither cAMP nor phosphate are increased in urinary excretion in response to PHT. In the type II defect, there is a cAMP response to PTH, but no phosphate diuresis (Table 5–4). A decade later, Farfel et al (17) and Levine et al (31) reported that a GTP-binding protein was defective in erythrocytes of some PHP type-I patients. This protein, called "stimulatory guanine nucleotide-binding protein" (Gs), is responsible for coupling the cellular receptor that binds PTH—an external cell membrane event—with the formation and release

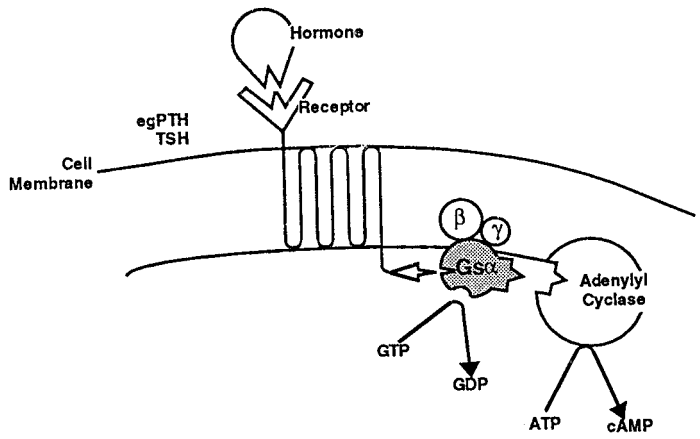
Table 5–4. Pseudohypoparathyroidism

Form	Ca^{2+}	Parathormone	cAMP response	G protein	S
Type Ia	↓	↑	↓	Lack	+
Type Ib	↓	↑	↓	Normal	−
Type II	↓	↑	Normal	Normal	−
PPHP	Normal	Normal	Normal	Lack	+

PPHP, pseudo-pseudohypoparathyroidism.

of cAMP on the internal membrane surface (Fig. 5–51). In signal transduction, a variety of G proteins is present (51). Distinct mutations in the gene encoding the Gs-α subunit, mapping to chromosome 20q13.2 (20), have been identified in affected individuals with PHP type Ia (31,34,50,61,64). In several unrelated patients with PHP, del(2)(q37) was found, perhaps pointing to a second disease locus (40,62). Some deletions were visible, whereas others required detection by fluorescence in situ hybridization (FISH) (62). These patients also exhibited brachymetaphalangy and mental retardation, and they have shown normal levels of Gs-α protein. Because the vasoactive intestinal peptide receptor (RDCI) has also been mapped to 2q37, this may be a candidate gene (42). Patients with PHP type Ia may show clinical signs of endocrinopathies, other than hypoparathyroidism, which are presumably due to generalized hormone resistance (28,30,53). Patients with PHP type Ia have a round face, are obese, and have short bones in the fingers, especially the fourth and fifth metacarpals, and subcutaneous calcification (2). Both PHP type Ia and PPHP can occur in the same family. Both are associated with mutations in the α unit of the G protein (Gs-α) and with a 50% reduction in Gs-α protein. In patients with PHP type Ib, physical appearance is normal, skeletal features are missing, and hormone resistance is limited to PTH. The defect is located proximal to cAMP formation, but unlike PHP type Ia, the defect is likely to involve a specific signal transduction component such as the PTH receptor (53). In PHP type Ib, the Gs-α-protein level is at 100%. A further subtype of PHP (type Ic) is characterized by low cAMP and phosphate responses to PTH, abnormal skeletal features, and 100% Gs-α protein levels. A defect more distal to PTH-stimulated cAMP production is involved in PHP type II (53), which was originally described in a child of normal appearance who was hypocalcemic and hyperphosphatemic, showed elevated serum PTH concentration, and had normal renal function—all of which are consistent with normal PTH-resistant hypoparathyroidism (14). This disorder may be an acquired disease; only a single instance of familial PHP type II has been reported (53).

Fig. 5–51. *Hormone receptor-Gs-adenylyl cyclase pathway*. Parathormone (PTH), like thyroid-stimulating hormone (TSH) and several other hormones, exerts its effects by stimulating adenyl cyclase to produce a second messenger cAMP. The receptor is coupled to adenyl cyclase by a signal transducing protein, Gs, one of a large family of heterotrimeric GTP-binding G proteins. Note that Gs is composed of α, β, and γ subunits, the subunit determining both effector and receptor specificity. (From LC Wilson and RC Trembath, J Med Genet 31:779, 1994.)



Genetics. The previously held concept of X-linked dominant inheritance for PHP (19) is no longer valid; autosomal dominant inheritance has been accepted. However, autosomal recessive examples have been reported (7). Reasons for the dispute were that relatively few instances of male-to-male transmission had been described (54,57) and females are affected twice as often as males. However, hemizygous males are not more severely affected than heterozygous females (32). When defects were identified in the G protein, autosomal dominant inheritance became clear (38,39). Johnson (25) suggested an inheritance pattern that is neither dominant nor recessive: one that results from metabolic interference, similar to that seen in *craniofrontonasal dysplasia*. Metabolic interference may occur when two allelic genes code for different subunits of a multisubunit enzyme or structural protein. Examples of possible metabolic interference in interspecies hybrids have been found (25). Evidence has been presented for genomic imprinting (6,11): an excess of maternal transmission results in the full syndrome and partial expression of the disease is associated with paternal transmission. It has been suggested that paternal transmission results in the PPHP phenotype (60). However, both paternal and maternal transmission of the PHP type Ia phenotype has been described within the same family (49). In another family with PHP type Ia, only maternal transmission of the Gs-α gene mutation was found (35), indicating that a maternal factor determines full expression of Gs-α dysfunction as PHP type Ia. In yet another family, the father had type Ib PPHP whereas at least three children had type II PHP (41).

Newborns with PHP are of normal length, but growth usually lags during childhood and about 60% of patients are less than the third centile for height at maturity (19). Birth weight may be slightly greater than normal; obesity characterizes 65% of patients under 18 years of age (19) (Fig. 5–52). Patients with PPHP tend to be taller and less obese.

Mental retardation is found in 70% of hypocalcemic PHP patients but in only 30% of normocalcemic PPHP patients (19). Farfel and Friedman (16) found that 65% of type Ia and none of type Ib patients were mentally retarded. Personalities are generally affable and pleasant. Seizures unrelated to hypocalcemia have been described. It is not clear whether seizures are secondary to earlier insult, such as hypothyroidism or intracranial calcifications, or whether they are primary (24).

In PHP type Ia, decreased olfactory ability supports the hypothesis that Gs-α (the deficient α chain of the stimulatory guanine nucleotide-binding protein) plays a major role in olfactory transduction (13). Patients with PHP type Ib appear to have olfactory dysfunction relative to matched controls (13). Patients with PPHP have relative normal olfactory function. So, in PHP, there is no direct causal relationship between generalized Gs-α protein deficiency and olfactory dysfunction. Other mechanisms must be responsible.

Craniofacial findings. The face is characteristically rounded with full cheeks, low nasal bridge, and short neck (Fig. 5–53); these features are more prevalent in PHP than in PPHP. With PHP, cataracts may be found in 25% in patients, but with PPHP, cataracts occur in less than 10% (19,28). Enamel hypoplasia, widened root canals, shortened roots with open apices, thickened lamina dura, and delayed eruption have been noted in over one-third of PHP patients (46,60). The second molars are often impacted (60).

Musculoskeletal changes. Most distinctive are short metacarpals and metatarsals, particularly of the fourth and fifth digits. Short metacarpals are manifest by absent knuckles when the patient makes a fist (Figs. 5–54 to 5–56). Also characteristic is a short distal thumb phalanx associated with a wide thumbnail (19,43). Such changes may not be evident until later childhood. Brachycephaly and premature suture closure have been reported. Hyperostosis of the cranial vault is seen in about one-third of patients. Long bone findings such as curvature of radius, bowing of tibia, and genua valga have also been noted.

Generalized osteopenia may be observed, and trabecular coarsening is a feature of PHP with skeletal resistance. In PHP with bone responsiveness, manifestations of hyperparathyroidism may be seen, including

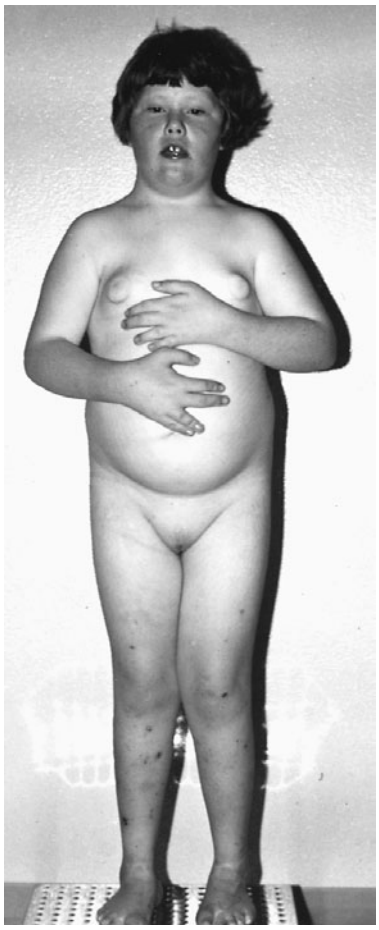
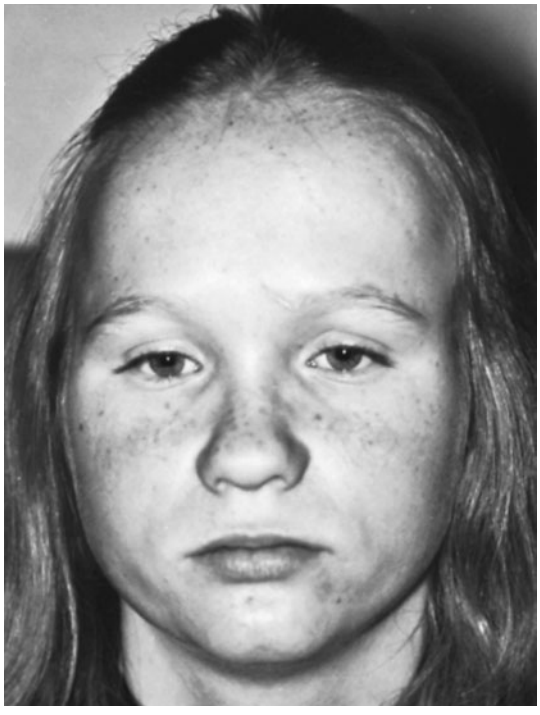


Fig. 5–52. *Pseudohypoparathyroidism*. Short stature and obesity.

Fig. 5–53. *Pseudohypoparathyroidism*. Facies is rounded with low nasal bridge.



subperiosteal bone resorption, bone cysts, and focal osteosclerosis (4,26).

Calcifications. Propensity for soft tissue calcification is well known. Subcutaneous deposits, often osteomas, are found in the scalp and along the extremities, particular the periarticular areas of the hands and feet (12,24,44). Calcifications may also be found in the brain, particularly the basal ganglia and choroid plexus (52). As a rule, deposits are not present in muscle, viscera, or cartilage (19).

Endocrine findings. Disturbances of other endocrine systems are present in some but not all PHP patients (19,27). Hypogonadism and hypothyroidism are frequently found in PHP and tend to show high concordance with deficiencies in Gs protein activity (28,48). Growth hormone–releasing factor deficiency has been reported (55). Other deficits include altered prolactin response to thyroid-releasing hormone (28,31) and a deficient metabolic response to glucagon (28). Such changes are predictable on the basis of the widespread abnormality in receptor-coupling protein, but syndromic variability and inconsistency in the biochemical findings in type Ia patients have not been satisfactorily explained (30). Reproductive dysfunction and oligomenorrhea are common, probably representing partial resistance to gonadotropins (21,37).

Differential diagnosis. In idiopathic hypoparathyroidism, tetanic and epileptiform convulsions, increased thickness of the skull, hypoplastic enamel, and cataracts may be present, but other features of Albright hereditary osteodystrophy are absent. Hypoparathyroidism may occur with *Kenny syndrome*, in which short stature is associated with internal cortical thickening and medullary stenosis of the tubular bones (15). Short metacarpals occur in 10% of the general population and in a variety of conditions (4,21), including type E brachydactyly, peripheral dysostosis, Bilginturan syndrome (brachydactyly, short stature, hypertension) (9), *Turner syndrome*, and *nevoid basal cell carcinoma syndrome*. A metacarpal index for normal children is by Rand et al (45); one for normal white adults is by Parish (37); and one for normal Jamaican children and adults is by Walker and Ashcroft (59). *Acrodysostosis*, once thought part of the spectrum of pseudohypoparathyroidism on the basis of peripheral dysostosis of all metapodial bones and phalanges of hands and feet, nasal hypoplasia, short stature, and mental retardation, was shown not to be part of the spectrum of PHP (1,5,10,22,47,54,56,58). Acrodysostosis is not caused by mutations in the *GNAS1* gene (63). Individuals with deletions of 2q37 can have short fourth and fifth metacarpals and have features that resemble those of PPHP (40,62).

Laboratory aids. In PHP, routine laboratory tests show hypocalcemia, hyperphosphatemia, and increased immunoreactive PTH. Type I PHP may be differentiated from type II by observing no elevation in urinary excretion of cAMP and phosphate after exogenous stimulation by PTH. Type II PHP patients exhibit a rise in cAMP but not in phosphate excretion. Overlap often makes it necessary to examine the renal response to exogenous hormone (53). Measurement of Gs receptor–coupling protein can be used to detect the type Ia subgroup; this finding may be clinically significant, as these PHP patients are at greatest risk for related endocrine disturbances. Infants with PHP should be carefully tested for hypothyroidism as this is a treatable cause of mental deficiency (24,29).

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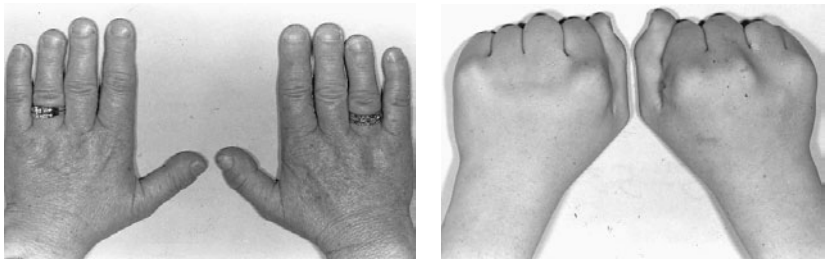

A B

Fig. 5–54. *Pseudohypoparathyroidism*. (A,B) Short metacarpals manifest by absent knuckles when patient makes a fist. Also note short distal thumb phalanx associated with wide thumb nail.

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Fig. 5–55. *Pseudohypoparathyroidism*. Severe shortening of toes from abbreviated metatarsals.

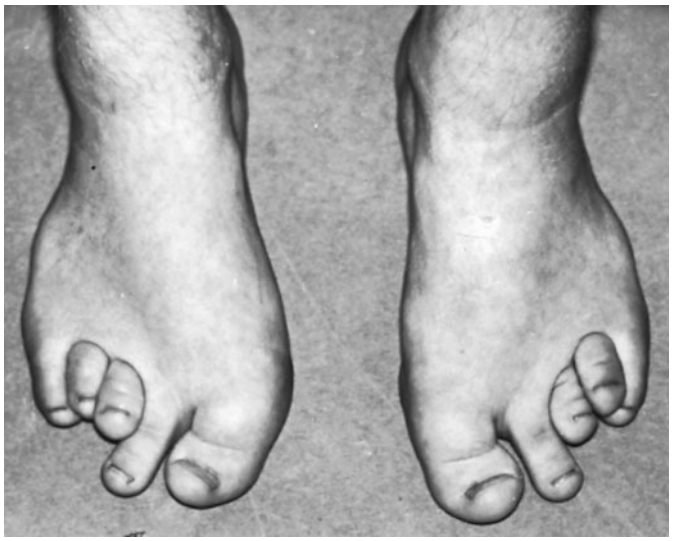
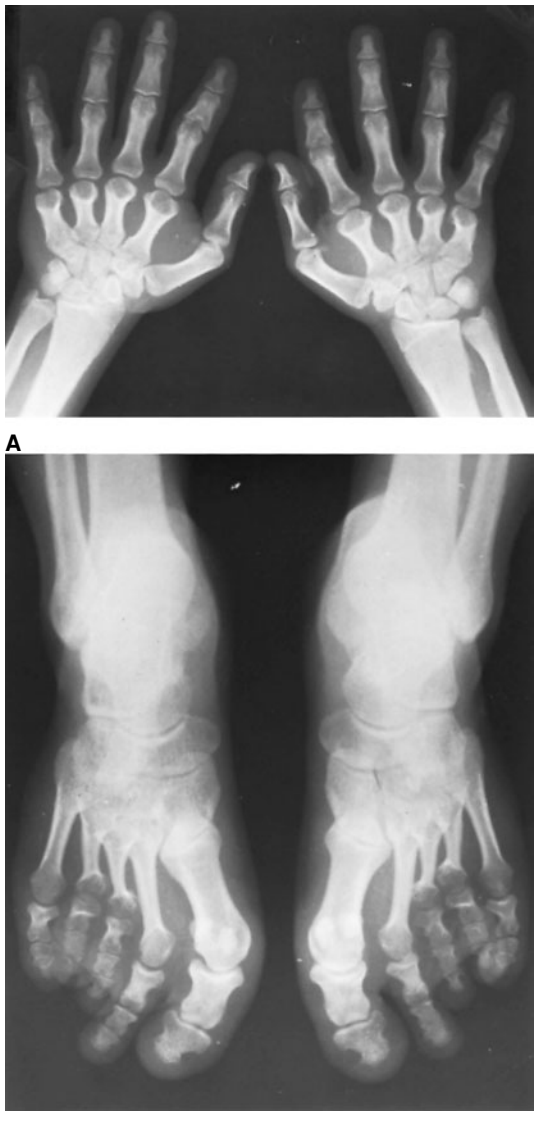


Fig. 5–56. *Pseudohypoparathyroidism*. (A) All metacarpals are shortened. Also observe cone-shaped epiphyses in index fingers. (B) Markedly shortened third and fourth metatarsals.



A B

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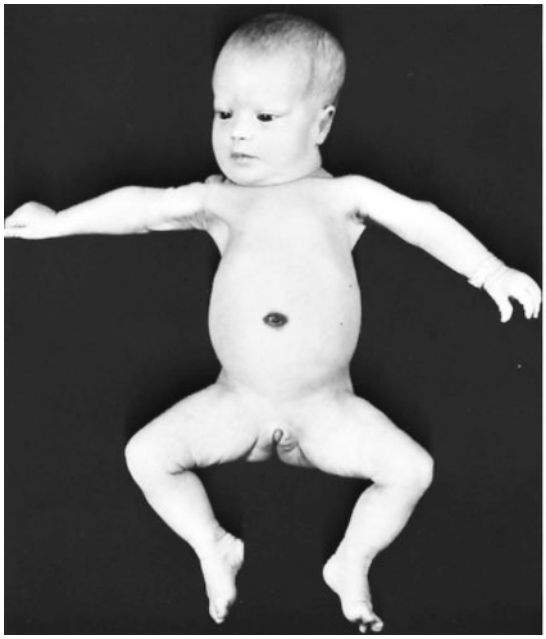
Zellweger syndrome (cerebrohepatorenal syndrome)

De Lange and Janssen (15) probably reported the first case of Zellweger syndrome in 1949. In 1964, Bowen et al (7) and, in 1965, Smith and co-workers (75) described a syndrome consisting of hypotonia, high forehead and other craniofacial anomalies, hepatomegaly, liver dysfunction, and renal cortical cysts (Figs. 5–57 to 5–60). In 1973, Goldfischer et al (22) reported that liver and kidney in affected individuals lacked peroxisomes. Other generalized disorders of peroxisomal function that are less severe than Zellweger syndrome have been studied and include the neonatal form of adrenoleukodystrophy (not to be confused with X-linked adrenoleukodystrophy), the infantile form of Refsum disease, hyperpipecolic acidemia, and rhizomelic chondrodysplasia punctata. The reader may wish to consult several reviews of peroxisomal disorders and their clinical manifestations (8,9,40,45,47,54,71,78,80,87,89,92). An extensive compilation of older Zellweger syndrome references has been published (50), and milder variants of the syndrome have been reported (18).

Zellweger syndrome has autosomal recessive inheritance. Two or more sibs were affected in 17 of 90 families studied, and parental consanguinity was noted in 17% of the 78 cases in which data were available (30,41). The frequency of the disorder has been estimated to be 1/100,000 live births (13), but identification of milder variants and atypical cases by biochemical means has shown a higher frequency of 1/25,000 to 1/50,000 (93). Among Karaites in Israel, Zellweger syndrome is very frequent (94). Cases with pericentric inversion and deletion suggest tentative gene assignment to 7q11 (48,49). A point mutation in both alleles of the peroxisome assembly factor-1 gene (*PAF-1; PMP35; PXMP3*) has been reported in at least two cases (73,74). The *PXMP3* gene has been mapped to 8q21.1 (42), and mutation in the 70K peroxisomal membrane protein (PMP70) has been mapped to chromosome 1p22–1p21 in two patients (19). PEX3 gene mutations are responsible for Zellweger syndrome, complement G (20a,47a). This gene is involved in peroxisomal membrane assembly. The gene product is called double cortin (62a). There is some genotype-phenotype correlation (90a).

Disorders of peroxisome biogenesis fall into 4 phenotypic classes. Three of these—Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease—form a spectrum of overlapping features, with the most severe being Zellweger syndrome and the least severe being infantile Refsum disease. This continuum is referred to as the "Zellweger syndrome spectrum" and includes patients from at least 16 complementation groups (46).



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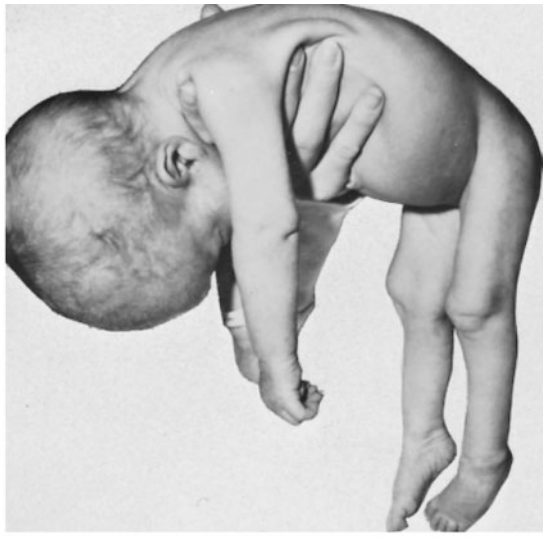


B

Fig. 5–57. *Zellweger syndrome*. (A) High forehead and up-slanting palpebral fissures in severely hypotonic female infant. (B) Extreme hypotonia. (A from JE Jan et al, Am J Dis Child 119:274, 1970. B from E Passarge and AJ McAdams, J Pediatr 71:691, 1967.)

Cell complementation studies indicate that neonatal adrenoleukodystrophy and rhizomelic chondrodysplasia punctata are biochemically distinct entities (Table 5–5) (10,43,55). Fibroblasts from patients with infantile Refsum disease and hyperpipecolic acidemia do not complement those from patients with Zellweger syndrome (20,44,57,78,81,83).

Peroxisomes can be identified by electron microscopy but can be more reliably differentiated from other organelles by histochemical techniques, immunofluorescence microscopy, or immunocytochemical procedures using antibodies against peroxisomal enzymes (22,67). In classic Zellweger syndrome, recognizable peroxisomes are essentially absent from liver and kidney and are greatly decreased in cultured skin fibroblasts (22,66,71).

Similarities between adrenoleukodystrophy and Zellweger syndrome led Brown and co-workers (9) to the discovery that both share a common defect in the catabolism of very long-chain fatty acids (VLCFAs) by a specific β-oxidation enzyme pathway (71). These distinctive lipids are readily quantitated in plasma, stored blood spots, cultured fibroblasts, brain, amniocytes, amniotic fluid, or chorionic villus tissue and therefore serve as useful markers for pre- and postnatal diagnosis (35,36,63,71,72,84).

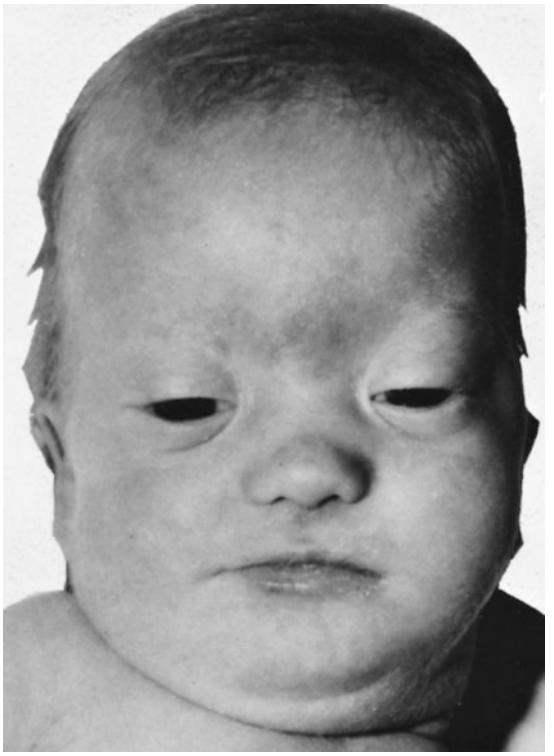
Similarly, the peroxisomal localization of the biosynthetic pathway for plasmalogens, a minor species of either phospholipids, led to the identification of plasmalogen deficiency as another characteristic of Zellweger syndrome (14). The first enzyme in the pathway, acyl-CoA:dihydroxyacetone-phosphate acyltransferase (DHAP-AT), is also readily assayed in a variety of tissues and has been used for pre- and postnatal diagnosis (31,32,39,70,71,85).

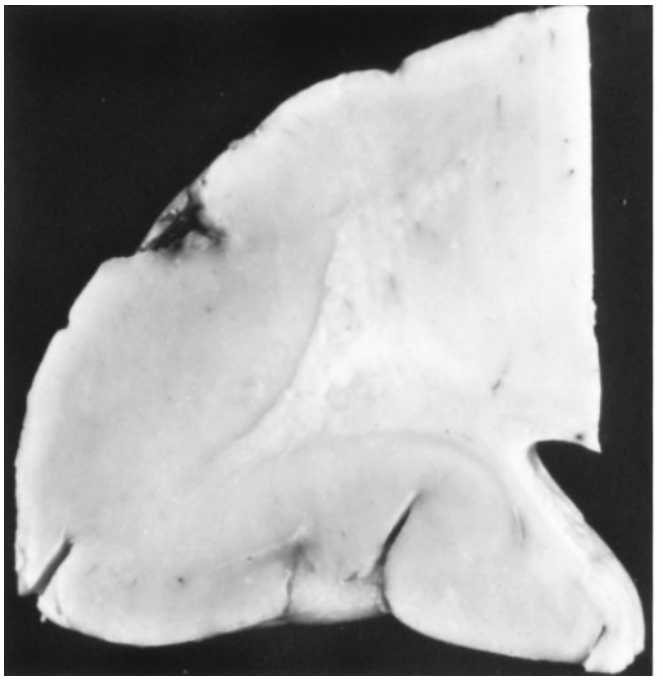
Phytanic acid accumulation also occurs in Zellweger syndrome, as it does in other peroxisomal disorders, notably infantile Refsum disease (57,58,90).

Gestation and delivery are usually uneventful, but the neonate is small and the complications of cerebral and hepatic disease commonly manifest shortly after birth (8). Failure to thrive and delayed development are characteristic (65). Although demise in the first year of life is common, survival into later childhood has occurred (6,24); milder variants may not present in the newborn period (2,3).

Craniofacial features. The forehead is high and the skull may be pear shaped or show some degree of turribrachycephaly. The occiput is sometimes flattened, particularly the supraorbital ridges (51,52). Puffy eyelids, ocular hypertelorism, mild downward slanting of palpebral fissures, and epicanthic folds may be observed. The cheeks are full and the nostrils anteverted (Figs. 5–57A and 5–58). Micrognathia may be found and there is redundant skin on the nape. The ears may be posteriorly angulated and the helices abnormal (51,75). Narrow, highly arched palate

Fig. 5–58. *Zellweger syndrome*. Characteristic craniofacies. Compare with facies shown in Figure 5–57A. (From E Passarge and AJ McAdams, J Pediatr 71:691, 1967.)





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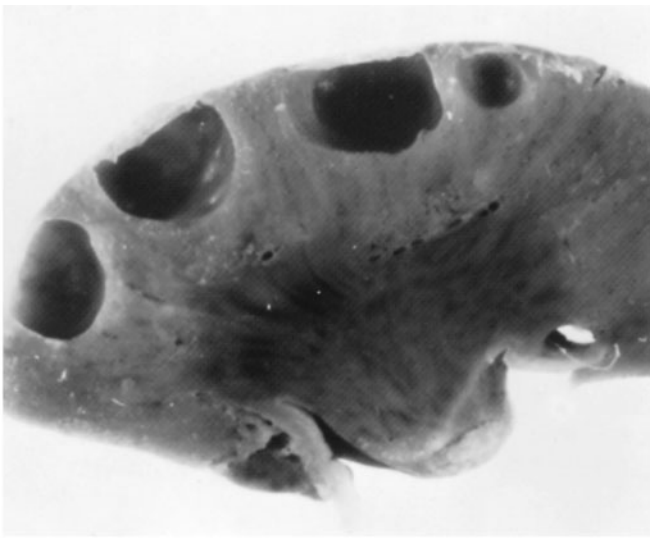


B

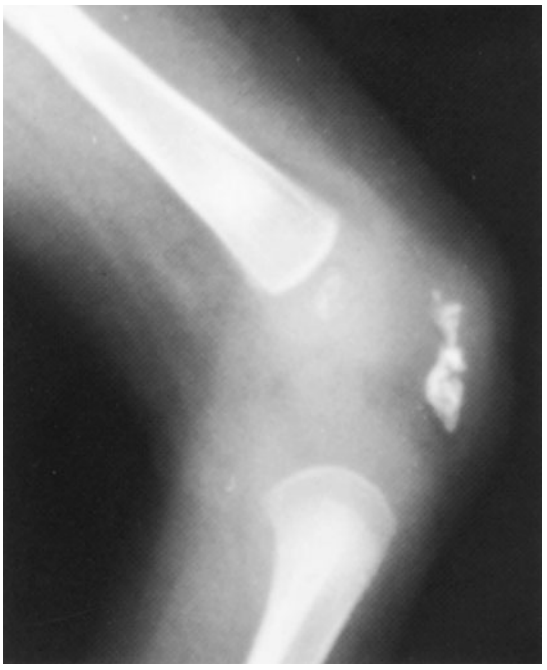
Fig. 5–59. *Zellweger syndrome*. Gross pathologic specimens. (A) Crosssection of cerebrum showing macrogyria, flattening of cortical surface, and thickened cortical gray matter. (B) Kidney showing large cortical cysts. (A,B from A Poznanski et al, AJR Am J Roentgenol 109:313, 1970.)

and protruding tongue have been reported (92). In the infantile form, the teeth were described as being yellow-orange (1a).

Brushfield spots, cloudy corneas, and cataracts are common. The cortical cataracts do not appear to progress; a prominent lenticular Y-suture may also be found (34,38). Funduscopic examination may reveal optic disc pallor or retinal pigment changes that resemble other forms of retinitis pigmentosa (16,56). Visual impairment is progressive and is accompanied by nystagmus and electroretinographic changes.

Central nervous system. Macrocephaly and large anterior fontanel are often noted. Profound hypotonia is almost universal (Fig. 5–57); mental retardation and seizures (oculogyric fits) are also characteristic.

Fig. 5–60. *Zellweger syndrome*. Radiographs. (A) Extensive calcification of patella. (B) Note calcification of hips and kneecaps. (A from A Poznanski et al, AJR Am J Roentgenol 109:313, 1970.)



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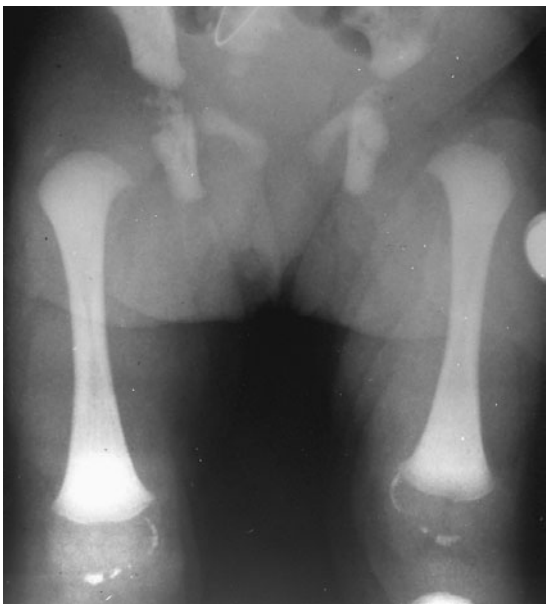

B

Table 5–5. Complementation groups and associated PEX genes in peroxisomal biogenesis disorders

Gifu	KKI[a]	AMC[a]	Phenotype(s)[b]	Peroxisomal-membrane ghosts[c]	Human gene	Mapping
A	8		ZS, NALD, IRD	+		
B	7 (5)		ZS, NALD	+		
C	4	3	ZS, NALD	+	*PEX 6 (PAF2)*	6p21.1
D	9		ZS	−		
E	1	2	ZS, NALD, IRD	+	*PEX 1*	7q21–22
F	10	5	ZS, IRD	+	*PEX 2 (PAF1)*	8q21.1
G			ZS	−		
H			NALD	+		
J			ZS	−		
	2	4	ZS, NALD	+	*PEX 5*	12p13.3
	3		ZS	+	*PEX 12*	
	6		NALD	+		
R	11	1	RCDP		*PEX7*	6q22–24

[a] The numbering listed under KKI (Kennedy Krieger Institute, Baltimore, MD and AMC (Amsterdam Medical Center) is based on the study by AB Moser et al, J Pediatr 127:13, 1995.
[b] NALD, neonatal adrenoleukodystrophy; IRD, infantile Refsum disease; RCDP, recessive chondrodysplasia punctata; ZS, Zellweger syndrome.
[c] A plus sign (+) indicates presence, and a minus sign (−) indicates absence. Modified from N Shimozawa et al, Am J Hum Genet 63:1899, 1998.

Neonatal reflexes are sometimes absent but electromyography may be normal. Ventricular dilatation is frequently detected on CT scan and the EEG is abnormal (9,24,25). At autopsy, distinctive maldevelopmental and degenerative changes are found (Fig. 5–59A), including micropachygyria (67%), lissencephaly and hypoplastic or absent corpus callosum (20%), dysplasia of olivary nucleus, olfactory tracts, and cerebellum (27%), ependymal abnormalities and heterotopias of the cerebrum and cerebellum (48%) (60). Microscopic changes include sudanophilic leukoencephalomyelopathy (26%), increased glycogen storage, and gliosis (35%) (7,59,61,62,68,92). Periventricular germinolytic cysts or pseudocysts can be detected by ultrasound and may be of diagnostic value (64).

Liver. An enlarged liver is rarely encountered at birth but is a common finding in the first year (92). Prolonged neonatal jaundice may be observed and abnormal liver function can be biochemically documented early in life. Histopathologic changes suggest a progression from hepatic giant cell transformation through periportal fibrosis to cirrhosis without widespread inflammatory disease or necrosis (21,39). In some patients, this sequence is completed within a few months time but in older children, hepatic liver function may stabilize (24) and hepatic fibrosis predominates (21). Increased hepatic iron content has been frequently reported (13,21,38,39) but the finding is not without exception (13,53). Hemosiderin deposits appear to be unrelated to progression of hepatic disease (21,38,39). Serum iron, iron saturation, and transferrin concentrations are also elevated in about 65% of patients, but values vary widely and are not necessarily correlated with the degree of tissue iron storage (13,21,36,38). Biliary dysgenesis and intrahepatic cholestasis have also been described (21,38).

Related gastrointestinal findings include islet cell hyperplasia and hypoglycemia (21,53), pyloric hypertrophy, malrotation of colon (7,59), intestinal lymphangiectasis (17), and pancreatic fibrosis (13,16).

Kidney. The kidneys are variable in size and sometimes studded with multiple macroscopic cortical cysts (Fig. 5–59B). Glomerular and tubular microcystic disease is almost always found. Horseshoe kidneys, foci of renal dysgenesis, and interstitial fibrosis have also been described (21,39,59). Proteinuria and generalized aminoaciduria are often found (13,39,59).

Pulmonary and cardiovascular findings. Focal pneumonia may be noted and pulmonary hypoplasia is frequent. Cardiovascular malformations, including PDA, VSD, and aortic arch anomalies, are also common (21,38,92).

Skeletal findings. Bone age is often retarded and hypomineralization and wormian bones have been noted (53,91). Calcific stippling (Fig. 5–60) has been observed, particularly in the acetabular cartilages and along the inferior medial margin of the patellae. Stippled epiphyses are present in long bones in about 70% of cases (53,92). Calcification of the hyoid bone and thyroid cartilage has also been noted. Metaphyseal radiolucencies have been reported (13,53,91).

Other findings. Other features include camptodactyly, single palmar creases, ulnar deviation of hands, cubitus valgus, flexion at knees and hips, talipes equinovarus, metatarsus adductus, rocker-bottom feet, and dorsiflexion of fourth toes. Other anomalies are widely spaced nipples, deep sacral dimple, hypoplastic dermal ridges, small penis, hypospadias, cryptorchidism, prominent clitoris, umbilical hernia, and diastasis recti (13,51,53,59).

Differential diagnosis. Zellweger syndrome may be confused on occasion with *trisomy 21*. Differential diagnosis also includes hyperpipecolic acidemia (20,39,71,83), neonatal adrenoleukodystrophy (39), infantile Refsum disease (41,55), Leber disease (16), and *rhizomelic chondrodysplasia punctata* (33). Biochemical overlap and genetic distinctions between these entities are discussed elsewhere (78,79). Pseudo-Zellweger syndrome and milder variants of Zellweger syndrome have also been discussed (3,23,65). Beemer and co-workers (4,5) reported a new peroxisomal disorder in sibs that was characterized by lethality, hydrocephalus, unusual facies, dense bones, and sex reversal. A 32-year-old man was reported with profound mental retardation, mild facial dysmorphism, retinal pigmentary degeneration, seizures, and sensorineural hearing loss with multiple peroxisomal enzyme deficiencies with preserved peroxisomes (11).

Laboratory aids. Elevated pipecolic acid concentrations in urine and plasma, detected by routine amino acid chromatography, are helpful but not diagnostic (12,13,20,24,26,39,44,81,83). Very long chain fatty acids can be quantified from plasma, cultured fibroblasts, amniocytes, and amniotic fluid (28,41,47,70,71,76). Dihydroxyacetone-phosphate acyl transferase is readily assayed from various tissues and can be used for pre- and postnatal diagnosis (28,32,39,41,70,71,92). Abnormal bile acid and low levels of plasmalogens can also be used in diagnosis (27,29,37,38,43). Trihydroxycoprostanic acid levels are decreased in amniotic fluid (77). An algorithm has been suggested by FitzPatrick et al (18) (Fig. 5–61). Nuchal translucency has been noted (11a).

References [Zellweger syndrome (cerebrohepatorenal syndrome)]

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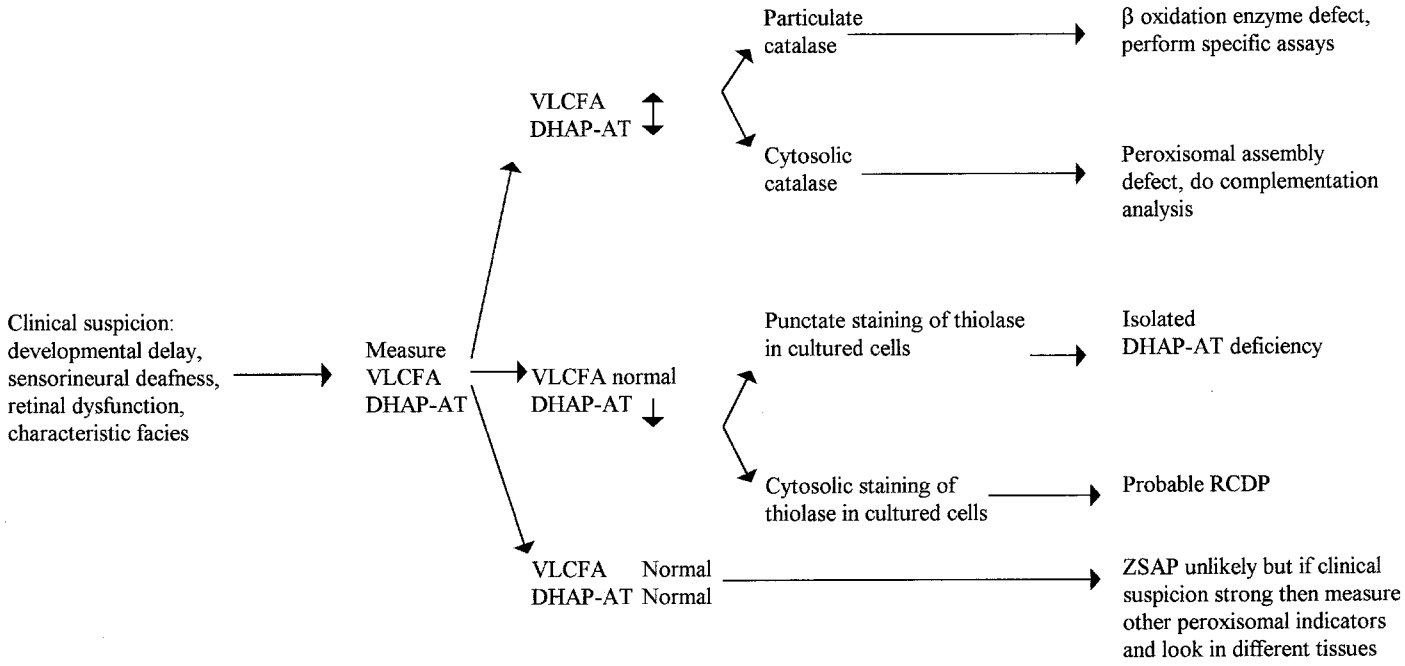

Fig. 5–61. *Zellweger syndrome*. Clinical algorithm for the diagnosis and investigation of a child suspected of having Zellweger syndrome or one of the associated phenotypes: DHAP-AT, acyl-CoA: dihydroxyacetone-phosphate acyltransferase; RCDP, rhizomelic chondrodysplasia punctata; VLCFA, very long-chain fatty acid; ZSAP, Zellweger syndrome-associated phenotype. (From DR FitzPatrick, J Med Genet 33:866, 1996.)

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Carbohydrate-deficient glycoprotein syndromes (congenital disorders of glycosylation)

The carbohydrate-deficient glycoprotein (CDG) syndromes are a newly recognized family of diseases. The basic defects are probably in the glycosylation pathway (endoplasmic reticulum, Golgi or post-Golgi apparatus). The central nervous system is always severely affected but nearly all organs are involved to variable degrees. Jaeken and co-workers (15) reported the first cases of CDG syndrome, later called type I or classical type. By 1998, more than 250 patients were known on a worldwide basis (14,19). The CDG syndrome is characterized by a partial deficiency of the N-linked glycans of secretory glycoproteins, lysosomal enzymes, and probably also membranous glycoproteins (15). Four clinical and biochemical types have now been identified. Type I (Jaeken syndrome), the first described, and best known, seems to affect early neuronal development, while types II and III may be associated with dysmyelination or hypomyelination (32). Types III and IV exhibit severe encephalopathy including resistant epilepsy (14). All types have variable manifestations outside the nervous system (3a,9,10,16,31,32,42).

The CDG syndromes have autosomal recessive inheritance. The frequency in Sweden is estimated to be 1/50,000 births (2). There is a paucity of reports from North America despite the large population of European descendants. The disorder may still be underrecognized and the true frequency unknown (37). It has been described in Latin America (4).

The diagnosis of CDG syndrome type I (Jaeken syndrome) is usually made by isoelectric focusing and immunofixation of serum transferrin (37). The basic defect in CDG syndrome type I is phosphomannomutase deficiency (PMM) (19,37). There are types that do not fit known forms (1).

The phosphomannomutase 1 gene has been mapped to chromosome 22q13 (27); a second phosphomannomutase gene had been located at 16p13 (24). Data from 44 families in the western part of Sweden suggested a founder effect (2). Twenty different missense mutations have been identified in fifty patients from different geographical origins (26). Type II CDG syndrome is caused by a deficiency of Golgi-localized *N*-acetylglucosaminyltransferase II (GnT-II) (17). This deficiency has been demonstrated in fibroblasts and mononuclear blood cells (17,18), and its gene has been mapped to 14q21 and has been cloned (35). In two patients, different point mutations were found in the catalytic domain of the gene (36,37).

Patients with any of the CDG syndromes have, to a certain extent, different presentations, according to age (Fig. 5–62) (12). In infancy, the striking, essentially constant, characteristics are neurological abnormalities, e.g., axial hypotonia, psychomotor retardation, alternating squint, abnormal ocular movements, and variable dysmorphic features. The most typical dysmorphic feature is abnormal adipose tissue distribution such as fat pads (Fig. 5–62C), "peau d'orange" skin, and inverted nipples (13). These infants also have feeding difficulties with failure to thrive. After infancy, neurological involvement becomes predominant. Mental retardation is present in all known patients (13). Strabismus is a constant feature while cerebellar ataxia is variable. Other features include peripheral neuropathy and increasing atrophy and contractures of limbs, particularly in the legs. Retinal pigment degeneration is noted in 75%-100% of patients. Symptoms of hypogonadism are noted in 100% of females (13). The mortality rate is about 20%; death occurs almost exclusively before the age of 6 years.

Approximately 20% of the patients with phosphomannomutase deficiency (CDGI) die during the first years of life due to liver failure, severe infection, cardiac insufficiency, nephrotic syndrome, or in status epilepticus (6,12,14,38). Postmortem findings include olivopontocerebellar hypoplasia, loss of neurons, and gliosis in the cerebral cortex, basal ganglia, thalamus, and spinal cord (14). The peripheral nerves show decreased myelin and multivacuolar inclusions in Schwann cells. Liver pathology is characterized by fibrosis, steatosis, and glycogen storage; electron microscopy shows myelin-like inclusions in the lysosomes of hepatocytes, but not in Kupffer cells (16).

A mild facial dysmorphism is characteristic, with large, somewhat dysplastic ears, high forehead, long eyelashes, prominent base of nose, beaked nose, upturned alae nasi, protruding upper incisors, and receding chin (Fig. 5–62) (14,19).

Retinitis pigmentosa may occur after infancy (3). Abnormal, slow-rolling vertical or horizontal eye movements are combined with slow head movements in the neonatal period, and alternating strabismus (14).

Axial hypotonia and hyporeflexia have been reported (14). Marked psychomotor retardation develops, and ataxia is present as is, at times, epilepsy (14,19). Only rarely are patients able to walk without support. Neuroradiological investigations show pronounced cerebellar atrophy with early-onset Dandy-Walker malformation, atrophy of pons, brain stem, and olives, supratentorial frontotemporal cortical atrophy, small corpus callosum, and small cysts in the white matter (1,16,20). Proton magnetic resonance spectroscopy shows a reduction of *N*-acetylaspartate and an increase in glutamine and γ-aminobutyrate in white matter (29).

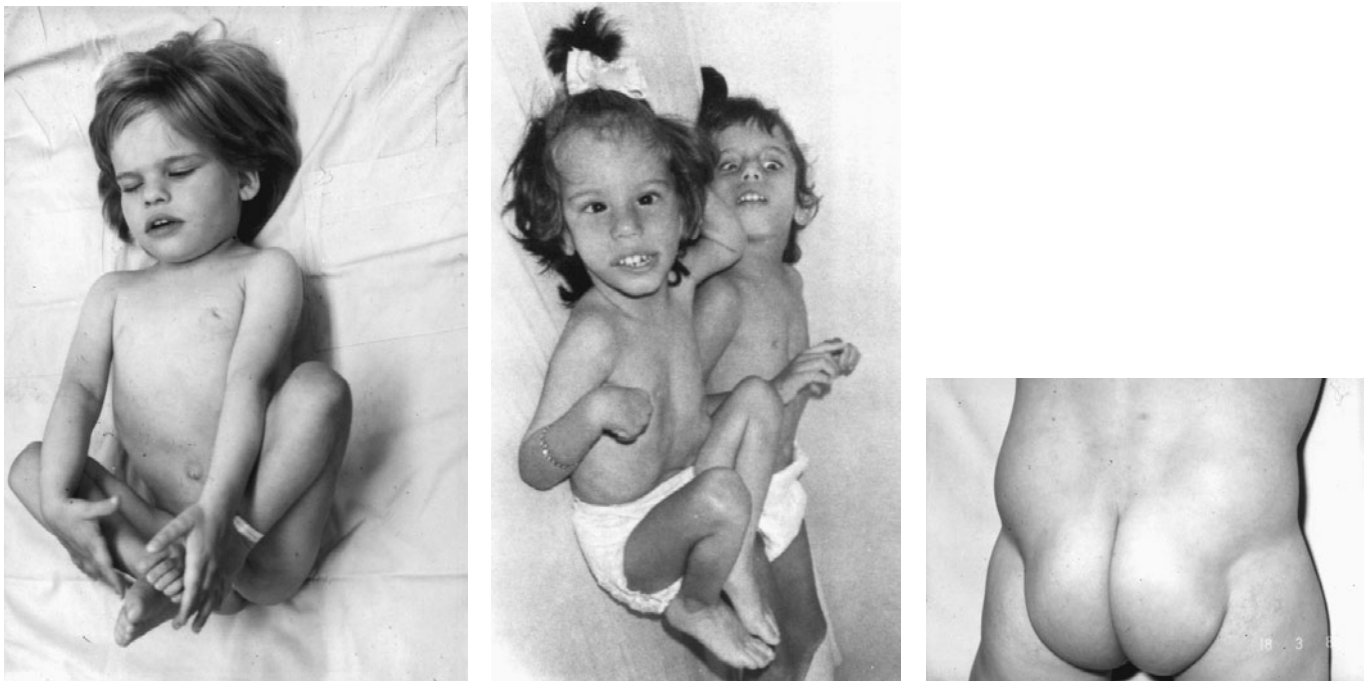
Retracted nipples are often found, as well as abnormal subcutaneous adipose tissue distribution in the form of fat pads and "orange peel" skin. Skeletal abnormalities include wide ribs, squared iliac wings, horizontal acetabular roofs, widening and modeling abnormalities of ischial and pubic bones, dorsolumbar kyphosis, and slight, hook-like dysplasia of the first lumbar vertebrae (30). Dystrophic extremities, mild to moderate hepatomegaly, hypogonadism, and proteinuria are found. Some infants develop pericardial effusion and/or cardiomyopathy (13,14,23,32). There is a great variability in clinical expression even in siblings (14,30). Renal cysts, fibrosis of the testes, and lymph node abnormalities have been observed (14).

Clinical findings in the two published cases of CDG type II patients are similar to those in CDG type I syndrome: facial dysmorphism with high forehead, beaked nose, large dysplastic ears, short neck, hollowed chest, increased internipple distance, and irregular implantation of toes. Tongue thrusting and hand washing movements are evident. Psychomotor retardation is severe.

Laboratory investigation showed lowered serum values for a number of glycoproteins, in part the same as in PMM deficiency. In particular, there is also a marked factor XI deficiency (17). The cerebrospinal fluid protein level was not increased in all patients. In one patient, MRI studies of the brain revealed white matter abnormalities fronto-occipitally.

Types III and IV of CDG syndrome have been reported in a very limited number of patients (31,33); the basic defect remains unknown. Three siblings from a consanguineous mating suffered from cyclic vomiting and congenital hepatic fibrosis. They exhibited a glycosylation disorder that was biochemically similar to CDG syndrome type I. However, normal phosphomannomutase activity was found in all three siblings (21). Phosphomannose isomerase was deficient in leukocytes, fibroblasts, and liver. An extremely mild form (type Ia) has cognitive dysfunction, cerebellar hypoplasia, and coagulation disturbances (40).

Laboratory findings. A large number of serum glycoproteins are abnormal, including transport proteins, glycoprotein hormones, complement factors, lysosomal and other enzymes, and enzyme inhibitors (14). A coagulopathy is also present with marked factor XI and antithrombin III deficiency as well as endocrinological abnormalities (5,7,14,22,39). Glycoprotein concentrations or enzyme activities in serum are decreased. Isoelectric focusing of these glycoproteins shows a cathodal shift due to partial deficiency of sialic acid (14,19,37). In addition, decreased serum levels of copper, iron, zinc, cholesterol, cortisol, and thyroid hormones are found due to decreased levels of the corresponding transport proteins (14). Partial thyroxine binding globulin deficiency is detected



A B C

Fig. 5–62. *Carbohydrate-deficient glycoprotein syndrome*. (A) Psychomotor developmental delay, debuting with gross motor ability delay. Note inverted nipples. (B) Note strabismus, subtle facial expression, and inverted nipples. (C) Bizarre fat deposits on buttocks. (A,C from J Jaeken et al, J Med Genet 34:73, 1997. B from D Michelena et al, Am J Med Genet 84:481, 1999.)

in some patients through neonatal screening for congenital hypothyroidism using T4 measurement (19). Cerebrospinal fluid protein is often increased, as are some amino acids (14,34). Decreased phosphomannomutase activity in leukocytes or fibroblasts confirms the diagnosis for type I CDG; this finding should be confirmed by mutational analysis. Heterozygote detection is possible; prenatal diagnosis has been performed (28) by measuring PMM activity in either cultured amniocytes or trophoblast tissue. Decreased activity of phosphomannomutase cannot be demonstrated in fibroblasts of all patients with CDG type I, confirming earlier suggestions of heterogeneity for CDG type I (25).

Differential diagnosis. Transferrin changes similar to those found in CDG syndrome can be found in chronic alcoholism, galactosemia, and fructosemia (19).

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Molybdenum cofactor deficiency

Molybdenum cofactor deficiency was first described in 1978 by Duran and co-workers (8). The molybdenum cofactor is a low-molecular-weight prosthetic group in which the metal is complexed to a unique pterin species termed "molybdopterin" (12). Its biosynthetic pathway has yet to be fully elucidated. Affected individuals exhibit a combined deficiency of sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase with symptoms that include severe neurologic abnormalities, dislocated eye lenses, and severe mental retardation (8,9,12).

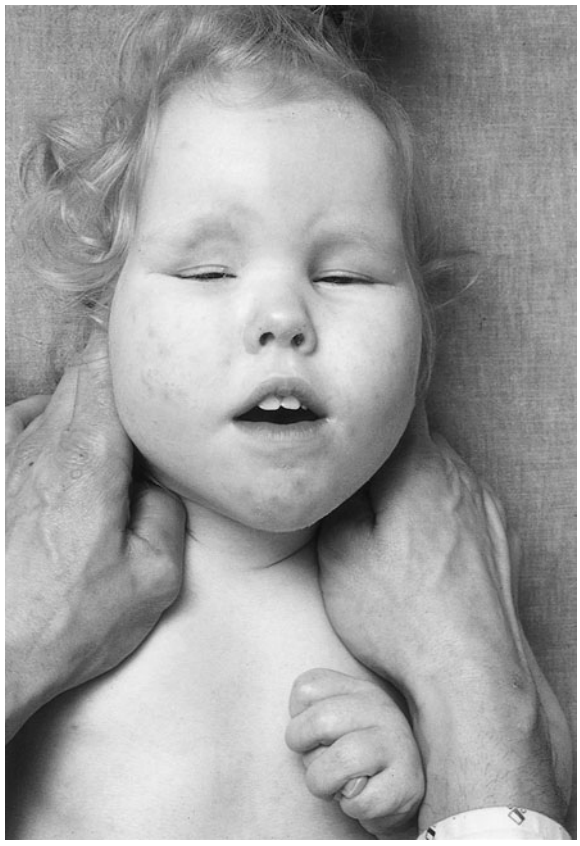
The first patients were diagnosed in Europe (8); subsequent patients were reported from various ethnic groups from all over the world (6,12,15,16). Phenotypic variability has been reported, as well as late onset of the disease (11). Inheritance is autosomal recessive. Obligate heterozygotes do not exhibit clinical symptoms; heterozygosity cannot be established biochemically (5). By using homozygosity mapping in consanguineous affected kindreds, a gene for molybdenum cofactor deficiency has been localized at 6p21.3 (24). The results of this study provide tools for carrier detection and for prenatal diagnosis with microsatellite markers as well. Through fibroblast studies, molybdenum cofactor-deficient patients have been shown to comprise two complementation groups (12). The gene for the neurotransmitter receptor-clustering protein gephyrin causes a novel form of molybdenum cofactor disorder (20,20a).

Clinical symptoms of molybdenum cofactor deficiency include severe neonatal seizures, growth delay, severe psychomotor retardation, lens luxation, and death in the first decade (6,12). The similarity of the CT appearances in molybdenum cofactor deficiency and postanoxic encephalopathy has been noted (1). Pathological studies have shown a severe multicystic leukencephalopathy with marked neuronal loss, particularly in all layers of the isocortex (3). There was demyelination of white matter, accompanied by gliosis and diffuse spongiosis (12,25). These abnormalities may be caused by the toxicity of sulfite and/or inadequate amounts of inorganic sulfate available for the formation of sulfated compounds present in the brain (23).

Isolated sulfite oxidase deficiency is rarely reported; only 8 patients with this deficiency are known (22). It causes a clinical picture that is indistinguishable clinically and neuropathologically from that of the molybdenum cofactor deficiency (17,22). In isolated sulfite oxidase deficiency, molybdenum cofactor and xanthine dehydrogenase functions are unaffected. The inheritance pattern is autosomal recessive; consanguinity was apparent in five of the eight families reported (22).

Facial features include a long face, narrow bifrontal diameter, enophthalmos, telecanthus, elongated palpebral fissures, puffy cheeks ("cherubic"), thick lips, long philtrum and small nose (Fig. 5–63) (4,7,12). Enophthalmos, nystagmus, and unresponsiveness to light have also been

Fig. 5–63. *Molybdenum cofactor deficiency*. Note long face, narrow bifrontal diameter, telecanthus, enophthalmus, elongated palpebral fissures, long philtrum, and small nose.



reported. Lens dislocation is usually found in all patients who survive the neonatal period (12,14). Spherophakia has been reported in at least one patient (18). Severe seizures which occur in both molybdenum cofactor deficiency and in isolated sulfite oxidase deficiency are refractory to treatment and difficult to suppress. The seizures are tonic-clonic with axial hypotonia and peripheral hypertonicity. Other neurologic symptoms such as myoclonus, pyramidal syndrome, opisthotonus, spastic tetraplegia, hemiplegia, dilatation of ventricles, Dandy-Walker malformation, and hydrocephalus have been described (12,16,19,22). The MRI changes in two children include progressive widening of sulci, ventricles, and cisterna magna and a cessation of myelination at 31 months and 16 weeks of age, respectively (1). In some studies, an abnormal shape of the frontal horns of the dilated ventricles was found; this was caused by a severe volume loss of the basal ganglia, especially of the caudate nucleus and of the corpus callosum (24). Head circumference is generally normal at birth; microcephaly developed in a number of cases (7).

Laboratory findings. Plasma uric acid levels are very low; the excretion in the urine of sulfite, thiosulfate, *S*-sulfocysteine, taurine, xanthine, and hypoxanthine is elevated. There is no urothione, a molybdenum cofactor metabolite, demonstrable in the urine (2). The diagnosis can be suspected using a simple sulfite dip strip test on a fresh urine sample, although false-positive and false-negative results do occur. Prenatal diagnosis is possible by assay of sulfite oxidase activity in a chorionic villus sample (10,13). Prenatal diagnosis has been achieved molecularly (26).

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Chapter 6
Syndromes Affecting Bone: The Osteogenesis Imperfectas

The osteogenesis imperfectas

Osteogenesis imperfecta is a heterogeneous group of heritable disorders of type I collagen metabolism characterized by bone fragility. Associated features in some affected individuals include blue sclerae, opalescent teeth with characteristic radiologic features, hearing loss, deformity of long bones and spine, and joint hyperextensibility. The first reported case was probably an Egyptian, whose remains, dating from 1000 BCE, are in the British Museum (81). Credit is usually given to Ekman (65) for performing the first comprehensive study of the syndrome in 1978 and discussing its inheritance. In the early nineteenth century, Lobstein (111) and Vrolik (207) described the disease in the adult and the newborn, respectively. Spurway (177) and Eddowes (63) described blue sclerae, and in the early 1900s, Van der Hoeve and de Kleijn (200) mentioned deafness as part of the syndrome. Preiswerk (153) may have been the first to describe the dental abnormalities. The basis for the current clinical classification is the study by Sillence et al (169). A monograph on the disorder has been written by Smith et al (175).

The severity of the disorder varies widely between and even within families; some individuals have minimum involvement of the skeleton and may never have a fracture, whereas others have very severe involvement and many fractures. Clinical and genetic studies delineate four major syndrome groups (Table 6–1) (169), although all of these syndromes are likely heterogeneous at the clinical, radiographic, and molecular levels (4,29,33,50,90,105,168,170,171).

Nomenclature classifying patients into congenital and tarda forms is not useful, as individuals with any osteogenesis imperfecta syndrome can be born with fractures; in addition, this feature cannot be consistently correlated with inheritance pattern, prognosis, or recurrence risk (168,169,194).

Classification into broad-boned and thin-boned types is also unsatisfactory, as change from one shape to another can occur with age. There appears to be little benefit in classification based on severity of long bone deformity (10), as severe deformity can occur in many osteogenesis imperfecta syndromes; in addition, this method of classification does not take into account the pattern of inheritance or other clinical findings (169,176,194).

Until recently, the phenotypes of patients with the syndrome, as well as the inheritance patterns, have not always been completely delineated. Thus, it is difficult to interpret much of the large body of literature on the disorder in view of the current classification. The estimated prevalence of all types combined is about 0.5/10,000 births (183).

Molecular pathology. The different forms of osteogenesis imperfecta are caused by mutations in the two genes that encode the chains of type I collagen—i.e., *COL1A1*, located on chromosome 17, and *COL1A2*, located on chromosome 7. They encode for the pro-α1 (I) and pro-α2 (I) chains of type I procollagen. Two pro-α1 (I) chains and one pro-α2 (I) chain together form one heterotrimer. This procollagen is secreted by fibroblasts, after which the aminopropeptides on each of the three pro-α chains are cleaved off by a protease, and the carboxy-propeptides are cleaved off by another protease. Thereafter, the collagen molecule self-assembles spontaneously to form fibril structures. The formation of fibrils depends heavily on the uniformity of the collagen molecules, and abnormal molecules have a deleterious effect on fibril structures. A more detailed review of the collagen biosynthesis and gene structure can be found elsewhere (3,33,50,154,155).

Each of the collagen genes contain more than 50 exons that contain the coding sequence for proteins of about 1400 amino acids. The primary sequence consists of a repeating tripeptide unit which can be written (Gly-X-Y). The amino acid glycine is in every third position, allowing for the tight helical structure because it is small and contains no side chains. Hydroxyproline is found only in the Y position, which it occupies in about a third of the triplets, often preceded by proline. The first exons encode the signal sequence, followed by the protease cleavage site. The final exons encode an additional protease cleavage site and the globular carboxyl-terminal domain. The stability of the triple helix is provided by interchain hydrogen bonds.

Patients with osteogenesis imperfecta type I show approximately 50% reduction in synthesis of type I procollagen. The causative mutations effect decreased synthesis; secretion and post-translational modification as well as rate of molecular assembly appear normal, in contrast with other types of osteogenesis imperfecta. Linkage studies show segregation with both the *COL1A1* gene and *COL1A2* gene (69,125,189,191,192,197,208,211). A variety of mutations has been described: promotor mutations, enhancer mutations, or those causing premature termination of transcription of one allele (33,209,214,215). The last may be the most common mechanism (215). Promotor mutations do not play a significant role (216).

In osteogenesis imperfecta type II, point mutations resulting in the substitution of glycine residues in the triple helix domain of the α1 (I) or α2 (I) chain are the most frequently found mutations (8,31,32,43,45,50,130,149,152–154,195,213). Such mutations disrupt the triple helix formation by a dominant-negative mechanism. A delayed triple helical assembly results in overmodification of type I collagen, which can be recognized electrophoretically. The phenotypic consequences are most severe if the mutation occurs near the carboxyl-terminal end and more mild toward the amino-terminal end (33,188). Exon skipping mutations are the more common mutations (50). There are no major mutational hot spots in the *COL1A1* or *COL1A2* genes. Most mutations are de novo, but there are reports of patients with type II in which the parents are mosaics (30,52,103,114). The parent may be normal or mildly affected. Until now, no molecular proof exists for an autosomal recessive form of type II (33,44,50). The phenotype in type II may be modified by the background of other components of connective tissue, such as decorin (62).

In osteogenesis type III, molecular studies have shown different mutations in *COL1A1* and *COL1A2*, resulting in substitution of glycine in the triple helix for another amino acid (128,150,209). Recurrence from unaffected parents could be explained by parental gonadal mosaicism (44), but homozygosity by descent for a *COL1A2* mutation has been described, thus proving autosomal recessive inheritance (59). In a group of South African families with type III, no linkage with the loci for *COL1A1* or *COL1A2* was found, indicating that probably other loci were involved that influence type I collagen processing (209).

Most patients with osteogenesis imperfecta type IV are linked with or have mutations in the pro-α2 (I) collagen chain (210,211), but linkage and mutations with *COL1A1* have also been found (33). The pathogenic pathway causes reduction in the amount of type I collagen by 50%, as in type I.

Table 6–1. Major osteogenesis imperfecta syndromes

Type	Salient features	Inheritance	Most common molecular background
I	Mild to moderately severe bone fragility Hearing loss (50%)	AD (common)	Nonfunctional COL1A1 gene (null allele)
IA	Normal teeth		
IB	Opalescent teeth		
II	Very severe bone fragility Blue sclerae	AD (common)	Point mutations resulting in substitution of Gly residues in triple helix domain of α1(I)/α2(I)
	Stillborn or death shortly after birth	AR (doubtful)	
III	Moderately severe to severe bone fragility	AD (common)	Point mutations in *COL1A1* and *COL1A2* genes
	Blue sclerae (in infancy) Generally not lethal in infancy, but death in first decades is not uncommon	AR (infrequent)	Deletions in *COL1A1* gene causing frame-shift
IV	Mild to moderately severe bone fragility Normal sclerae, but may be pale blue in early infancy Hearing loss	AD	Point mutations in *COL1A2* gene
IVA	Normal teeth		
IVB	Opalescent teeth		

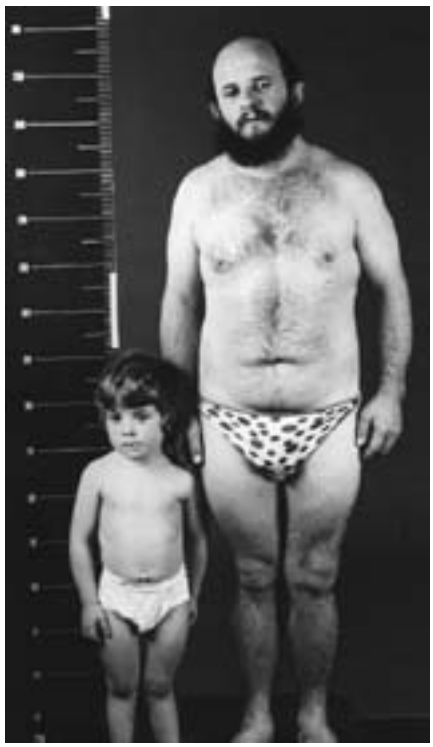


Fig. 6–1. *Osteogenesis imperfecta, type I.* Both father and son had intensively blue sclerae, numerous fractures, and mild shortening of stature. (From DO Sillence, Symposium of Heritable Disorders of Connective Tissue, C.V. Mosby, St. Louis, 1982.)

Type I

General features. This disorder is characterized by autosomal dominant inheritance (169) (Fig. 6–1). Carothers et al (36) analyzed a heterogeneous group of patients with osteogenesis imperfecta type I and type IV, presumed to have resulted from new mutations. These investigators demonstrated that the mean paternal age at birth was significantly higher than that of controls and that paternal age effect in new mutation osteogenesis imperfecta type IA, when analyzed alone, was also significantly increased. The effect of paternal age on the mutation rate, however, was smaller than in other dominant disorders, such as achondroplasia. Sillence et al (169), Byers et al (30), and Orioli et al (131) found hardly any increase in paternal age.

Facies. Apart from the blue-gray sclera, we do not believe that there is a facies. The maxilla may be hypoplastic with a relative mandibular prognathism (49).

Ophthalmologic abnormalities. A hallmark of this syndrome is blue sclerae. It was noted early (10) that the severity of osteogenesis imperfecta was different depending on the presence or absence of blue sclerae. Scleral color appears to be consistent within families, although the degree of blueness varies from one family to another (173). Scleral blueness is believed to arise from disordered molecular organization (174). Sclerae are of normal thickness, but there is evidence for increased noncollagenous matrix (64). Low ocular rigidity in a heterogeneous group of patients with osteogenesis imperfecta has been found (95); some had blue sclerae, and thus may have had osteogenesis imperfecta type I. Lanting et al (104) found reduced optical scattering properties in the sclerae of two patients with this syndrome, findings they attributed, in part, to reduction in collagen fiber thickness and decreased variability of fiber diameter.

The cornea may appear thinner than usual by slit-lamp examination (175). Embryotoxon has also been noted (37). It is unknown whether this abnormality is the result of chance association of hypercholesterolemia or whether it is one of the pleiotropic effects of the syndrome, at least in some families. Rarely, retinal detachment occurs (118).

Otolaryngologic abnormalities. Hearing loss, rarely detected before 10 years of age, usually begins with a conductive deficit in the late second or early third decade (159). With age, mixed and sensorineural hearing losses are observed (53,159,164), the sensorineural component being the major one (74). Riedner et al (159) and Garretsen and Cremers (74) noted that by the fifth decade, half of all patients had hearing loss, whereas by the seventh decade, all individuals had hearing loss, although the number of older individuals tested was small. Cox and Simmons (53) reported similar findings. Shapiro et al (166) reported audiologic abnormalities in a heterogeneous group of patients: half of the patients younger than 30 years of age and 95% of the patients over 30 had hearing loss. Half of all patients examined had sensorineural loss. Conductive loss in this syndrome has been attributed to ossicular immobility at the stapes footplate (144,159). Fracture of the stapedial crura and atrophy of the stapes may also contribute to loss of hearing acuity (159). Results from ear surgery are available (73).

Neurologic manifestations. Results of computed tomography (CT) scans of the head have been normal in the few patients tested (198), and ventricles are normal in size. In the three-member family with osteogenesis imperfecta type I and dental abnormalities reported by Pozo et al (152), advanced basilar impression (platybasia) resulted in ventricular dilatation, multiple neurological disturbances of the foramen magnum compression syndrome, and death from acute brain stem compression; these findings, however, are likely rare in other patients with this syndrome. These investigators noted that all patients reported with osteogenesis imperfecta and basilar impression had mild skeletal disease. Rarely, radicular compression (40), trigeminal neuralgia (157), and communicating hydrocephaly (40) occur. Half the 56 patients with osteogenesis imperfecta studied by Reite and Solomons (158) had abnormal electroencephalograms; however, their patients were a heterogeneous group and were not classified.

Cardiovascular involvement. The frequency of symptomatic cardiovascular anomalies is low. Hortop et al (91) reported nonprogressive aortic root dilatation in about 12% of affected patients. In one study of dominant osteogenesis imperfecta, 9% of males and females had asymptomatic mitral valve prolapse; 24% of males but only 4% of females had asymptomatic aortic root dilatation (156). Aortic regurgitation has been observed in patients after the third decade, as has mitral regurgitation (1,156,178). Aortic aneurysm and dissection do not occur, although left atrial rupture has been reported in one patient (160). Vetter et al (203) reported 1 of 18 patient with valvular aortic stenosis. Mitral valve leaflets were thin in half the patients reported by White et al (212). They may cause mitral valve prolapse and regurgitation (91). Microscopic findings in the valves include myxoid degeneration and atrophy and, in the aorta, cystic medial necrosis (1).

Joint abnormalities. Joint hypermobility and joint dislocation are found (139). Separate entities with either a phenotype resembling *Ehlers-Danlos syndrome* (103,205) or with rigid joints or contractures (Bruck syndrome) (19a,25,25a,104a,123,206) exist.

Skeletal manifestations. Macrocephaly has been reported (169, 198). Head size is usually large for height: the median of the distribution of head sizes is above the 50th centile (169). Wormian bones may be present (169). Platybasia and occipitalization of the upper cervical vertebrae may produce a "tam o'shanter" appearance (93,139,152).

Multiple fractures usually occur, although about 10% of patients may not have fractures (169). There is considerable variability within and between families in age of onset and frequency of fractures. During infancy and childhood, fracture frequency remains constant, but reduction in fracture frequency at puberty has been noted, followed by an increase in fracture frequency in women after menopause (140) or after the sixth decade in men. Long bone deformity consists of bowing and angulation (169); however, it is not as severe in type I osteogenesis imperfecta as it can be in other forms. About 20% of adults have kyphosis or scoliosis, which may be progressive (85,169). Trunk shortening has also been described (16). Osteopenia may be minimal and undetectable on skeletal radiographs. In fact, radiography may fail to show any anomaly if pictures are taken during a period without a fracture. The ability to walk depends upon the type of osteogenesis imperfecta (68).

Paterson et al (138) found a significantly higher fracture rate in 5- to 20-year-old patients with type I osteogenesis imperfecta and opalescent teeth (type IB) than in those with type I who had normal teeth (type IA). They also found that individuals with type IB were more likely to have had a fracture at birth, to have a higher fracture frequency, and to have a height below the second centile. Patients with normal teeth were more likely than patients with opalescent teeth to have prolonged fracture-free periods during childhood. These two groups, however, were similar in frequency of joint hyperextensibility, bruising, hearing impairment, and joint dislocations.

Birth weights and birth lengths are generally normal. Short stature is of postnatal onset and usually mild; by adulthood, half the affected patients are less than the third centile for height (169). Given the (usual) absence of significant skeletal deformity, the shortness of stature appears to be constitutional. However, individuals with the disorder whose height exceeds 6 feet have been noted.

Gillerot et al (77) reported a family with osteogenesis imperfecta type I in which a newborn infant had features of type II. Heyes et al (88) reported a kindred with osteogenesis imperfecta type I and opalescent teeth; a stillborn had sustained multiple fractures in utero and had a membranous cranium, resembling that of osteogenesis imperfecta type II; no radiographs were depicted.

Oral manifestations. Dental abnormalities have been described in many individuals with osteogenesis imperfecta; unfortunately, in many of these reports, the complete phenotype and inheritance pattern have not been described, and interpretation in view of current classification is not possible. Heterogeneity based on the presence or absence of dental abnormalities has been noted (105,138,163). Paterson et al (138) recognized that two groups of families with osteogenesis imperfecta type I can be distinguished: a group with normal teeth (type IA) and a group with specific dental abnormalities (type IB). In patients with dental abnormalities, deciduous and permanent teeth are opalescent, and amber or blue–gray on eruption (107) (Fig. 6–2).

On radiographic examination, there is increased constriction at the coronal–radicular junctions, and pulps become obliterated with secondary dentin. However, pulps may be wider than normal during early development (107). Roots are thinner and shorter than normal (163). There is little variation in expression within the deciduous dentition, and these teeth may wear rapidly; on the other hand, there may be considerable variability in color within an individual's permanent dentition. Dental radiographs may be necessary to establish the diagnosis where tooth discoloration is mild. When dental abnormalities are present, they may be helpful in making the diagnosis of osteogenesis imperfecta when the presence of other abnormalities is equivocal.

Lukinmaa et al (112), Paterson et al (139), and Lund et al (114) noted that opalescent teeth were rarer in families with type I (8%) osteogenesis imperfecta than in those with type IV (37%). Malocclusion has been described and may be more common in individuals with opalescent teeth than in those with normal teeth (163).

Lukinmaa et al (113) described "thistle-tube" or flame-shaped pulps in several patients with osteogenesis imperfecta, one of whom may have had type I, although scleral color was not stated. These dental findings are similar to those found in dentin dysplasia type II (76). Levin et al (110) found similar abnormalities in the permanent dentitions of five members of a family with osteogenesis imperfecta type I.

There are few systematic studies of the histopathology of the teeth in what is unequivocally osteogenesis imperfecta type I. In general, however, the dentin–enamel junction has been reported by some investigators to be flatter than normal and to lack normal scalloping (161,217). However, on scanning electron microscopy (106) and light microscopy (112), others described a normal junction. On light microscopic examination, laminated dentin, tubules of abnormal size and shape, and structures resembling entrapped blood vessels have been described (147,161,216). Enamel surface and prism organization were found to be normal in osteogenesis imperfecta type IB (106). However, dentinal tubules were short, narrow, and tortuous compared with those of normal teeth from other osteogenesis imperfecta families and controls. Gage et al (72) studied teeth from a group of patients with a variety of osteogenesis imperfecta syndromes. They concluded that the majority of teeth from these patients were biochemically abnormal even if dental abnormalities were not present; however, the criteria for determining whether clinical abnormalities of the dentition existed in the patients studied were not presented.

Other abnormalities. Easy bruisability has been found in about 75% of affected patients (139). Angiomatosis (60), hernias, and excessive sweating have also been reported (139). Nephrolithiasis has been described (203).

Type II

General features. This clinically and biochemically heterogeneous group of osteogenesis imperfecta syndromes is characterized by extreme bone fragility consistently leading to intrauterine or early infant death (31,50,121,169,194). Sillence et al (171) subclassified this form into three subtypes (groups A, B, and C) distinguished from one another on the basis of radiographic features. Subtype IIA is the most common subtype, IIC the most infrequent. The distinction between the three subtypes is not always clear, as the radiographic findings represent a continuum. In general, the better the bone morphology and mineralization at birth, the longer the survival of the newborns (194).

At birth, newborns in group A are small for gestational age and usually premature. Twenty percent are stillborn and the remainder die within hours or days of birth; 90% are no longer living by 4 weeks of age. Breech delivery occurs in 15%. General connective tissue fragility is present and the head or a limb may be torn off during delivery (169). Infants in group B have a mean gestational age of 37.6 weeks; mean survival is about 14 hours (194). Length of gestation and survival of individuals in group C have not been described in detail because few

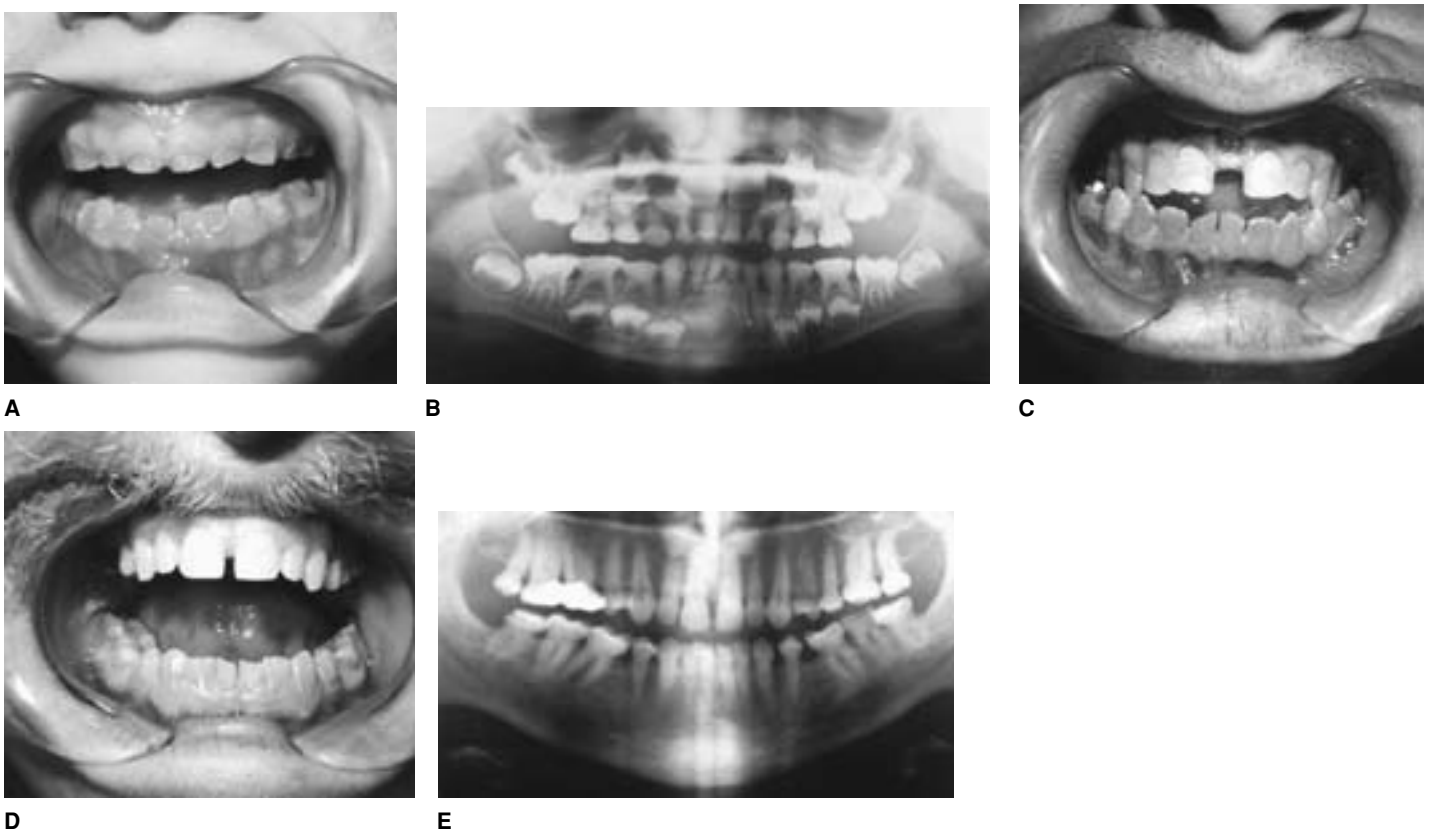


Fig. 6–2. *Osteogenesis imperfecta, type I.* (A) Opalescent deciduous teeth in a 5.5-year-old with type IB. Marked incisal wear is evident. (B) Radiographs of deciduous and developing permanent dentition in a 5.5-year-old with type IB. Pulp chambers and root canals of the deciduous teeth are almost completely obliterated, and greater constriction than normal is present at the crown-root junctions of these teeth. Pulp chambers and root canals are wider than normal in the permanent first molars. (C) Permanent dentition in type IB. All teeth are clinically opalescent. (D) Permanent dentition in type IB. Only mandibular teeth are opalescent. (E) Radiograph of permanent dentition in type IB. The root canals of some teeth, however, are patent. (B from LS Levin, Clin Orthop Rel Res 159:64, 1981.)

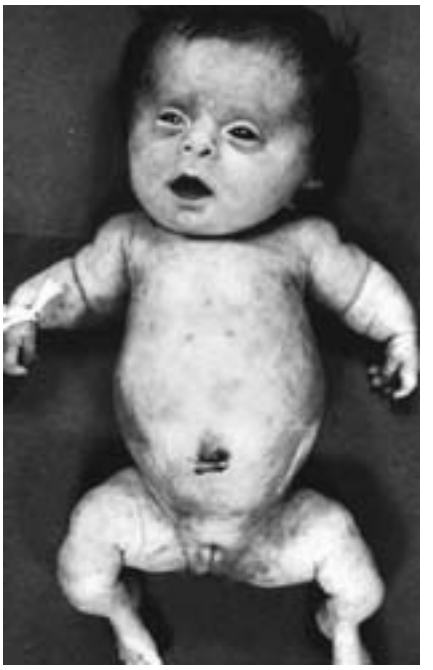
examples have been reported; however, two cases reported by Thompson et al (194) were stillborn at 28 and 30 weeks, respectively. Since most, if not all, cases of osteogenesis imperfecta type II have been ascertained through early death, the true average length of survival is unknown (30).

Although instances of familial recurrence and parental consanguinity have been observed in group A (171,194), the majority are sporadic examples. It was originally thought that most cases have autosomal recessive inheritance (135,148,171). However, from a study of 30 cases, Young et al (218) concluded that most cases of osteogenesis imperfecta type IIA were the result of new dominant mutations; no sib pairs were ascertained, 25 were born to nonconsanguineous couples, and increased paternal age effect was observed. This was later also confirmed by molecular studies (33,44,50). The sibling recurrence in type IIA can be explained by germline and somatic mosaicism in parents, which has been confirmed by molecular studies (31,52,103,115). Thompson et al (194) calculated an empirical recurrence risk of 7.7% for type IIB; no increase in parental age over the general population was found. It seems probable that a proportion of cases arises from de novo autosomal dominant mutations, and another part arises from autosomal recessive inheritance. Type IIC may follow autosomal recessive inheritance, although too few cases are available for analysis (171,194). The empiric overall recurrence risk of type II, irrespective of the subtype, is approximately 6% (31).

Facies. The face and cranium are molded and soft and the cranium often appears disproportionately large for the face (Fig. 6–3). Commonly, mild micrognathia and a small narrow nose are noted (50,171).

Ophthalmologic findings. Deep blue–gray sclerae are present in virtually all affected infants. On examination of the cornea of an infant who

Fig. 6–3. *Osteogenesis imperfecta, type II.* Perinatal death with frontal and temporal bossing, limb shortening with external rotation, and abduction of the thighs and angulation of the legs (From DO Sillence, Am J Med Genet 17:407, 1984.)



died at 17 days of age with presumed osteogenesis imperfecta type II, collagen fiber diameter was reduced, normal cross-striations were not seen, and collagen fibers were more densely packed than normal (21).

Cardiovascular system. Information about the cardiovascular system in osteogenesis imperfecta type II has been derived from autopsy studies. Abnormalities include thickening of the valve leaflets, myxoid degeneration of valves, calcification of pulmonary, cerebral, or peripheral arteries, intimal proliferation and medial calcification of the pulmonary artery, thickening of the media and adventitia in small and medium-sized pulmonary arteries, and atherosclerotic changes in the aorta. Microscopic calcification throughout the aorta and endocardium has also been noted (171).

Skeletal manifestations. In type IIA, there is marked reduction in ossification of the facial bones and cranial vault (Fig. 6–4), and numerous wormian bones are present. The chest is small. Ribs are slightly short, thick, and continuously beaded. The humeri and femora are crumpled (accordion-shaped), short, and broad. Thighs are held in abduction at right angle to the body. Tibias are broad, accordion-shaped, and angulated. Vertebrae are flattened, the ilia are broad and round, and the ischia and pubic bones are broad and without form (50,171,194).

Few cases of osteogenesis imperfecta types IIB and IIC have been studied. In type IIB, the skull exhibits spotty mineralization and the ribs are thin and wavy without beading, but ribs exhibit only occasional beading and are not uniformly thick (171). Femurs are short, broad, and crumpled, and tibias are thickened and angulated. In type IIB there are more well-modeled humeri with wide metaphyses, and there is more normal vertebral body height than type IIA. In type IIC, the face is not remarkably abnormal. The arms are longer than in type IIA, but the legs are similarly bent inward. Marked underossification of the skull and slender but not so uniformly beaded ribs as in type IIA have been noted. Long bones are slender and shafts are inadequately modeled. Angulation deformities of the shafts of all long bones and multiple fractures are seen. Heights of vertebral bodies are near normal (50,171,194).

Oral abnormalities. Dental abnormalities have been reported. Dean and Hiramato (56) noted argyrophilic fiber-like structures in the dentin, absence of predentin, irregular pulpal–dentin junction, paucity of argyrophilic granules in the odontoblast cytoplasm, abundance of argyrophilic fibers in the coronal pulp, and dilated capillaries in the coronal pulp. No abnormalities were found in the enamel organ or in the morphology of developing teeth. Calonius et al (34) reported the dental findings in an infant who died 8 days after birth: the dentin was thinner than normal, interglobular dentin extended to the cemento-enamel junction, dentin tubules in the circumpulpal dentin were few and wide, and degenerated osteoblasts were found entrapped in the dentin. Mantle dentin was normal and irregular at the enamel–dentin interface; the dental papilla and pulp were normal. Similar findings have been reported elsewhere (9,12,13,94). Haebara et al (83), however, reported normal teeth in a newborn with presumed osteogenesis imperfecta type II who died shortly after birth, suggesting heterogeneity, and Levin et al (108) also reported normal dentition in an infant with a lethal osteogenesis imperfecta syndrome of unknown type who survived for 10 months. Although other studies have reported dental abnormalities in patients with lethal osteogenesis imperfecta, phenotypes have not been sufficiently characterized; thus, it cannot be determined whether they had osteogenesis imperfecta type II or another lethal osteogenesis imperfecta syndrome (79,86,201).

Type III

General features. This osteogenesis imperfecta syndrome, characterized as progressively deforming with normal sclerae, is usually not lethal, at least in the newborn period (169).

Beighton and Versfeld (15) and Viljoen and Beighton (204) have reported a high prevalence of an autosomal recessive form among the black population in South Africa.

The diagnosis in sporadic cases with an osteogenesis imperfecta type III phenotype is confounded by clinical and radiographic heterogeneity, and by clinical similarity to other patients with severe osteogenesis imperfecta (171,194). The extent of this heterogeneity is unknown; Hanscom and Bloom (84) recognized four subtypes. In a recent study (172), approximately one-third of patients survived long term, reflecting not only the severity of the disorder but also heterogeneity within the group. Of 17 patients with this disorder, 4 died in the first year and 5 in the second and third decades. Death usually results from complications of severe bone fragility, skeletal deformity including kyphoscoliosis, pulmonary hypertension, and cardiopulmonary failure.

Thompson et al (194) calculated an empirical recurrence risk of 7% for families of children who have severe osteogenesis imperfecta but who survive the perinatal period. They concluded that about 75% represented new autosomal dominant mutations, whereas 25% were autosomal recessive. In a black population originating from South Africa, the chance for an autosomal recessive form was much higher (209). Both autosomal

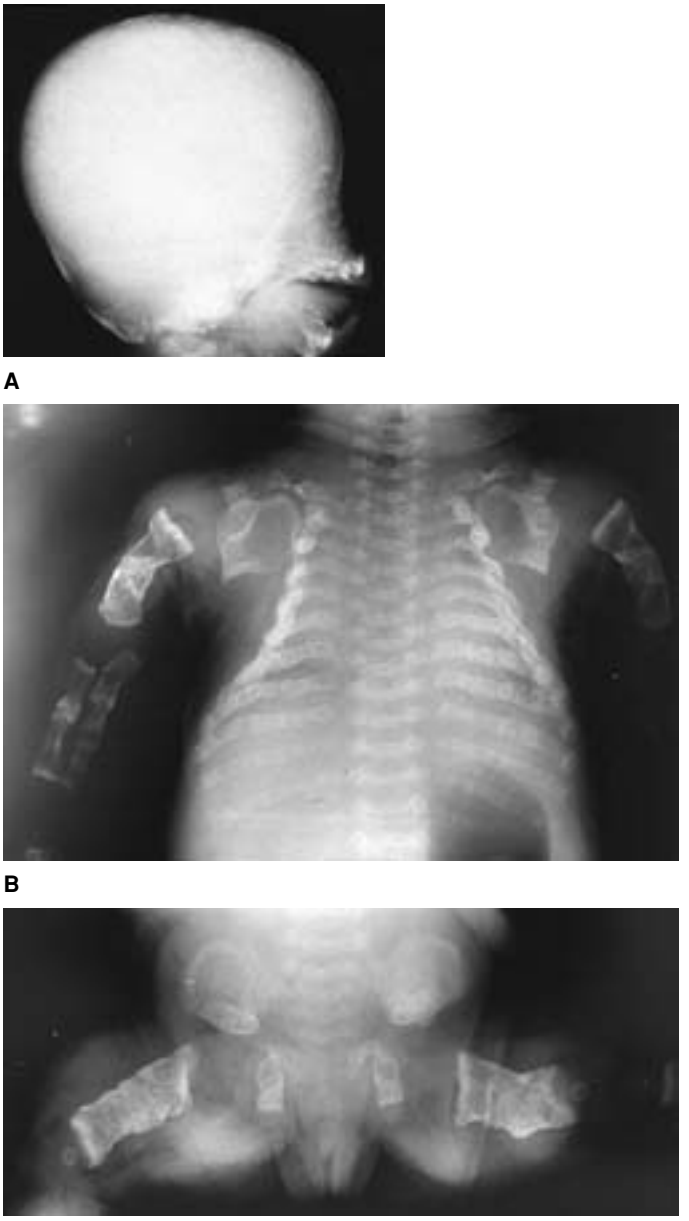


Fig. 6–4. *Osteogenesis imperfecta, type II.* (A) Lateral radiograph of skull and face showing extreme osteopenia and multiple bone islands (wormian bones) in frontal bone and vertex. (B) Chest radiograph showing continuously beaded ribs and short, broad, dysplastic humeri. (C) Femora showing crumpled and dysplastic (concertina-like) appearance. Pelvis showing osteopenia and dysplastic changes. (From DO Sillence, Am J Med Genet 17:407, 1984.)

recessive inheritance (59) and gonadal mosaicism for type III (44) have been demonstrated molecularly. Clinical, genetic, and radiologic findings have been reviewed by Sillence et al (169–172), Thompson et al (194), and Hanscom and Bloom (84).

Ophthalmologic abnormalities. Although blue sclerae are observed in infancy, the blueness fades by 1 year of age, so that older patients have pale blue or white sclerae (169).

Otolaryngologic abnormalities. Although hearing loss has been said to occur infrequently (169), audiologic findings have not been well documented in patients with unequivocal osteogenesis imperfecta type III.

Neurologic abnormalities. On head CT scans, diffuse ventricular dilatation and diffuse cortical atrophy have been described (198). There is one report of a child with osteogenesis imperfecta type III and an arachnoid cyst (51). No associated increase in intracranial pressure, cranial nerve dysfunction, or herniation syndrome was noted.

Cardiovascular system. Significant cardiac or vascular lesions have not been described, but asymptomatic mitral valve prolapse and type II atrial septal defects have been found (203).

Joint abnormalities. Ligamentous laxity is marked in children but is less severe in adults (169).

Skeletal findings. Infants with this syndrome are usually born at or near term with normal birth weight; birth length is usually normal, but some have marked deformity (169) (Fig. 6–5). With age, all fall well below the third centile in height for age and sex (171,194).

Head size is disproportionately large compared to the rest of the body. The ossification defect in the skull is not as severe as in osteogenesis imperfecta type II. Frontal and temporal bossing contribute to the triangular facies. The anterior fontanel, sutures, and posterior fontanel are wide, and wormian bones or bone islands may be palpable along the posterior sutures (169).

Fractures are present at birth in half or more of these infants; all have numerous fractures by 1 or 2 years of age (172). Although multiple rib fractures occur, continuous beading as seen in osteogenesis imperfecta type II is not found. Long bones are also subject to multiple fractures and bowing and, in some cases, there is metaphyseal flaring. The lower extremities are often already bowed at birth. The limbs are not as short or as deformed as in osteogenesis imperfecta type II. Some femora are normal, whereas others are short and broad (169). Femurs and tibias may be markedly angulated. In some patients, neonatal radiographs demonstrate broad metaphyses with centrally overmodeled diaphyses and angulation deformities; during the first year of life, diaphyses broaden (172). Sillence et al (169) demonstrated in a longitudinal study that many patients had marked thickening of the femoral shafts during the first few years of life; this morphology makes it difficult to distinguish these patients from those with osteogenesis imperfecta type IIB. With time, however, progressive narrowing occurs, so that in older patients, femurs are thin. Protrusio acetabulum is often severe.

In the first few years, metaphyses develop increasing density and irregularity, which progress so that by the end of the first decade, metaphyses and epiphyseal zones are replaced by whorls of radiodensity, giving a cystic appearance. Progressive and marked vertebral flattening with "cod-fish" changes are also observed (172). Trunk shortening is common (16). Severe kyphoscoliosis also develops (169).

Most patients become markedly handicapped (169,185). Bowing and angulation deformities are likely to be progressive.

Oral abnormalities. Dental abnormalities similar to those found in the other osteogenesis imperfecta syndromes may be present, but complete radiographic and morphologic evaluation of the teeth has been reported for few patients. The patient described by Nicholls et al (128) and Pope et al (151) had normal teeth. Within families, some patients have normal teeth, whereas others have teeth that are opalescent. Lund et al (114), using in vitro protein-chemical features and molecular mutations for classification, found that 81% of type III patients had dentinogenesis imperfecta.

Type IV

General features. Paterson et al (139,141) have provided the most complete clinical description of this disorder, although Sillence et al (169) first proposed this condition as a separate syndrome. Segregation in more than two generations and male-to-male transmission have been reported (139,169). Evidence thus favors autosomal dominant inheritance. The condition may be less common than type I. Beighton et al (16) have proposed that this disorder is heterogeneous.

Paterson et al (139) determined that, in addition to differences in scleral color compared to osteogenesis imperfecta type I, patients with osteogenesis imperfecta type IV more commonly have fractures at birth and opalescent teeth. Bruising and nosebleeds were found to be less common in osteogenesis imperfecta type IV than in type I.

Facies. Facial appearance is similar to that of osteogenesis imperfecta type I (Fig. 6–6).

Fig. 6–5. *Osteogenesis imperfecta, type III*. Seven-month-old with many healing fractures and limb deformity but relatively normal sclerae. (From DO Sillence, Symposium on Heritable Disorders of Connective Tissue, C.V. Mosby, St. Louis, 1982.)

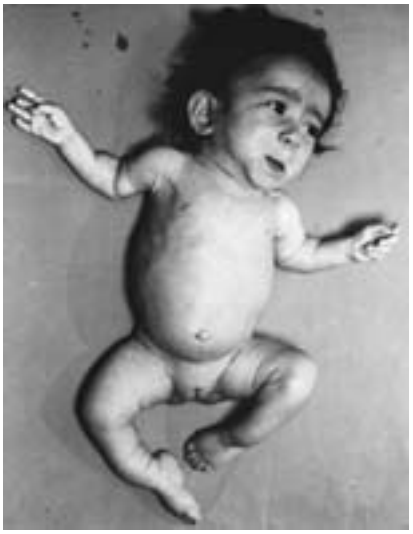


Fig. 6–6. *Osteogenesis imperfecta, type IV*. Boy age 18 months with macrocephaly and mild frontal and temporal bossing.

Ophthalmologic abnormalities. Sclerae are usually normal, although they may be pale blue in early childhood. Paterson et al (139) noted that no adolescents or adults with the condition had abnormal sclerae.

Otolaryngologic findings. In type IV patients over 30 years old, the frequency of hearing impairment (30%) is significantly less than that in osteogenesis imperfecta type I.

Neurologic manifestations. Basilar impression resulted in neurologic signs and symptoms in the family with dominant osteogenesis imperfecta, opalescent teeth, and wormian bones reported by Hurwitz and McSwiney (93); scleral color, however, was not mentioned.

Cardiovascular system. A few reports describe a tendency to aortic root dilatation (156).

Joint abnormalities. A frequency of joint hypermobility, joint dislocations, and hernias similar to that found in osteogenesis imperfecta type I is noted in type IV.

Skeletal abnormalities. About 25% of patients have fractures at birth (139). There is wide variation in the total number of fractures. However, fracture frequency is maximal during childhood but decreases markedly after puberty. Some individuals with this syndrome may never have fractures (169). Sillence et al (169) proposed that some patients have a progressively deforming phenotype; thus, it might be difficult in some cases to distinguish this syndrome from osteogenesis imperfecta type III.

Although radiographs taken at the time of first fracture may show no osteoporosis, with repeated fractures, osteoporosis and cystic changes are found (139). Stature is generally significantly decreased: 40% of newborns have a length below the tenth centile, and the height of 95% of affected adults is below the third centile (139). The frequency and average number of wormian bones in the skull in this syndrome are unknown.

Oral findings. Dental findings are similar to those found in osteogenesis imperfecta type I. Dentinogenesis imperfecta was reported to be either consistently present or consistently absent in a family (105,106,139). Dental abnormalities are significantly more common in type IV (37%) than in type I (8%) (114). It was also noted that these abnormalities, when present, were the one consistent marker within a family, although other clinical features might vary (139). Thus, specific dental abnormalities, when present in a family, may be very helpful for diagnosis when other clinical abnormalities are mild.

Other features. A tendency toward bruising, hernias, and excessive sweating has been noted (139).

Differential diagnosis. There are numerous entities with an increased fracture frequency (Table 6–2), as well as a relatively large number of syndromes that can be classified as osteogenesis imperfecta but are distinguishable from the major groups by their associated features (Table 6–3).

Levin et al (109) described three kindreds in which multiple radiolucent-radiopaque lesions in the jaws, as well as fractures and other skeletal abnormalities, were found; teeth were normal and inheritance was autosomal dominant.

Cole and Carpenter (47) recognized a previously unreported form of osteogenesis imperfecta in which metaphyseal fractures were most prominent during the first 4 months of life, followed by diaphyseal fractures and bowing deformities as weight bearing increased. This is now known as *Cole-Carpenter syndrome*. Other distinctive features included craniosynostosis, proptosis, hydrocephaly, and distinctive facial appearance. Also noted were blue sclerae, micrognathia, and high-pitched voice. One patient had dentinogenesis imperfecta (Figs. 6–7 and 6–8). Both patients were males born to unrelated parents and both represented essentially sporadic occurrences in their respective families. A similarly affected child was reported by Amor et al (3a). Other as-yet unreported cases are known to MM Cohen Jr and RJ Gorlin.

Table 6–2. Other entities with increased fracture frequency

Antley-Bixler syndrome
Calvarial doughnut lesions
Camurati-Engelmann syndrome
Child abuse
Cutis laxa (different types)
Dermatosparaxis
Dysosteosclerosis
Ehlers-Danlos syndrome + osteogenesis imperfecta
Epidermal nevus syndrome
Gaucher disease
Gerodermia osteodysplastica
Hajdu-Cheney syndrome
Hyperparathyroidism (neonatal type)
Hyperphosphatasia
(Pseudo)*hypophosphatasia*
Jaffe-Campanacci syndrome
Lipodystrophy type Nasu-Hakola
Maffucci syndrome
Metaphyseal dysplasia Jansen type
Megepiphyseal dysplasia (*OSMED*)
Nemaline myopathy
Ollier enchondromatosis
Osteofibrous dysplasia
Osteopetrosis
Osteoporosis-pseudoglioma-mental retardation
Pena-Shokeir syndrome
Pyknodysostosis
Pyle disease
Rubinstein-Taybi syndrome
Schwartz syndrome
Yunis-Varón syndrome

Several sets of sibs have been described (3,87,146) with severe osteoporosis, fractures, dislocated hips, macrocephaly, wormian bones, frontal bossing, persistent anterior fontanel, brachytelephalangy, hyperextensible joints, congenital retinitis pigmentosa with blindness, and severe mental retardation (Figs. 6–9 and 6–10). Bone age was retarded, and there was severe dental malocclusion. Inheritance is probably autosomal recessive (3). A somewhat similar case was described by Blechmann and Crommer (20).

Beighton (14) described a kindred with dentinogenesis imperfecta, blue sclerae, multiple wormian bones, generalized moderate osteoporosis, mild femoral bowing, and mild vertebral flattening. One person had multiple fractures with mild trauma. Stature and intelligence

Fig. 6–7. *Cole-Carpenter syndrome*. (A,B) Compare facies. Note bulging forehead, striking proptosis, midfacial deficiency, and micrognathia. (From DEC Cole and TO Carpenter, J Pediatr 110:76, 1987.)

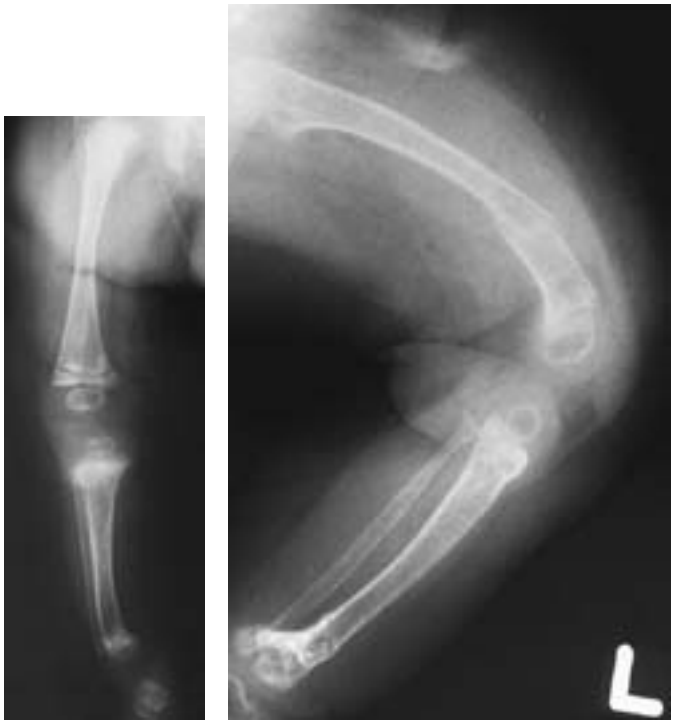
A **B**

Table 6–3. Other osteogenesis imperfecta syndromes in which multiple fractures are common

Salient features	Inheritance pattern	Reference
Normal sclerae Multiple radiolucent-radiopaque jaw lesions Normal teeth	AD	Levin et al
Generalized osteoporosis Destructive generalized joint disease	Unknown	Pentinnen et al
Osteoporosis Sclerotic skull lesions Normal teeth?	Unknown	Colavita et al
Area of rarefaction in pelvis and long bones Normal sclerae Normal hearing	AD	Keats and Anast
Bowed long bones Premature loss of teeth Hearing loss	AD	Osterberg et al Hughes et al
Wormian bones Short arms Radiolucencies in long bones	Unknown	Suarez and Stickler
Blue sclerae Wormian bones Generalized moderate osteoporosis Dentinogenesis imperfecta	AD	Beighton ?Crawfurd and Winter
Blue sclerae Wormian bones Mandibular hypoplasia Joint laxity Easy bruisability	Dominant	McLean et al
Joint hypermobility Wrinkled skin Blue sclerae Other osseous abnormalities	Unknown	Biering and Ivesen
Osteoporosis Wormian bones Frontal bossing Hyperextensible joints Retinitis pigmentosa	AR	Pfeiffer et al Heide Blechmann and Crommer Al Gazali et al
Contractures Spinal muscular atrophy	?AR	Borochowitz et al
Contractures in knees/elbows Pterygia Kyphoscoliosis	AR	Brady and Patton Viljoen et al McPherson and Clemens
Campomelia Ankyloglossia superior Cleft palate	Unknown	Stevenson
Ocular proptosis Craniosynostosis Hydrocephaly Distinctive facies	Unknown	Cole and Carpenter
Congenital cataract Microcephaly Thin calvaria Blue sclerae	AR	Buyse and Bull
Cataract Narrow thorax Distinctive facies	?AR	Dennis et al
Myopathy Cataract Hypogonadism Mental retardation	AR	Lundberg
Hearing loss Dystonia Choroidal-areolar dystrophy Mental retardation	XLR	Tranebjaerg et al
Marfanoid habitus Slight basilar impression Wormian bones Other osseous abnormalities	?Recessive	Meigel et al
Thin ribs/long bones Undermineralization of skull Short stature	Unknown	Bonaventure et al
Micromelia Posterior encephalocele Polysyndactyly Duplication of tibia	Unknown	Carpenter and Hunter
Excessive callus formation Short limbs Bowing forearms	Unknown	Feingold et al
Short limb dwarfism Craniosynostosis Brachydactyly	Unknown	Kozlowski and Kan
Short limb dwarfism Dense skull/vertebrae	Unknown	Muller et al
Bone cyst Rhizomelic short arms Scoliosis Delayed tooth eruption	Unknown	Schinzel
Osteoporosis Transverse bone interruptions Hydrops Monosomy X	X-linked recessive	Azouz et al
Osteoporosis White matter degeneration Mental retardation	AR	Neimann et al
Myelofibrosis Osteopenia Pigmented spots Distinctive face	Unknown	Cole et al
Osteopetrosis Hydrocephaly Neuronal loss	AR	El Khazen et al
Radial ray anomalies Bowing tibia Mental retardation	AR	Chitty et al
Blue sclerae Sparse hair Mental retardation	AR	Kaler et al
Skeletal hemangiomas Extraskeletal hemangiomas	Unknown	Devaney et al
Midface hypoplasia Micromelic short stature Wormian bones	Dominant	Nishimura et al

were normal. Crawfurd and Winter (54) reported a patient similar to the one reported by Beighton (14) who lacked femoral bowing and vertebral flattening, but who had frontal bossing, joint laxity, and easy bruisability. McLean et al (122) reported a father and daughter with wormian bones, blue sclerae, mandibular hypoplasia, loose joints with dislocations, and femoral and tibial bowing; dentition was normal and there were no fractured bones.

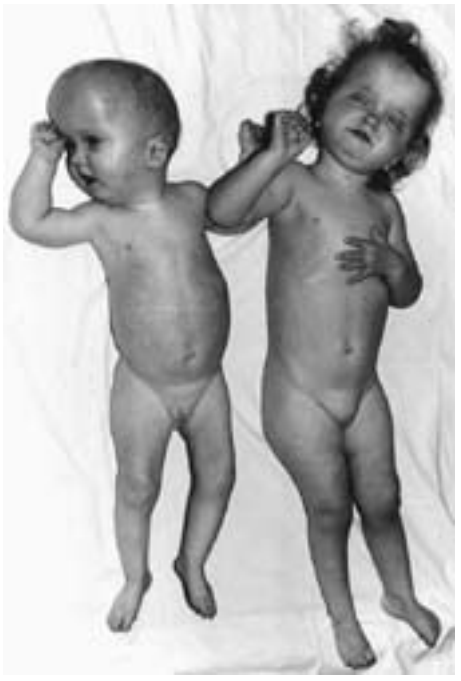
Buyse and Bull (28) described three sibs with congenital cataracts, microcephaly, thin calvaria, prenatal fractures, and blue sclerae. The brain had a smooth cortex without convolutions, sulci, or gyri. These sibs were stillborn or died shortly after birth. The parents were normal.



A B

Fig. 6–8. *Cole-Carpenter syndrome*. (A) At age 4 months, distinctive metaphyseal lucencies or compression fractures were apparent in all long bones. (B) By age 8 months, cortical thinning and demineralization had progressed. Diaphyseal fractures subsequently healed, but deformities and bowing were already well advanced. (A,B from DEC Cole and TO Carpenter, J Pediatr 110:76, 1987.)

Fig. 6–9. *Osteoporosis, fractures, macrocephaly, blindness, and severe mental retardation*. Two sibs with macrocephaly, frontal bossing, and congenital blindness. (Courtesy of W Lenz, Münster, West Germany.)



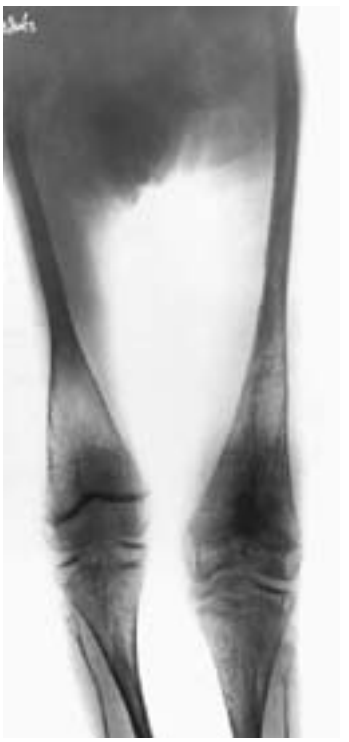


Fig. 6–10. *Osteoporosis, fractures, macrocephaly, blindness, and severe mental retardation*. Radiograph showing severe osteoporosis and leg length disparity due to dislocated hips. (Courtesy of W Lenz, Münster, Germany.)

Pentinnen et al (145) described a 14-year-old girl who had two fractures, generalized osteoporosis, and destructive generalized joint disease resembling juvenile rheumatoid arthritis; on biochemical investigations, an increased ratio of type III collagen to type I collagen was found. It should be pointed out that rarely a mutation in type I collagen may be found in type I Ehlers-Danlos syndrome (130a). *Campomelic dysplasia* should also be considered in the differential diagnosis.

Colavita et al (46) reported a 21-year-old male with fractures, bumps on the head, osteoporosis, and multiple sclerotic lesions of the skull; although the patient was said to have dentinogenesis imperfecta, radiographs showed normal teeth. See section on *calvarial doughnut lesions, osteoporosis, and dentigerous cysts* for further details on differential diagnosis. Osteogenesis imperfecta has been found with congenital joint contractures in an autosomal recessive condition called "Bruck syndrome" (25,25a,104a,123,206). In addition to multiple joint contractures, these patients exhibit club feet, pterygia, multiple fractures leading to deformed extremities, short stature, and progressive kyphoscoliosis. All have had normal hearing and normal intelligence, and white sclerae in childhood or later on.

Keats and Anast (97) reported a three-generation kindred with normal sclerae, normal hearing, multiple bone fractures, and circumscribed areas of rarefaction in the pelvis and long bones. It is also of note that a premature, stillborn infant with short, bowed lower extremities as well as fractures was born to this kindred. Meigel et al (124) described a 10-year-old male born to a consanguineous couple. The boy had multiple fractures, marfanoid habitus, narrow thorax, thin extremities and mild arachnodactyly, lumbar lordosis, genua valga, moderate muscular hypotonia, and mildly hyperextensible joints. Radiographs showed slight basilar impression, wormian bones, flattened vertebral bodies, and bowing of long bones; cystic irregularities in the bones were noted. Biering and Ivesen (18) described a 5-month-old male with blue sclerae, wrinkled, loose, and pale skin with a conspicuous venous network, excessive joint laxity, hypotonia, bilateral hip dislocation, multiple spontaneous fractures of vertebrae and femurs, thoracic kyphosis, severe generalized osteoporosis, and slender long bones.

Greenfield et al (82) reported a family with blue sclerae, keratoconus, childhood onset of otosclerotic-like hearing loss, and spondylolisthesis, but no fractures. Inheritance was autosomal recessive. We suspect a form of Ehlers-Danlos syndrome. Carey et al (35) described three children with bone fractures, blue sclerae, embryotoxon, gradual hearing loss beginning in the second decade of life, arachnodactyly, tall stature, dolichostenomelia, pectus excavatum, joint hypermobility, and scoliosis but no ectopia lentis. The proband had marked dilatation of the ascending aorta and severe aortic incompetence; he died suddenly at age 32. The father was a member of a large kindred with dominantly inherited osteogenesis imperfecta; the mother had scoliosis, pectus excavatum, clinodactyly and camptodactyly of the fifth fingers and toes, ligamentous laxity, and flat feet.

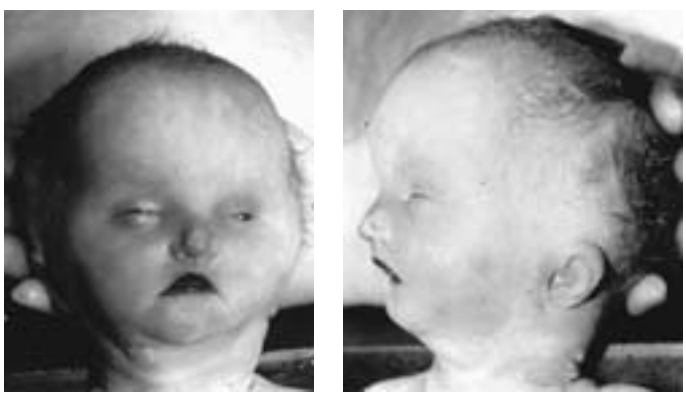
Osterberg et al (132) described a huge Northern Irish family in whom 40 individuals were affected with hearing loss in early childhood, bone pain at puberty or shortly thereafter, and early loss of dentition. Radiographically, the long bones showed abnormal modeling, disordered trabecular pattern, and gradually expanding areas of translucency leading to cortical thinning and an increase of fractures. The responsible gene was located at 18q21–q22 (92).

Suarez and Stickler (186) described a single girl with short arms, short fifth fingers and fourth and fifth toes, and radiolucent defects with cortical thinning in the humeri, forearms, and lower legs. Multiple wormian bones were seen in the skull. Borochowitz et al (24) described two male sibs with infantile spinal muscular atrophy who had spontaneous fractures shortly after birth. One had an unilateral preauricular tag. The sclerae were not blue. The parents were first cousins.

Stevenson (181) reported an infant with bowed femora, radii, and ulnae, a poorly ossified cranium, and fractures of the ribs. There were also cleft palate, adhesion of the tongue to the palate, hypertelorism, high nasal bridge, and small mandible. Two sibs were reported by Dennis et al (58) who had cataract, microphthalmia, thin beaked nose, short philtrum, and micrognathia. The facies resembled that of *Hallermann-Streiff syndrome* (Fig. 6–11). In addition, the thorax was narrow, and the fingers were tapered with small nails. Radiologically, the ribs, clavicles, and long bones were very thin and showed many fractures.

Lundberg (116) described a brother and two sisters with cataract, proximal myopathy involving the face, eyes, and swallowing, ataxia, and hypogonadotrophic hypogonadism. Development was delayed. Inheritance is probably autosomal recessive. Tranebjaerg et al (196) reported the mapping to chromosome Xq22 of an entity that showed progressive hearing loss, as well as ataxia and dystonia, starting in childhood, and progressive visual disturbances starting in puberty and manifesting as photophobia and central scotoma. Some affected males had psychiatric disorders and peripheral neuropathy. Several affected individuals had developmental delay and increased frequency of hip fractures. Three unrelated infants described by Bonaventure et al (23) had low birth weight, undermineralization of the skull but no wormian bones, and very thin ribs and long bones with multiple fractures. Biochemically, collagen type V was increased.

Fig. 6–11. *Dennis syndrome*. (A,B) Note microphthalmia, thin beaked nose, and micrognathia. (From NR Dennis et al, Am J Med Genet 59:517, 1995.)



A B

Carpenter and Hunter (37) described an infant with severe short-limbed dwarfism, posterior encephalocele, microphthalmia, absent external nares, cleft palate, postaxial polydactyly of hands and feet, duplication of right tibia, and multiple fractures of long bones. Autopsy showed pachygyria, absent olfactory bulbs, and atrial septal defect.

Moog et al (124a) reported male and female sibs with bilateral wave-like defects of the cortex of the tibia with alternate hyperostosis and thinning. Also noted were wormian bone, dentinogenesis imperfecta, hypertelorism, and periorbital fullness.

Feingold et al (70) reported a child with rhizomelic shortening of limbs, contractures of elbows, bowed forearms, and multiple fractures. In early childhood, radiographs showed marked osteoporosis and excessive callus formation. The skin broke down over these areas. Biochemically, the callus showed PAS-positive deposits. Osteocraniostenosis was first described by Kozlowski and Kan (102) and is characterized by short-limb dwarfism, craniosynostosis (often mild cloverleaf skull), hypomineralization of the skull, thin and sclerosed long bones, multiple fractures, brachydactyly, sometimes with absent distal phalanges, and poorly developed nails.

Muller et al (126) reported a stillborn girl with short-limb dwarfism and hydrops. Radiographically the skeleton was undermineralized except for the base of the skull, face, and spine. Shortening of the limbs was rhizomelic with wide metaphyses and fractures.

A pubertal boy described by Schinzel (162) showed rhizomelic shortening of arms, bone cysts, increased fractures, and delayed tooth eruption. He had short stature, severe scoliosis, and hypermobile small joints. Azouz et al (7) described a fetus with monosomy X and hydrops. Multiple fractures, osteoporosis, bent bones, and symmetric submetaphyseal transverse bone interruptions or pseudofractures were noted.

Neimann et al (127) reported four sibs and an isolated patient with white-matter degeneration, quadriplegia, amyotrophy, peripheral neuropathy, subluxation of hips, osteoporosis, and multiple fractures. They had severe developmental delay. Several patients have been described with widespread fibrous bone dysplasia, fractures of the femora, some bowing of long bones, myelofibrosis, and pigmented skin spots (48). They had hypertelorism, synophrys, saddle nose, anteverted nostrils, large mouth, and highly arched palate. The disorder is possibly caused by increased adenylate cyclase activity. El Khazen et al (67) described two sibs with increased bone density, multiple fractures, and hydrocephaly. Autopsy showed extensive loss of neurons and gliosis.

Chitty et al (42) reported two sibs with brachydactyly, variable radial ray anomalies, bowed tibiae, and, in one, bowed femora, osteopenia, and multiple fractures. The sibs had a square, flat face. Development was delayed. The parents were consanguineous. Two sibs with consanguineous parents, reported by Kaler et al (96), had sparse hair, macrocephaly, prominent forehead, hypertelorism, and joint hypermobility. Development was delayed. They had multiple fractures, osteopenic skeleton, and white sclerae.

Nishimura et al (129) reported a new brittle bone disorder consisting of dolichocephaly with frontal bossing, midfacial hypoplasia, postpubertal prognathism, micromelic short stature, coarse bony trabeculi, and bone fragility of variable degrees. Mild alteration in the vertebral bodies and iliac hypoplasia were other hallmarks. Multiple wormian bones were seen in the calvaria. There were progressive bowing of the legs and forearms and pseudofractures of the long bones with metaphyseal narrowing. Inheritance is either autosomal or X-linked dominant.

There are several reports of the occurrence of multiple hemangiomas of the skin, mouth, conjunctiva, various viscera, and bones; Devaney et al (60) provide a good review. Radiographs show widespread multiple lytic lesions. The origin of the disorder is unknown.

Wormian bones are found in *cleidocranial dysplasia, pycnodysostosis, progeria, mandibuloacral dysplasia, acroosteolysis,* and *Menkes disease.* Fractures can also be the result of child abuse (11,127,136,142,167). Opalescent teeth with radiologic abnormalities similar to those found in some patients with osteogenesis imperfecta are also seen in dentinogenesis imperfecta, a disorder affecting the dentition only. This disorder, sometimes called "hereditary opalescent dentin," has autosomal dominant inheritance (19,55,76).

Laboratory aids. Sonography has been used as a method of prenatal diagnosis for individuals at risk for osteogenesis imperfecta type I. Preimplantation diagnosis has been reported (60a). Hobbins et al (89) reported a displaced femoral fracture in a fetus of 19 weeks at risk for osteogenesis imperfecta. Chervenak et al (41) reported another fetus that was normal at 20 weeks of gestation; however, at 24 weeks, both femurs were markedly bowed, and at 32 and 38 weeks, long bone demineralization was suggested; no fractures were found. As only a limited number of newborns with osteogenesis imperfecta type I are born with fractures [8% in the series of Sillence et al (169)], and often no skeletal deformity is evident at that time, it is likely that many cases at risk will be missed. Prenatal diagnosis by molecular studies using linkage studies (117,198) or mutation analysis (198) has been accomplished. The same holds for osteogenesis imperfecta type IV.

Many authors have reported the prenatal diagnosis of osteogenesis imperfecta type II by ultrasound (61,66,75,134,165,180,193,194,217). Thompson (193) summarized the findings in 30 cases, many of which were diagnosed from 20 weeks of gestation to as early as 13.5 weeks of gestation (180). Both cases at risk and sporadic cases in which scans were made for other reasons have been reported. The most important findings have been reduced echogenicity, especially of the calvaria, marked reduction of long bone length (mainly femur), multiple fractures, and deformity of long bones, ribs, and skull. No false-negative diagnoses have yet been reported (193). Thompson (193) suggested serial scans from 14 weeks gestation in pregnancies at risk, and stated that osteogenesis imperfecta type II should be diagnosable at 17 weeks gestation. With intravaginal transducers, diagnosis may even be made earlier. Prenatal diagnosis by molecular methods is also possible (50).

The number of cases in which osteogenesis imperfecta type III was diagnosed prenatally by ultrasound is low (6,193,194). Three dimensional ultrasonography is better than two dimensional (72a). In several cases, early ultrasound scans at 14 or 15 weeks gestation were found to be normal. Abnormalities were found only at 19 to 20 weeks gestation. The findings were the same as those in type II, but were more mildly expressed (193). No false-negative results have been published, but the number of reports is still low.

An animal model of osteogenesis imperfecta with opalescent teeth has been described in Friesian calves (57), and a transgenic mouse model has been reported for mild dominant osteogenesis imperfecta (22).

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Chapter 7
Syndromes Affecting Bone: Chondrodysplasias and Chondrodystrophies

We cannot emphasize strongly enough the need for radiographic examination of lethal bone dysplasias. The minimum number of radiographic views that should be taken include anterior–posterior (AP) and lateral views of the whole body (babygram), lateral skull, and hand and foot views. At autopsy, views of the trachea, vertebrae, costochondral junction, and the head of the humerus and femur should be obtained (3,9). Chromosomes may be cultured from human cartilage within seven days following death (7).

Osteodysplasias include disorders of osteopenia or osteosclerosis, while chondrodysplasias result in either short trunk or short limb. From 1960 to 1980, there was such a radiographic proliferation of disorders that a biennial meeting was held to classify the disorders of cartilage and bone into families. This culminated in the International Nomenclature and Classification of the Osteochondrodysplasias (4). Within recent years, the use of linkage, positional cloning, and positional candidate gene analyses have revealed basic genetic defects underlying several of these conditions (2,5,6). We refer the reader to an article by Wynne-Davies and Gormley (8) for a discussion of relative frequency. An excellent review of ossification and the molecular aspects of bone formation is that of Cohen (1).

Understanding the roles of the various collagens, the parts played by glycosaminoglycans and various enzymes involved in the degradation of bone, and especially new information regarding signaling between cell surface receptors, their ligands, signal transduction to the nucleus, and transcription factors has allowed for reclassification of many of the disorders on a molecular basis (1a).

Space limits us to those disorders that also involve the cranium and facial skeleton.

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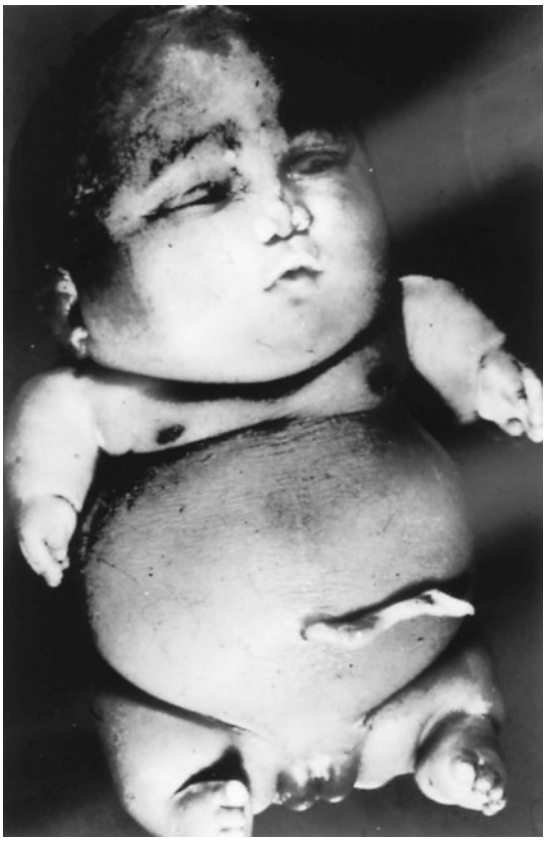
Achondrogenesis

Achondrogenesis, separated in 1936 by Parenti et al (41) from achondroplasia, is a type of lethal chondrodysplasia characterized by short trunk, severe micromelia, normal size head, and specific skeletal changes. There are, however, earlier examples (12). The term "achondrogenesis," first coined by Fraccaro (15) in 1952, represents a heterogeneity of at least three types (Figs. 7–1 to 7–4) (29,55). There has been considerable confusion regarding terminology. Camera et al (8) have suggested that type 1 with dense bones be designated "pycnochondrogenesis," citing earlier examples (50). Borochowitz et al (5) indicated further heterogeneity of type 1 with two distinct subgroups. We suggest that the reader peruse Whitley and Gorlin (61), Borochowitz et al (4), Yang et al (65), Chen et al (10), and Superti-Furga (55) for discussion of nomenclature. Over 200 cases have been recorded in aggregate, and several large series have

Fig. 7–1. *Achondrogenesis.* Phenotype of lethal dwarfism with disproportionately large head, disproportionately short limbs, and pot belly.



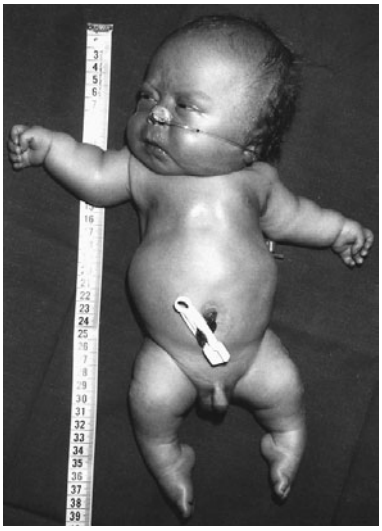


Fig. 7–2. *Achondrogenesis, type IV.* Hypochondrogenesis. (From G Hendrickx et al, Eur J Pediatr 140:278, 1983.)

been analyzed (48,66). The frequency has been estimated at 1/40,000 births (3,53).

We will use the classification of Table 7–1 (55). Type 1B has autosomal recessive inheritance. For type 1A, inheritance remains unproven. All patients with type 2 have been isolated examples (37), and probably represent new autosomal dominant mutations (18,19). The milder form of type 2 is also called "hypochondrogenesis." Affected sibs with achondrogenesis have been of the same type within the classification.

Achondrogenesis type 1B was proven to be caused by mutations in the gene for a sulfate transporter (*DTDST*), which is also the causative gene for diastrophic dysplasia (54,56). Impaired activity of the sulphate transporter in chondrocytes and fibroblasts results in synthesis of insufficiently sulfated proteoglycans, which in turn has a pronounced effect on the composition of the extracellular matrix (55). Genotype–phenotype correlations indicate that the amount of residual activity of *DTDST* modulates the phenotype, from lethal conditions such as atelosteogenesis type 2 and achondrogenesis type 1B, to nonlethal diastrophic dysplasia (7,57). Achondrogenesis type 2 is caused by mutations in the $\alpha(1)$II chain of type II collagen (14,15,18,19,28a,40,41). Mutations in *COL2A1* give rise to a spectrum of clinical phenotypes, the so-called type II collagenopathies (52), which in addition to achondrogenesis type 2 includes

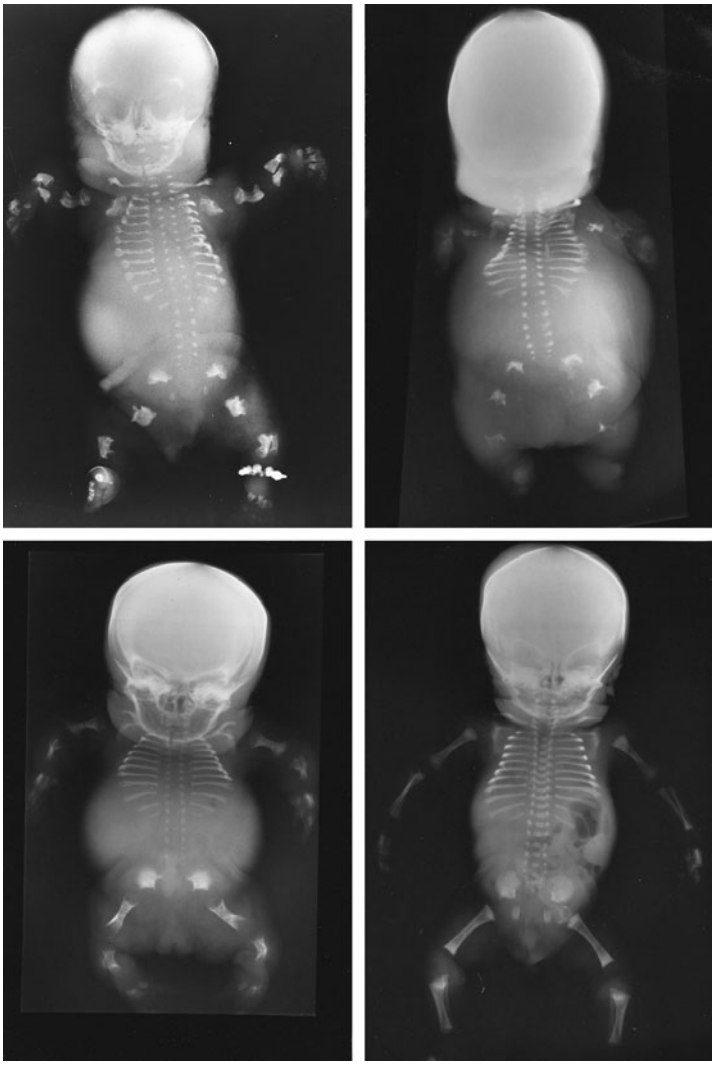


Fig. 7–3. *Achondrogenesis.* Radiographs of the four different types of achondrogenesis. Top left: Type I (Houston-Harris) with severe limb and multiple rib fractures. See also Figure 7–4, top left. Top right: Type II (Fraccaro), with severe limb reduction and no rib fractures. See also Figure 7–4, top right. Bottom left: Type III (Langer-Saldino), with mushroom-stem femora, intermediate limb reduction, and halberd ilia. See also Figure 7–4, bottom left. Bottom right: Type IV (hypochondrogenesis), with the least severe limb reduction. See also Figure 7–4, bottom right. (From CB Whitley and RJ Gorlin, Radiology 148:693, 1983. Top left courtesy of R Wapner and LG Jackson, Philadelphia, Pennsylvania. Top right courtesy of RM Saldino, San Diego, California. Bottom left courtesy of PE Andersen, Odense, Denmark. Bottom right courtesy of K Kozlowski, Sydney, Australia.)

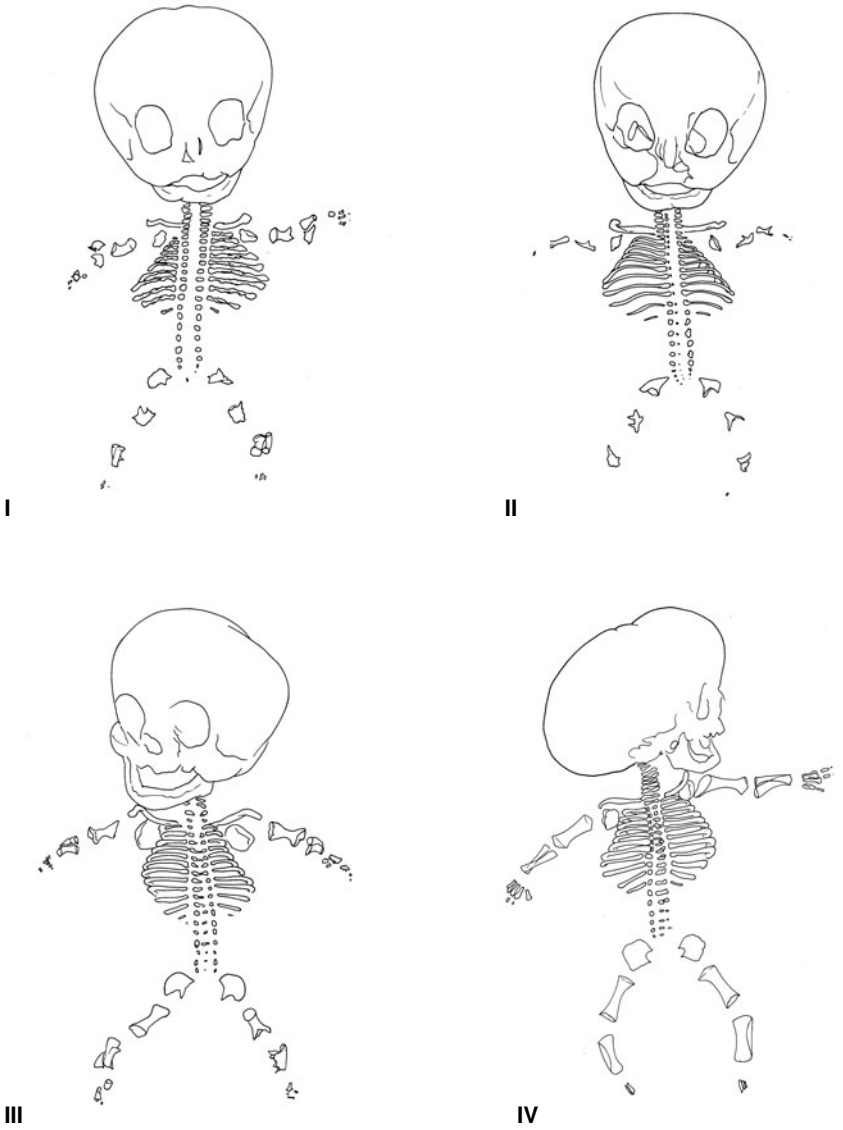


Fig. 7–4. *Achondrogenesis.* Diagrammatic sketches of the four types of achondrogenesis. Top left: Type I (Houston-Harris). Top right: Type II (Fraccaro). Bottom left: Type III (Langer-Saldino). Bottom right: Type IV (hypochondrogenesis). (From CB Whitley and RJ Gorlin, Radiology 148:693, 1983.)

congenital spondyloepiphyseal dysplasia, *Kniest dysplasia*, *Stickler syndrome*, *type 1*, spondyloperipheral dysplasia, and *spondyloepimetaphyseal dysplasia*, *Strudwick type* (17). The nature of the mutations and their localizations within the protein seem to explain this diversity in manifestations, although further modulating factors may be involved as well.

Achondrogenesis type 1 is incompatible with life, with half of the infants being stillborn and the rest succumbing within the first few hours. Mean weight for type 1A patients is about 1200 g, whereas type 1B infants average 2100 g. Infants with the mildest form of type 2 (hypochondrogenesis) have survived for as long as a few months, but no long-term survivors have been reported (4,22,36,37). There is a history of polyhydramnios in over 50% of type 1 patients (48). Gestation is about 30 weeks in type 1A and 35 weeks in type 1B. Fetal hydrops is common, although this appearance may also be caused by the abundance of soft tissue relative to the short skeleton.

Table 7–1. Classification of achondrogenesis

Name	Former types	Gene
Achondrogenesis type 1A	Houston-Harris	Unknown
Achondrogenesis type 1B	Fraccaro	*DTDST* (5q32)
Achondrogenesis type 2	Langer-Saldino	*COL2A1* (12q13)

Facies. The (usually normocephalic) head is disproportionately large relative to reduced neck, trunk, and limb length, causing the infant to be erroneously considered to have hydrocephaly. The head is often greater than 40% of body length and appears to sit on the chest. In type 1A, the forehead slopes and the face appears puffy. The nose is small with anteverted nares and long philtrum, and there is retrognathia with double chin. Type 1B and 2 infants have a large prominent forehead, flat face, depressed nose with marked anteversion of nostrils, normal philtrum, and more normal chin. The neck is short in all types. The face is not remarkable in the mild form of type 2.

Skeletal alterations. The extremities are bowed, rarely exceeding 10 cm in length, and have been compared to flippers (55). The fingers and toes are similarly short and stubby. In type 2, polydactyly may be found (45). Total body length is seldom greater than 36 cm at term (range 22–40 cm). The belly is greatly enlarged, partly from the short chest cavity and partly from hydrops. The genitalia are normal.

General radiographic characteristics shared by the severe types consist of marked underossification of vertebral bodies, sternum, ilia, ischia,

Table 7–2. Achondrogeneses

	Type 1A	Type 1B
Skull	Poorly ossified	Mild ossification disturbance
Vertebral column	Bodies unossified	Body minimally ossified
	Pedicles ossified	Arches ossified only in cervical and upper thoracic region
Ribs	Short with multiple fractures, cupped ends	Short without fractures, flared cupped ends
Clavicles	Short, wide	Mildly elongated
Scapulae	Irregularities, hypoplastic	Distal radial dichotomy, hypoplastic
Pelvis	Ilia crenated; ischia poorly ossified, widely spaced, low; pubic bones ossified	Ilia crenated, ischia and pubic bones unossified
Humerus	Short, stellate	Short, stellate
Radius/ulna	Short, metaphyseal irregularities	Short, poorly ossified,
Femur	Proximal metaphyseal spike, clubbing	Crenated, distal flare
Tibia/fibula	Short, wide, irregular metaphyses	Short, stellate, fibula unossified
Hands/feet	Unossified	Unossified
	Type 2	**Mild type 2 (hypochondrogenesis)**
Skull	Normally ossified, occipital defect	Normally ossified, occipital defect
Vertebral column	Bodies poorly ossified, arches ossified	Bodies flattened, but ossified
Ribs	Short, not flared	Short, not flared
Clavicles	Normal	Normal
Scapulae	Almost normal	Almost normal
Pelvis	Ilia small; halberd-shaped ischia; pubic bones unossified	Ilia better modeled, ischia ossified, pubic bones unossified
Humerus	Short, flared, cupped	Short, rounded ends
Radius/ulna	Short, flared, cupped	Short, rounded ends
Femur	Short, flared cupped	Short, rounded ends
Tibia/fibula	Short, flared at both ends, cupped	Short, rounded ends
Hands/feet	Short, talus and calcaneus unossified	Short, talus and calcaneus unossified

pubic bones, talus, and calcaneus. The ribs are short and cupped with flared ends. Since failure of endochondral bone growth, which manifests as reduced linear growth of long bones, appears to be a major defect in achondrogenesis, a ratio between length and width of the femora (the femoral cylinder index) has been used (61). A boneless variant has been reported (26). The specific characteristics of each type are summarized in Table 7–2 and will be discussed briefly.

Type 1A (Houston-Harris). In this form, the calvaria is very poorly mineralized. There is marked limb shortening and striking multiple rib fractures. The long bones are very short. The vertebral bodies are so inadequately mineralized that they may appear to be absent, particularly in the lower thoracic and lumbar spine (38,43,62,64). Multiple affected sibs have been reported (2,21,24,32,42,50,59,60).

Type 1B (Fraccaro). In this form, there are crenated ilia and stellate long bones. The vertebral bodies exhibit minimal ossification; the pedicles are ossified. There are no, or only one or two, rib fractures (6,55) (Table 7–1). Clinically, the limbs are shorter than those in type 1A and the calvaria is ossified. However, the degree of ossification is age dependent, and caution is needed in comparing radiographs from patients with different gestational ages. The distinction between type 1A and type 1B on radiographs is not always possible (55). Multiple affected sibs have been described (47,60,62).

Type 2 (Langer-Saldino). Infants have well-ossified calvaria and exhibit better developed mushroom-stem femora and almost triangular halberd-shaped ilia (Table 7–1). Ossification of the spine is variable. Ischial and pubic bones are unossified. Multiple affected sibs have been reported (11).

Mild type 2 (hypochondrogenesis). By radiographic criteria, the same pattern of chondrodysplasia is observed, but to a relatively mild degree (Table 7–1). Thoracolumbar vertebral bodies are only slightly ossified and manifest as thin lamellae. Ossification is incomplete in the cervical, upper thoracic, and lower lumbar regions. The sternum is very short. The ilia are hypoplastic but more sculptured. Ischial ossification is variably present but pubic ossification is never observed. The sacrum is deficient. Limb bones are thick and short with metaphyseal widening and irregularity. There are no epiphyseal centers. The distinction between type 2 and hypochondrogenesis has been challenged on the basis of the apparent continuity of clinical, radiographic, and histopathologic changes in a large series of patients (4,37).

Pathologic findings. Histopathologic studies have demonstrated different patterns of morphologic abnormalities in the most severe types (4). In type 1A, the cartilage is hypercellular with clustered chondrocytes within a diffuse matrix. The resting chondrocytes contain PAS-positive, diastase-resistant, round to oval intracytoplasmic inclusions. The lacunae are dilated. There is defective column formation. Type 1B has more randomly dispersed chondrocytes (16). Their cytoplasm is vacuolated but there are no inclusions. The lacunae are not dilated. As in type 1A, there is no columnization. In type 2, the chondrocytes are densely packed with dilated lacunae (49,60,66).

Other findings. Other than hypoplastic lungs, the viscera are usually normal (3). Patent ductus arteriosus (PDA) (11,32,47,62), cardiac septal defects (44), hydronephrosis (28,32), cryptorchidism (28,32,62), and inguinal hernia (27) have been noted. In type 1A, occipital encephalocele has been described (9,39).

Oral manifestations. Cleft palate has been observed in type 2 cases (62,63), and in one-half of hypochondrogenesis cases (4,37).

Differential diagnosis. The clinical appearance alone would allow the clinician to separate this disorder from *thanatophoric dysplasia*, homozygous *achondroplasia*, *atelosteogenesis type II*, *hypophosphatasia*, and *fibrochondrogenesis*. Multiple rib fractures in achondrogenesis type 1B may suggest *osteogenesis imperfecta*. Differentiation from *Schneckenbecken dysplasia* is more difficult but can be made on the basis of the characteristic "snail back" iliac silhouette in the latter. Another unique disorder in the achondrogenesis spectrum has been identified (30) but is

distinguished by more delicate and curved clavicles and other long bones. Mild type 2 (hypochondrogenesis) greatly resembles *spondyloepiphyseal dysplasia congenita*.

Laboratory aids. Prenatal diagnosis has been made sonographically in the first trimester (51) or early in the second trimester by several investigators (2,11,20,24,47,50,58,60,62a). Findings include polyhydramnios, hydrops, extremely short limbs, short trunk, prominent abdomen, cervical hygroma, and underossification of spine.

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Achondroplasia

The term "achondroplasia" was first used by Parrot (68) in 1878 to describe a rhizomelic form of short-limbed dwarfism associated with enlarged head, depressed nasal bridge, short stubby trident hands, lordotic lumbar spine, prominent buttocks, and protuberant abdomen (Figs. 7–5 to 7–7). Achondroplasia is a misleading term because cartilage is, in fact, formed in the disorder; however, the term is well established. Until recently, a variety of chondrodysplasias were frequently confused with achondroplasia (42,65,88). The Egyptian gods, Bes and Ka, are depicted as having the disorder (84). Aesop also presumably had the disorder (26). The reader is referred to an excellent report on the 1986 International Symposium on Human Achondroplasia (64), and the series of papers by Hunter (36–38).

More than 80% of recorded cases of achondroplasia are sporadic, representing new mutations. Increased paternal age at time of conception is associated with sporadic cases (60,66,96). Among the familial cases, autosomal dominant inheritance can be demonstrated (60). The recurrence risk, in the case of normal parents, is 0.02% (53a).

The frequency of achondroplasia has been estimated as ranging between 1/16,000 and 1/35,000 live births (3,21,50,60,64,94), making it one of the most common of the nonlethal bone dysplasias. Earlier ascertainments of frequency (55,92) were probably overestimates because other chondrodysplasias, in addition to achondroplasia, were undoubtedly included in these surveys.

Affected individuals are heterozygous for the causative gene. Presumed homozygosity has been reported in a few instances in which both parents had achondroplasia (4,69,82,110). Homozygous achondroplastic infants are more severely affected, clinically and radiologically, than are infants heterozygous for the disorder, and the condition is lethal during infancy (69), although aggressive respiratory and surgical measures kept one infant alive for several years (57). Death appears to result from brain stem compression (29). Deaths attributable to cardiovascular causes are increased in patients between 25 and 54 years of age (30). The homozygous state resembles thanatophoric dysplasia in many respects but is still distinguishable.

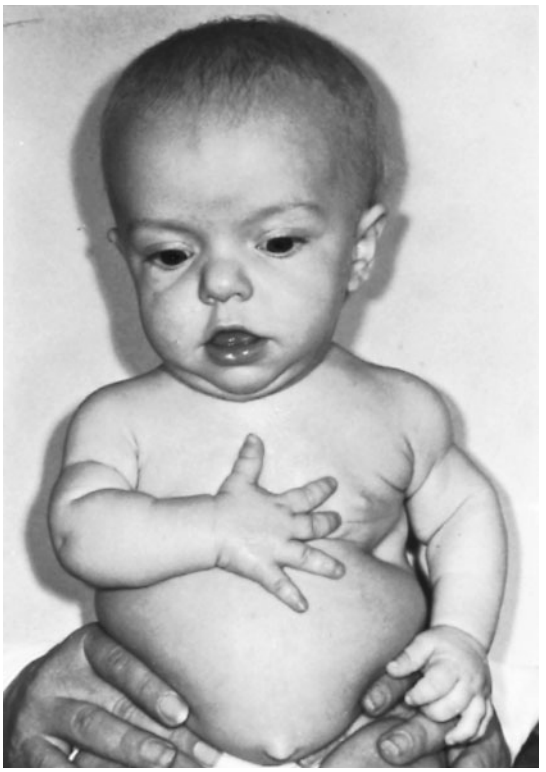
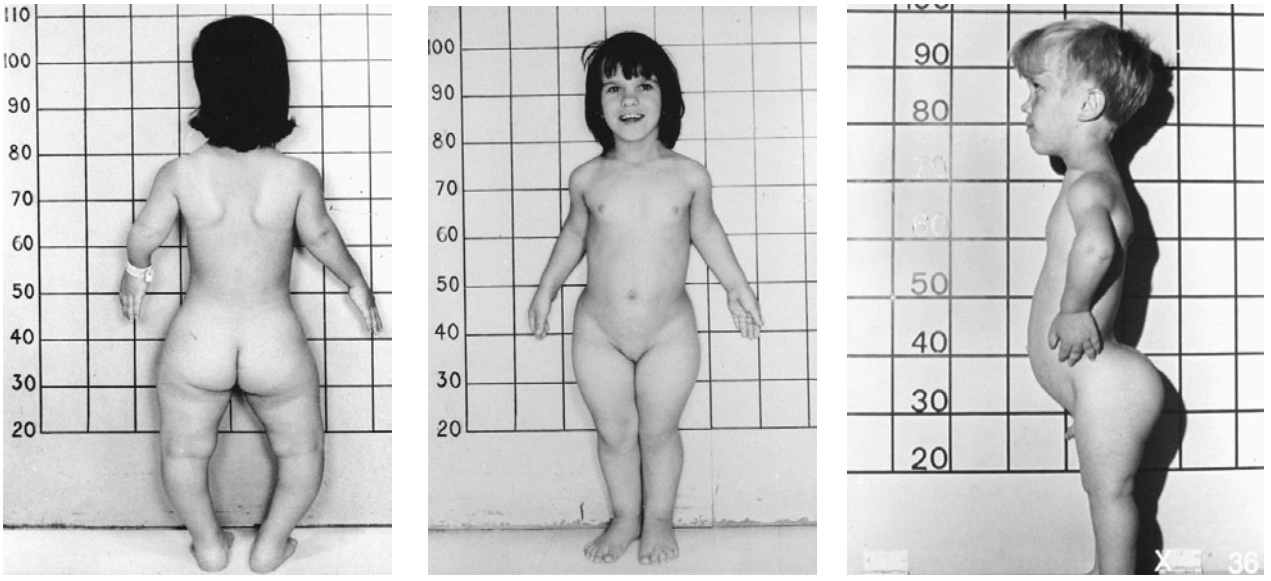


Fig. 7–5. *Achondroplasia.* Note enlarged head with frontal bossing and low nasal bridge. Rhizomelia and short hands with trident deformity of fingers are evident.

Presumed examples of an autosomal recessive achondroplasia describe either a recessively inherited chondrodysplasia misdiagnosed as achondroplasia or are insufficiently documented to establish the diagnosis with certainty (49). Instances of affected sibs with normal parents

Fig. 7–6. *Achondroplasia.* (A–C) Before and after leg straightening, and pronounced lordosis. (Courtesy of J Hall, Vancouver, BC.)



A B C

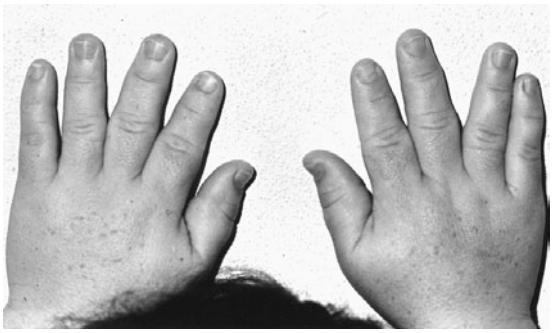


Fig. 7–7. *Achondroplasia.* Small hands with short fingers. Note trident hand deformity.

can probably be explained by gonadal mosaicism (10,17,20,78). Cases of achondroplasia within the same kindred that seemingly do not show complete penetrance have been reported on rare occasions (65,77,102). Probably, these cases can be explained by coincidence of two independent mutations due to the high mutation rate in achondroplasia. Examples of gonadal mosaicism have been reviewed (32a). Mosaic achondroplasia has been reported by Rimoin and McKusick (80) and Henderson et al (32a). Achondroplasia and hypochondroplasia can be allelic, although hypochondroplasia not linked to chromosome 4p has been reported. Cases of achondroplasia–hypochondroplasia compound have been reported (12,35,53,89). The outcome is poor (12). Examples of achondroplasia–pseudoachondroplasia compound (44,108) and achondroplasia–spondyloepiphyseal dysplasia congenita compound (111) have been documented. The clinical and radiologic abnormalities were intermediate between those of heterozygous and homozygous achondroplasia and mental retardation was marked.

Molecular and histological findings. The basic defect is a mutation in fibroblast growth factor receptor 3 (*FGFR3*). Linkage to 4p16.3 was established in 1994 (45,99), within months followed by discovery of mutations in *FGFR3* (14a,83,85).

The fibroblast growth factor receptor gene family encodes four structurally related receptors of the tyrosine kinase subclass IV type. Each is composed of an extracellular ligand-binding domain, a connecting or transmembrane region, and an intracellular kinase domain that is responsible for receptor dimerization and cell signaling. The ligands are the fibroblast growth factors (FGFs), a family of nine heparin-binding polypeptides. The intracellular kinase domain is activated if one of the FGFs binds to both heparan sulfate and FGFR, forming a trimolecular complex. The reader is referred to several excellent reviews for further background (14,22,51,59,67).

In achondroplasia, 98% of the patients have the same amino acid substitution: glycine to arginine at codon 380, almost always caused by a G-to-A transition at nucleotide 1138 within the transmembrane domain, the remaining cases having a G-to-C transition at the same nucleotide, resulting in the same amino acid substitution (9,83,85). It is the single most frequent mutation known in humans. Two patients have been described with a Gly375Cys transition, who showed a few unusual signs (63,95). The *FGFR* mutations cannot be loss-of-function mutations, as a deletion of the short arm of chromosome 4 results in the Wolf-Hirschhorn phenotype that does not have resemblance to achondroplasia. Indeed, Naski et al (61) have shown that mutations activate the receptor. In studying 40 sporadic cases, Wilkin et al (107) found that the mutation always occurred on the paternal chromosome, indicating the predisposition to the achondroplasia mutation through influences of DNA replication or repair during spermatogenesis and not during oogenesis.

Early histologic studies, which suggested gross disorganization of endochondral ossification, have been misleading because they described patients with thanatophoric dysplasia, metatropic dysplasia, or achondrogenesis, rather than true achondroplasia (81). Rimoin and associates (81) found well-organized endochondral ossification with longitudinal columns of cartilage cells at chondroosseous rib junctions. Iliac crest cartilage was normal. These findings suggest an abnormal rate of cartilage growth. However, Stanescu (91) found clusters of proliferative cells in biopsies of tibial growth plate, rather than columns. The clusters were separated by wide septa of fibrous material. Maynard et al (52) and Ponseti (74) also found abnormalities in the growth plates of the fibula, whereas the iliac crest cartilage and growth plate were nearly normal. Histologic, histochemical, ultrastructural, and biochemical studies of growth plates from different anatomic locations (including both weight-bearing and non–weight-bearing areas) in different age-groups are necessary to resolve further the pathogenesis of achondroplasia.

Defective oxidative energy formation with decreased phosphorylation at the NADH dehydrogenase region of the terminal respiratory system has been demonstrated in achondroplastic muscle (46). Absent oxidative phosphorylation has been observed in homozygous achondroplasia (47). A defect in peripheral glucose utilization has also been shown (16).

Growth and development. Mean birth length is 47.7 cm for males and 47.2 cm for females. Mean birth weight is 3500 g for males and 3150 g for females. Growth curves have been described by Horton et al (33). Mean adult height is 130 cm for males and 123 cm for females. Mean adult weight is 55 kg for males and 46 kg for females. Several studies of the effects of growth hormone therapy are available (34,90,106). The data suggest that, in some children, the therapy modestly increases short-term overall growth velocity, mainly in the children with low growth velocity prior to treatment. There is a tendency toward obesity (31). Hunter et al (36) established weight-for-height curves specific for achondroplasia.

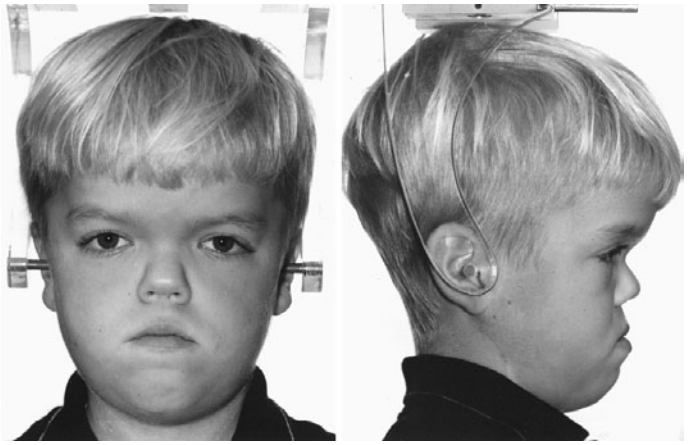
Motor milestones are slow, possibly because acquisition of motor skills is influenced by the large head and short extremities (13,97). Head control may not occur until 3 to 4 months and affected children may not walk until 24 to 36 months. Ultimately, however, development falls within the population-based normal range and most individuals with achondroplasia are able to lead an independent and productive life. In a study of the cognitive skills of 30 children with achondroplasia, verbal comprehension was found to be significantly impaired (11). It was suggested that this impairment was related to frequent middle ear infections, and possibly also to delayed oropharyngeal muscle coordination and an altered response of parents and others to the changed body scheme. A practical guide for health supervision is available (2).

Reproductive fitness is considerably reduced among those with achondroplasia because of social difficulties in finding mates and because of obstetrical problems of achondroplastic women (prematurity and the necessity for cesarean deliveries due to cephalopelvic disproportion) (1,98). Furthermore, premature menopause and an increased incidence of leiomyomata have been reported (1).

Facies and skull. The head is enlarged, with frontal bossing and low nasal bridge (Fig. 7–8). Occasionally, these features are not present at birth, but disproportionate growth of the head occurs during the first year of life and then parallels the normal curve (13,18,43,62). Cephalometric analysis has been performed by Cohen et al (15) and Pederson (72).

Central nervous system. Mild ventricular dilatation has been reported by several authors (13,19,27,40,58). Gross mechanical block caused by obliteration of the basal cisterns, obliteration at the level of the foramen magnum, or kinking of the cerebral aqueduct has not been demonstrated in most cases (42). However, there is a relatively higher rate of sudden, unexpected death during infancy and early childhood (8,70). Cervicomedullary compression and its evaluation have been discussed by several authors (23a,27,41,63,71,76,104). The best predictors of the need for suboccipital decompression include lower limb hyperreflexion, central hypopnea on polysomnography, and reduced foramen magnum measurements (71). Brain stem compression may give rise to obstructive sleep apnea (105). Significant hydrocephaly (stepwise increase in the head growth slope) with neurologic signs and symptoms has occurred in a few instances (13,58,73,108) and is probably caused by cerebrospinal fluid obstruction at the level of the foramen magnum.

Most evidence to date seems to favor communicating hydrocephaly (40). Mueller et al (58) postulated two possibilities. First, early hydrocephaly may be caused by cerebrospinal fluid outlet obstruction



A B

Fig. 7–8. *Achondroplasia.* (A,B) Enlarged calvaria with frontal bossing, low nasal bridge, and midface recession. [From MM Cohen Jr, Mutations affecting craniofacial cartilage. In: Cartilage: Biomedical Aspects, Vol 3, Hall BK (ed), Academic Press, New York, 1983, p 191.]

resulting from a small posterior fossa that becomes compensated later in life secondary to bony structural maturation. Second, patients with achondroplasia may have obstruction of cerebrospinal fluid flow at the subarachnoid villi or in the venous sinuses secondary to retrograde pressure from marginal jugular veins. These could be compensated in size secondary to small jugular foramina that resulted from faulty endochondral ossification in the posterior fossa.

Pierre-Kahn et al (73) studied hydrocephaly in 25 achondroplastic patients and suggested that the hydrocephaly was related to constriction of the sigmoid sinus at the level of narrowed jugular foramina, resulting in a rise in intracranial venous pressure. They further noted that, in most instances, the hydrocephaly stabilized spontaneously in early life. Additional studies are necessary to determine if the jugular foramina are small or if their emissary vein foramina are enlarged in achondroplasia.

The narrow spinal canal predisposes to neurologic complications with age. Compression of the spinal cord and nerve rootlets results from osteophytes, prolapsed intervertebral disks, or deformed vertebral bodies (27,29,56,75,100,101).

Skeletal system. Enlarged calvaria and basilar kyphosis are constant features. The anterior cranial base length is normal, but the posterior cranial base length is shorter than normal (15). The foramen magnum is small (27,32). The maxilla is hypoplastic, resulting in midface deficiency and relative mandibular prognathism (15). The frontal and occipital bones and, in some cases, the temporal bones may be prominent (42,43). Partial occipitalization of the first cervical vertebra occurs in most cases.

The interpediculate distances progressively narrow from the upper to the lower lumbar spine, the pedicles are shortened in anteroposterior diameter, the posterior aspect of the vertebral bodies is concave, and the bony spinal canal diameters are decreased, particularly in the lumbar region (Fig. 7–9). Anterior wedging of the vertebral bodies (particularly in the region of the thoracolumbar junction) with resultant kyphosis may be prominent (42,43,87). Kyphosis occurs in about 20% and scoliosis in 7% (106). A thoracolumbar gibbus is more common in South African achondroplastic patients (6).

The lumbar spine appears to articulate low in relation to the crests of the iliac bone. The sacrum is narrow and horizontally oriented. The pelvis is broad and short. Narrowing of the pelvic inlet prevents vaginal delivery in pregnant achondroplastic females. The superior acetabular margins are oriented horizontally, and the sacrosciatic notch is acute (Figs. 7–9 and 7–10). The thoracic cage is relatively small in anteroposterior diameter (5,37,42,43). Legs are frequently bowed because of lax knee ligaments.

Limb bones are shortened in a rhizomelic pattern, which is more prominent in the upper extremities. There is incomplete extension at the elbows. The carpus is relatively large. The metacarpals and phalanges, although

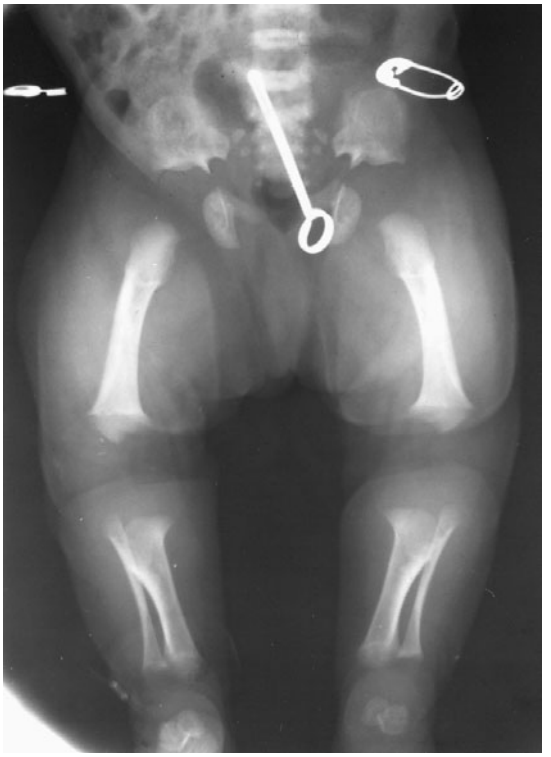


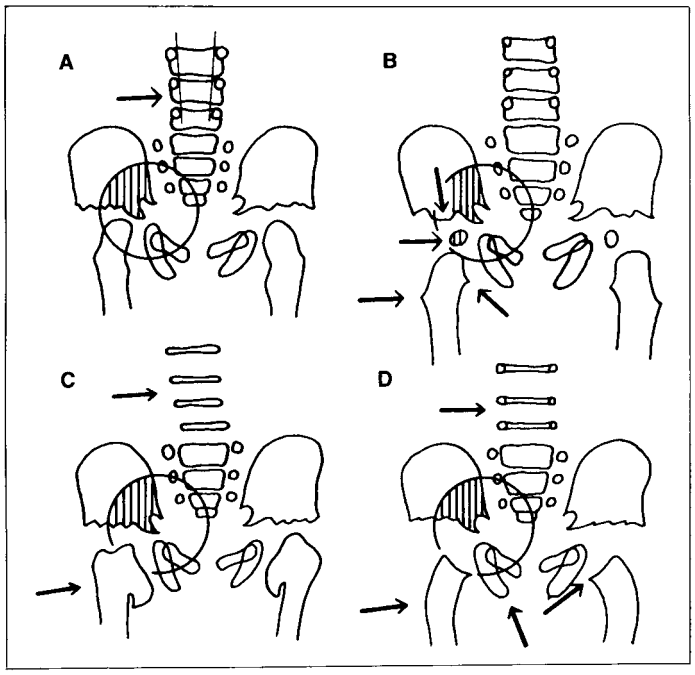
Fig. 7–9. *Achondroplasia.* Radiograph showing shortening of long bones, low articulation of lumbar spine in relation to iliac crest, short broad pelvis, and downward diminishing interpediculate distances in lumbar spine.

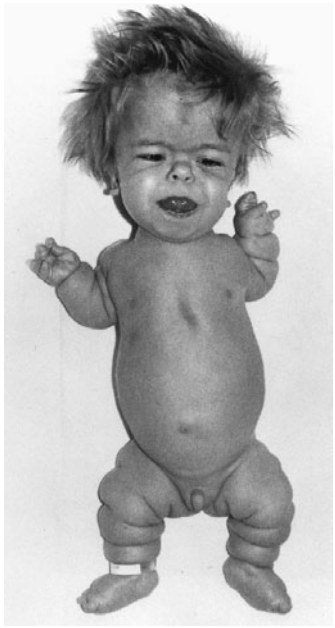
shortened, are disproportionately large in relation to the humerus, radius, and ulna. Metacarpophalangeal relations have been described in detail (39). Genua vara is found in 15% of cases (109). The fibula is overlong at the ankle compared to the tibia, leading in some cases to varus foot deformity. Elbow extension is limited.

Otolaryngologic findings. Otitis media is likely common during the first 6 years of life. Hall (25) surveyed 150 individuals with achondroplasia over age 18; 75% had a history of ear infections and 11% indicated that they had significant hearing loss. Among 88 patients studied by Glass et al (23), 97% reported having had ear infection and/or hearing loss; on audiometric testing, 72% had hearing loss of 22 dB or greater. Hunter et al (38) found an even higher rate of otitis media among 193 patients, varying in rate among different age classes and, in a questionnaire study of 437 adult patients, 17% of cases were reported to have chronic ear infections and 33% to have hearing impairment (48). In two studies of limited series of patients, most of whom were younger than 30 years, conductive hearing loss was noted in half; sensorineural and mixed hearing losses were also noted, but less frequently (23,62). The degree of hearing loss did not correlate with the abnormal temporal bone structure (86).

Differential diagnosis. Achondroplasia should be distinguished from *achondrogenesis, thanatophoric dysplasia, Ellis-van Creveld syndrome, metatropic dysplasia, diastrophic dysplasia, asphyxiating thoracic dystrophy, hypochondroplasia,* pseudoachondroplasia, *Nance-Sweeney chondrodysplasia,* Schmid type metaphyseal dysplasia, various spondyloepiphyseal and spondylometaphyseal dysplasias, and other types of short-limbed dwarfism (24,42,43,49,53,88,103) (Fig. 7–10B–D). The changes that distinguish heterozygous achondroplasia from homozygous achondroplasia and thanatophoric dysplasia reside largely in the vertebral column, the pelvis, and the limb bones (Fig. 7–10E,F). The differences have been elegantly discussed by Pauli et al (69).

Laboratory aids. Radiographic studies enable differentiation from other forms of dwarfism that simulate achondroplasia. Prenatal diagnosis





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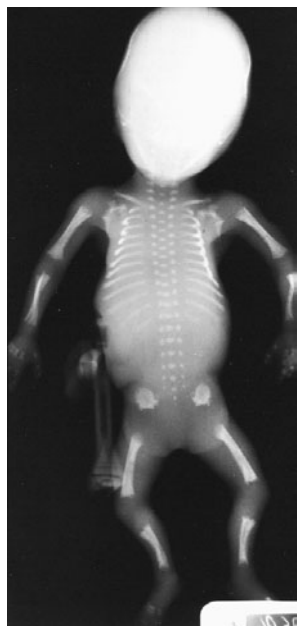

F

Fig. 7–10. *Achondroplasia.* Schematic drawing of pelvic features of (A) achondroplasia, (B) chondroectodermal dysplasia, (C) metatropic dysplasia, and (D) thanatophoric dysplasia. Deformity of acetabulum is nearly the same in all four conditions. In achondroplasia, interpediculate distances diminish downward. In chondroectodermal dysplasia, ossification centers of femora and spike-like exostoses at the trochanters are present. In metatropic dysplasia, reduced height of vertebral bodies, halberd form of femur, and, occasionally, scoliosis are seen. In thanatophoric dysplasia, vertebral bodies are flat, spike-like exostoses are present at the os pubis and at the femur, and the femur is bowed. (E,F) *Homozygous achondroplasia*. In E, note large head, small extremities, redundant skin folds, and narrow rib cage. Radiograph (F) shows small thoracic cage, marked platyspondyly, small iliac bones with scalloped lower margins, and short tubular bones, especially the humeri and femora. (A–D from K Gefferth, Prog Pediatr Radiol 4:137, 1973. E from RM Pauli et al, Am J Med Genet 16:459, 1983.)

by ultrasound has not been possible (19), although second-trimester ultrasound studies have been recorded on occasion (54). Bellus et al (7) reported first-trimester molecular diagnosis, emphasizing the importance for studies in couples at risk for homozygous offspring. Saitoh et al (83a) described prenatal diagnosis from maternal serum.

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Hypochondroplasia

Hypochondroplasia is a common form of disproportionate short stature (Fig. 7–11) with relatively few clinical manifestations but with radiographic features similar to those found in achondroplasia, although milder in degree. Over a hundred cases have been recorded to date (3,8–13,15,19,20,25,29,32) and several excellent reviews are available (11,15,29). Inheritance is autosomal dominant. Most instances represent new mutations, but familial instances have been encountered (4,7,15,25,39). Hypochondroplasia has been found to be heterogeneous: in several patients mutations were found in fibroblast growth factor receptor (*FGFR*) type 3 (4,7,12,14,21,23,25) but other patients did not harbor a detectable mutation and several familial cases were unlinked to chromosome 4p (7,14,21,23,25,27). Mullis et al (18) reported linkage to 12q23 and suggested the insulin-like growth factor 1 gene as a candidate gene. The background of *FGFR3* is discussed in more detail in the section on achondroplasia (above).

In 43% to more than 50% of cases, a C-to-A or C-to-G mutation at position 1659 was reported, both leading to a lysine-for-asparagine substitution at codon 540 (4,7,21,22,23,25). Other mutations have been reported (4,7). All mutations were in the transmembrane domain of *FGFR3*. Clinically, no differences have been found in patients with different mutations in *FGFR3*. Some reports did not find clinical differences in patients linked and unlinked to 4p16.3 (4,7), others found differences: patients linked to *FGFR3* were found to have more often macrocephaly, large forehead, short hands, and disproportionate shortening of the back (22,23,25). A very severe mutation is that of Asn540Lys (10). This has been confirmed by R. Hennekam.

Diagnosis is difficult and is often made by exclusion. It is not commonly established in the newborn period (15), although Hall and Spranger (11) noted that 66% were macrocephalic at birth. Short stature is not usually recognized until approximately 22 months of age. Final height attainment varies between 128 and 153 cm (mean for males, 146 cm; mean for females, 137 cm) (2,3,10,15,29). Clinical and radiographic features are summarized in Table 7–3.

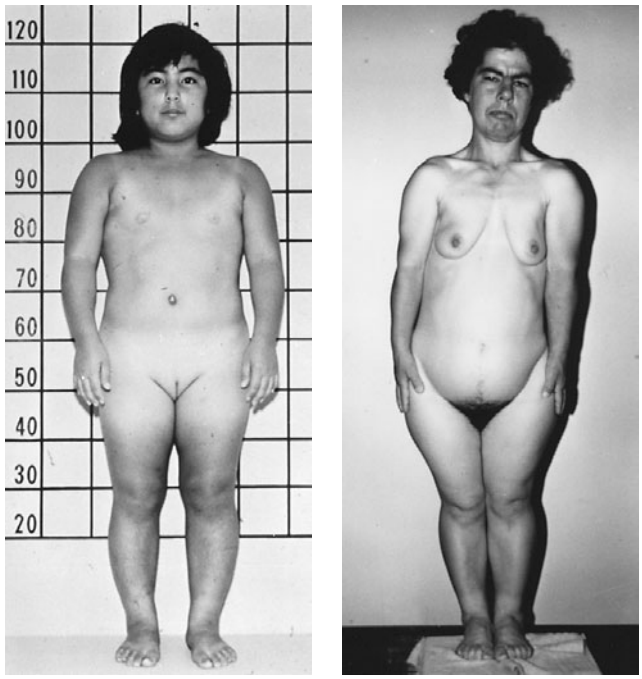

Fig. 7–11. *Hypochondroplasia.* (A,B) Disproportionately short limbs. (A courtesy of DL Rimoin, Los Angeles, California. B from MM Cohen Jr, The Child with Multiple Birth Defects, Raven Press, New York, 1982, p 103.)

The skull may be rectangular in shape with a slightly prominent forehead. Facial appearance is normal. Macrocephaly is present in 57% of all cases and in two-thirds of newborns. Cloverleaf skull has been found in one patient (1). Mental retardation is found in approximately 10% (10), but others have suggested this to be an overestimation (31). A family with an *FGFR3* mutation has been described in which one member had mild developmental delay, with the others being normal, which suggests the influence of other environmental or genetic factors (7).

Bowlegs appear in early childhood but tend to straighten spontaneously with age. The limbs are disproportionately short (100%), elbow extension is limited (100%), and brachydactyly is mild to moderate (97%). Lumbar lordosis is observed in about 35% of cases. Mild joint pain during exercise is often observed in adults (3,29). Patients may have a rather muscular appearance.

Radiographically, interpediculate distances are moderately narrowed, pedicles are shortened anteroposteriorly, and vertebral bodies of the lumbar spine have increased dorsal concavity. Tubular bones are shortened and relatively squared. The femoral neck is broad and short. The distal end of the fibula is elongated in relation to the tibia. The ilia are squared and shortened (3,11,15,19,29). Rarely, basilar impression may be found, as in achondroplasia (30).

For delivery, cesarean section may be necessary. Prenatal diagnosis has been reported in a fetus at risk for hypochondroplasia (13,28). Ultrasound examination at 22 weeks showed decreased length of limb bones by measurement in one fetus; the other was found to show a discrepancy at 35 weeks between limb length and head circumference.

Differential diagnosis. Differential diagnosis includes achondroplasia, which is similar but much more severe both clinically and radiographically. In achondroplasia, both the craniofacial appearance and the pelvic configuration are very distinctive in contrast to those in hypochondroplasia. In achondroplasia–hypochondroplasia compound, clinical and

Table 7–3. Clinical and radiographic features of hypochondroplasia

Striking features	Approximate percentage
Clinical	
Macrocephaly	57
Mental retardation	10
Disproportionately short limbs	100
Limited elbow extension	100
Mild-to-moderate brachydactyly	97
Lumbar lordosis	34
Tubular bones	
Short broad femoral neck	92
Short long bones with mild metaphyseal flare	100
Long distal portion of fibula	92
Long distal portion of ulna	73
Long ulnar styloid[a]	68
Lumbar spine	
Narrow or unchanged interpedicular distance	80
AP shortening of lumbar pedicles (lateral view)	89
Dorsal concavity (lateral view)	81
High vertebrae (lateral view)	33
Platyspondyly (lateral view)	37
Pelvis	
Squared shortened ilia	100

Adapted from BD Hall and J Spranger, Radiology 133:95, 1979 and NG Heselson et al, Clin Radiol 30:79, 1979.
[a] Presence related to age.

radiographic findings are different from those of achondroplasia or hypochondroplasia (16,26).

Long bone changes in hypochondroplasia may be similar to those in metaphyseal chondrodysplasia, Schmidt type, although the vertebral abnormalities of hypochondroplasia are not present in the Schmidt type.

Desch and Horton (6) reported an autosomal recessive bone dysplasia resembling hypochondroplasia. In the former condition, birth length was much less than normal, the interpediculate distances were normal, and the humeri were shortened with no significant shortening of the tibiae and the ulnae, no significant brachydactyly, and normal head circumference.

Finally, hypochondroplasia may be confused with familial short stature at the lower end of the normal curve in the general population.

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Acrodysostosis

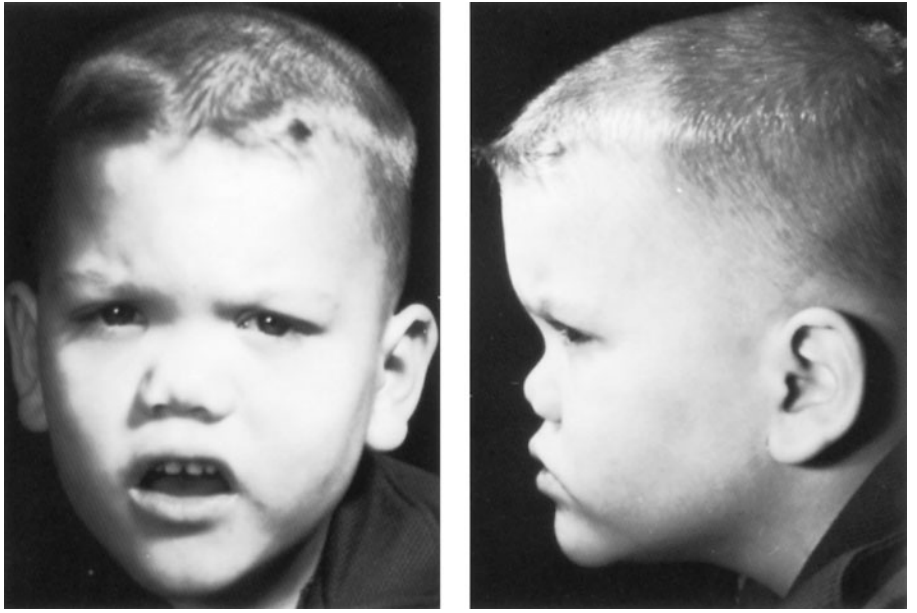
First reported by Arkless and Graham (2), Giedion (6), and Maroteaux and Malamut (10), acrodysostosis has undergone several reclassifications, finally emerging to stand on its own (13). It consists of short stature, severe brachydactyly, nasal hypoplasia, and varying degrees of mental retardation. Spinal stenosis and its complications have been a radiographic feature seen in 75% of cases (3) but only rarely is it symptomatic (7,9). About 85 cases have been reported to date.

Although most examples are sporadic, inheritance is autosomal dominant (1,5,8,10,14). New mutations are associated with advanced paternal age (7). The sibs born to normal parents possibly represent gonadal mosaicism (15). Normal Gs-α activity has been found (18).

The face is round, the nose is flat and short (Fig. 7–12). The cheeks are flat. Blue eyes have been noted in Japanese individuals (11).

Radiographic changes include brachycephaly, thick calvaria, hypoplastic nasal and maxillary bones, absent nasal spine, relative mandibular prognathism, peripheral dysostosis (short metacarpals, metatarsals, and phalanges), cone-shaped epiphyses, premature skeletal maturation, epiphyseal and vertebral stippling in infancy, narrow interpediculate distances, and relatively broad halluces (1,5–7,11,12,17) (Fig. 7–13).

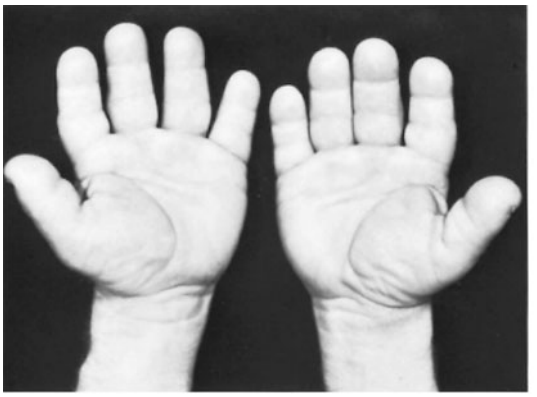
Mental retardation has been found in almost 80% of patients. The hands and feet are less severely involved in pseudohypoparathyroidism and pseudopseudohypoparathyroidism. Endocrine abnormalities are not found in acrodysostosis (1). We believe that the case of Davies and Hughes (4) is not acrodysostosis. In at least one case, resemblance to Marshall syndrome was pointed out (16).



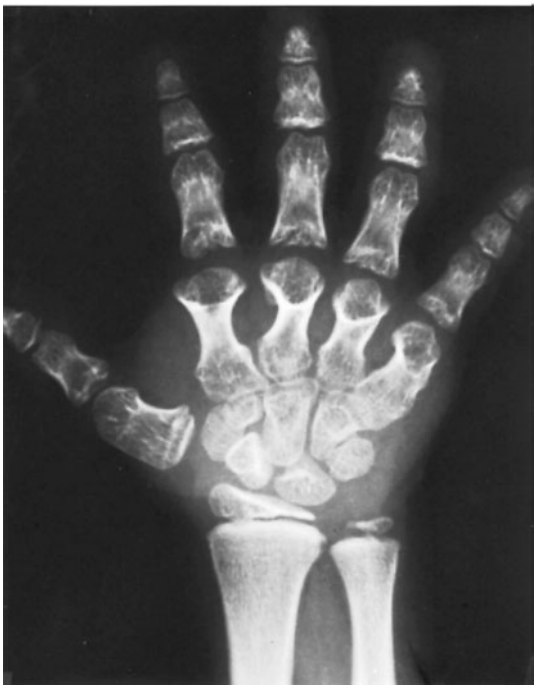
A B

Fig. 7–12. *Acrodysostosis.* (A,B) Marked hypoplasia of nose and midface. (From M Robinow et al, Am J Dis Child 121:195, 1971.)

Fig. 7–13. *Acrodysostosis.* (A) Hands are short and stubby. Feet are similarly deformed. (B) Radiograph shows shortened metacarpals and phalanges. (C) Radiographic shows similar alterations in another patient. (A,B from A Giedion, Fortschr Geb Roentgenstr Neuen Bildgeb Verfahr 110:507, 1969. C from S Reiter, Pediatr Radiol 7:53, 1978.)



A



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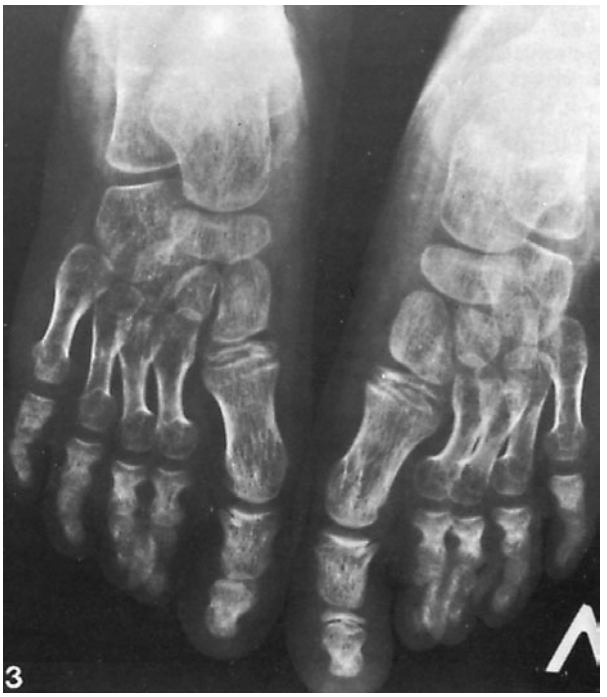

C

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Acromesomelic dysplasia

In 1971, Maroteaux et al (20) defined a rare short-limbed dwarfism that they termed "acromesomelic dysplasia." There are earlier recorded cases (10,18), and an 11,000-year-old acromesomelic skeleton was exhumed in southern Italy (11). Approximately 40 examples of the disorder have been documented (1–5,7–9,14–16,21–26). There are two types of acromesomelic dysplasia: acromesomelic dysplasia in the strict sense, which has also been called the "(Maroteaux-) Campailla-Martinelli type," and a more severe Hunter-Thompson type (12,17), which resembles chondrodysplasia, Grebe type. Both severe Hunter-Thompson type and chondrodysplasia, Grebe type are caused by mutations in cartilage-derived morphogenetic protein (CDMP1) (28,29) located at 20q11.2. When mutated, the protein CDMP1 cannot be secreted. It produces a dominant negative effect by preventing secretion of other bone morphogenetic proteins (BMPs), probably by the formation of heterodimers (27,29). Mutations in CDMP1 may also cause a very mild phenotype in heterozygous expression, i.e., in autosomal dominant brachydactyly type C (29). Acromesomelic dysplasia was found to be linked to chromosome 9q12–22.2 in four families (12a,14). Kant et al (14) noticed that this is the same region in which familial hypomagnesemia was mapped, whereas Minty and Hall (21) reported a family with both disorders.

Diagnosis is usually not made until about 2 years of age. Inheritance is autosomal recessive. There has been parental consanguinity (3,20), and sibs have been affected (7,14,15,18,20,21,25). However, there is one report of acromesomelic dysplasia in a father and son (22).

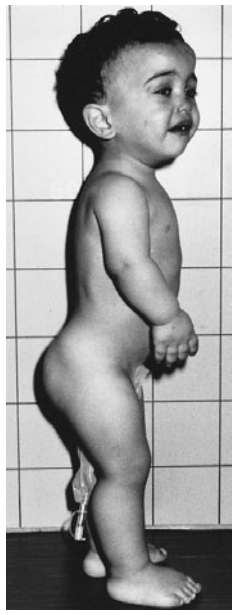


Fig. 7–14. *Acromesomelic dysplasia.* Relatively large head, frontal bossing, low nasal bridge, short forearms and hands, and lumbar lordosis. (From M Raes et al, Helv Paediatr Acta 40:415, 1985.)

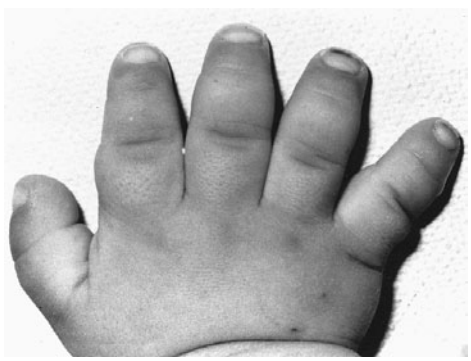
The disorder is characterized by disproportionate short stature. Adult height ranges from 94 to 123 cm. Puberty may be delayed. The fingers and toes are particularly abbreviated. The forearms are relatively shorter than the lower legs. The arms are often bowed whereas the legs are straight. The facies is characterized by frontal bossing, low nasal root, and slightly flattened midface (Figs. 7–14 and 7–15). Rarely, hydrocephaly with mild developmental delay (5) and corneal ulcers (4) are found. Low thoracic kyphosis and lumbar hyperlordosis are common. Hyperlaxity of joints, particularly of the hands and feet, is marked.

Radiologic changes include frontal bossing and marked occipital prominence and generalized shortening of long bones with metaphyseal flaring. The radii are bowed, and there is increased distance between the ulnae and carpal bones. The metacarpals, metatarsals, and phalanges are extremely short, the latter being cone shaped. There is premature fusion between epiphyses and metaphyses. Vertebral height is reduced, particularly in the thoracolumbar region with anterior beaking (Figs. 7–16 and 7–17).

Differential diagnosis includes *pseudohypoparathyroidism* and pseudoachondroplasia. In the former, the vertebral changes seen in acromesomelic dysplasia are absent. The nose is smaller and mental retardation is common. *Acrodysostosis* must also be excluded.

Some other unusual disorders with acromesomelia have been described. Israel and Vasan (13) noted a condition with acromesomelic

Fig. 7–15. *Acromesomelic dysplasia.* Broad hand with short, stubby fingers. (From M Raes et al, Helv Paediatr Acta 40:415, 1985.)



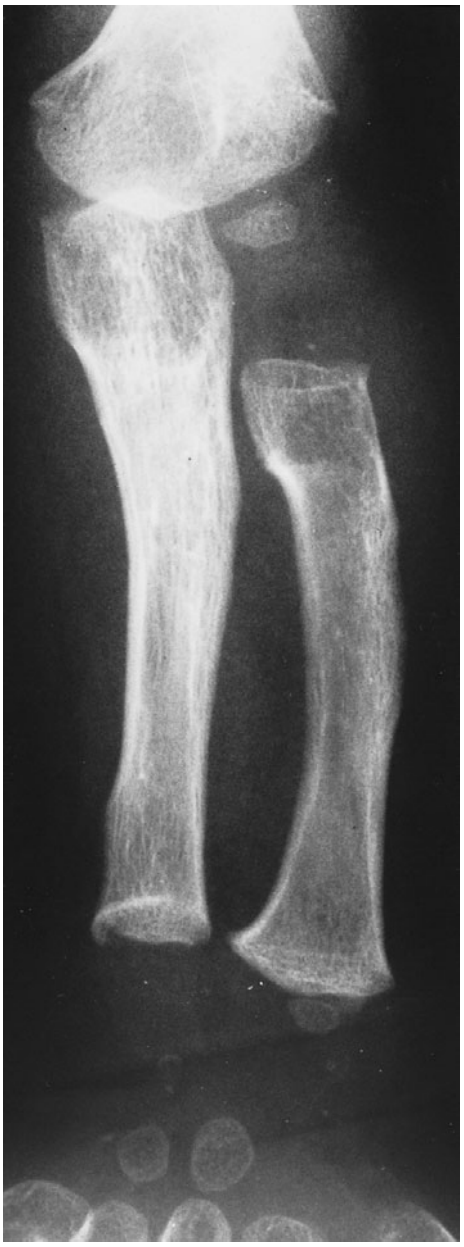
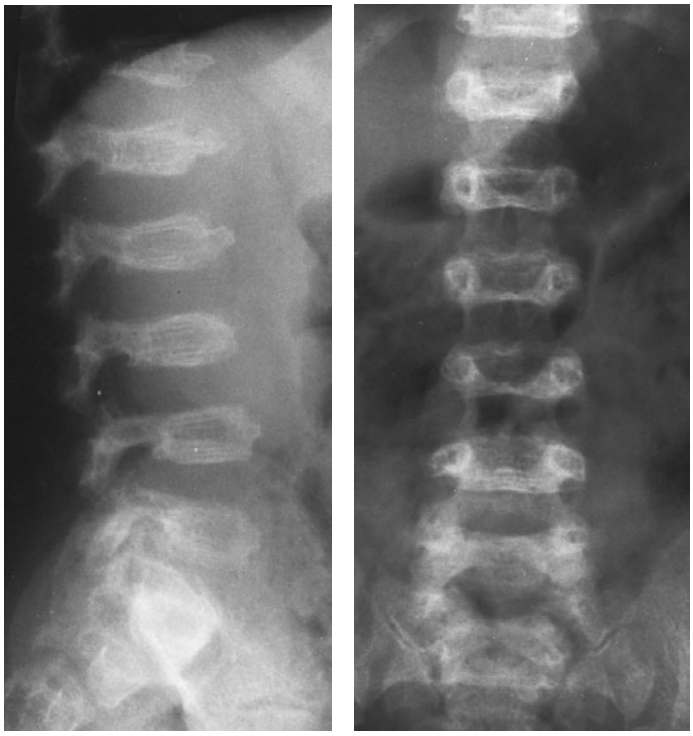


Fig. 7–16. *Acromesomelic dysplasia.* Short bent radius and ulna, and increased radioulnar distance. (From M Raes et al, Helv Paediatr Acta 40:415, 1985.)

dysplasia; bony abnormalities of the cervical spine, pelvis, ribs, and long bones; atrial septal defect (ASD), webbed esophagus; and stenosed larynx. The case was sporadic and chromosomes were normal. Leroy (19) observed two unrelated infants with acromesomelic dysplasia, growth and psychomotor retardation, synophrys, small nose, and flat face, giving a mild de Lange-like appearance. Ferraz et al (6) described a mother and son with acromesomelic dysplasia, as well as curved radii, marked shortening of the second and fifth finger, and angulation of the distal ulna in the mother. Pfeiffer et al (25) described an acromesomelic disorder with renal and facial changes. The head was large and there was congenital ptosis and telecanthus. Ureteral stenosis with hydronephrosis was seen. Bone abnormalities consisted of ulnar dysplasia, tibial hypoplasia, multiple synostoses of carpal and tarsal bones, proximal synostoses of metatarsals, and brachydactyly.

Also see *Verloes-David syndrome*.



A B

Fig. 7–17. *Acromesomelic dysplasia.* (A,B) Vertebral bodies show reduced vertical height and anterior beaking. (From M Raes et al, Helv Paediatr Acta 40:415, 1985.)

References (Acromesomelic dysplasia)

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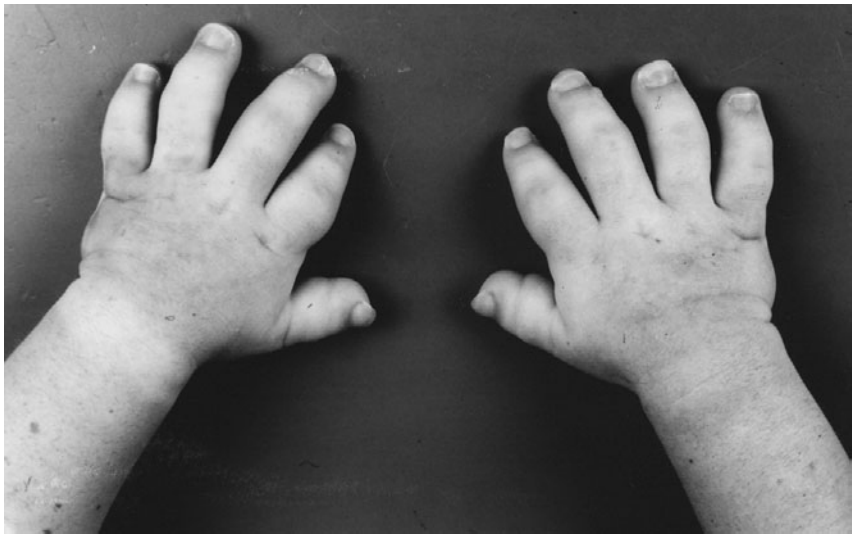
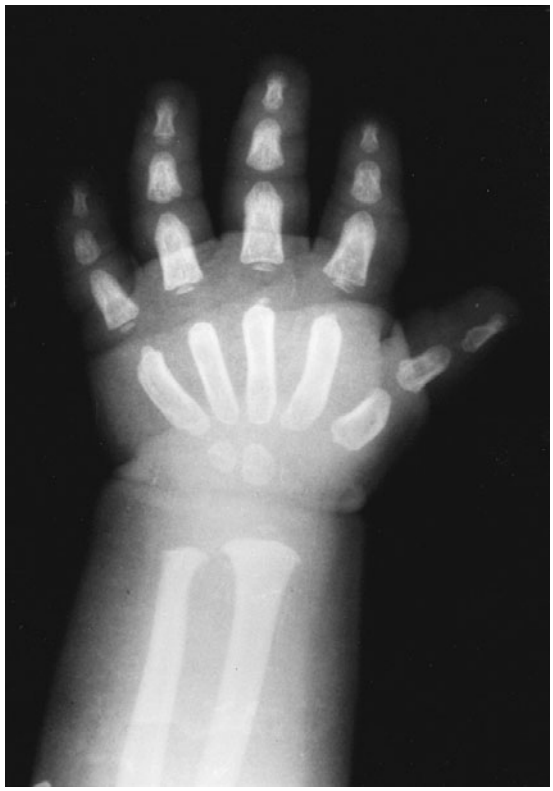


A



B

Fig. 7–18. *Acromicric dysplasia.* (A,B) Short, stubby fingers and thumbs. (From RCM Hennekam et al, Eur J Pediatr 155:311, 1996.)

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Acromicric dysplasia

In 1986, Maroteaux et al (4) described six isolated patients with short stature, mild facial anomalies, brachydactyly, and diminished joint movements (Fig. 7–18). Several authors described possible examples who, in addition, had symptoms of geleophysic dysplasia (2,3,5) or Moore-Federman syndrome (1a,6). It has been suggested that geleophysic and acromicric dysplasia are identical, allelic, or different disturbances in the same metabolic pathway (2,5,6). Faivre et al (1), in a survey of 18 examples, noted dominant transmission in three cases. The face shows narrow palpebral fissures and a short stubby nose with anteverted nostrils. One patient had cleft lip.

Height is far below the third centile. The limbs are short, but, in comparison, the hands and feet are even shorter. Flexion in fingers and toes may be limited (Fig. 7–18).

There are no major internal anomalies. One patient was noted to have atrial septal defect. None of the original patients showed any clinical symptom of a storage disorder. However, two patients with features that resembled those of both geleophysic and acromicric dysplasia had progressive thickening of cardiac valves (2,5) or enlarged liver and thickened skin (2). Histologically, there was considerable accumulation of glycogen in most chondrocytes (3,4); in another patient, this was lacking (2).

Radiologically, the metacarpals and phalanges are short and stubby with cone-shaped epiphyses. The proximal portion of the last four metacarpals is somewhat pointed with a notch at the base of the second (external) and fifth (internal) metacarpals. The femoral heads are slightly deformed, but otherwise, the long bones are normal. Bone age is delayed. The remainder of the skeletal frame is normal. There is no spondyloepimetaphyseal dysplasia.

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Table 7–4. Clinical findings of atelosteogeneses types I, II, and III and boomerang dysplasia

	Atelosteogenesis			
	Type I	Type II	Type III	Boomerang dysplasia
Clinical data				
Prominent forehead	++	++	−	+/−
Hypertelorism	+	+	++	++
Midface hypoplasia	++	+/−	++	+
Cleft palate	+	++	+	+/−
Micrognathia	+	++	++	+
Short thorax	++	+	++	++
Very short limbs	++	++	++	++
Syndactyly	−	+/−	+	++
Oligodactyly/polydactyly	−	−	+	+
Hitchhiker thumb/hallux	−	++	−	−
Dislocations[a]	+	+	++	−
Talipes equinovarus	++	+		+/−
Survival beyond neonatal period	−	−	++	−
Radiological data				
Poorly ossified calvarium	−	−	−	+
Platyspondyly	++	++	++	+
Coronal clefting lumbar vertebrae	++	+/−	++	++
Hypoplastic pubic bones	+	+/−	+	++
Rounded iliac wings	+	++	+/−	++
Horizontal acetabulae	+	++[b]	++	+
Severe hypoplastic humerus	++	D	+/D	++
Bowing of long bones	+	+	+	++
Dysharmonious ossification of small hand bones	+	++	−	++
Absent ossification fibula	++	−	+	++
Severe hypoplastic calcaneus	++	++	++	++

Adapted from HJ Stern et al, Am J Med Genet 36:183, 1990.
++ (75%–100%); + (25%–75%); +/− (<25%); − (absent); D, distally pointed.
[a]Dislocations of hip or elbow.
[b]Occurs sometimes with medial spicules.

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Atelosteogenesis type I

Atelosteogenesis, a term derived from the Greek referring to incomplete bone formation and coined by Maroteaux et al (9), is a rare neonatally lethal chondrodysplasia characterized by marked rhizomelic shortening of limbs. Later, it became clear that atelosteogenesis encompasses a heterogeneous group of disorders with overlapping features (13). A dozen cases of atelosteogenesis type I have been reported, all isolated examples (1,2,5–15). Hence, the pattern of inheritance of the disorder remains uncertain. Each may represent a new autosomal dominant mutation or there may be an insufficient number of cases for affected sibs to have been born. Several cases, for instance, those of Maroteaux et al (9), are hard to classify and, furthermore, there may be variable expression. A comparison of atelosteogenesis types I, II, and III and Boomerang dysplasia is given in Table 7–4. The difference between type I and Boomerang dysplasia may be especially difficult (3,4). One case with type I was erroneously classified as type II (10). Atelosteogenesis type I has also been called "giant cell chondrodysplasia" and "spondylohumerofemoral hypoplasia" (11,12).

The facies is characterized by frontal bossing, prominent globes, edematous eyelids, depressed nasal bridge, hypoplastic nose, micrognathia, and short neck (Fig. 7–19). Some patients have cleft palate. Laryngeal stenosis has been described (1,15). The extremities are shortened rhizomelically and talipes is usually severe. Male infants have cryptorchidism. In some cases, there has been polyhydramnios.

Radiographically, there is hypoplasia of the distal humeri and often of the distal femora. The fibulae may be hypoplastic or absent. In some examples, the forearm bones may be hypoplastic. The vertebral bodies are hypoplastic with coronal clefts, and there is uneven ossification of most of the proximal and middle phalanges of hands and feet. The pubic bones may be small but otherwise the pelvis is essentially normal (Fig. 7–20).

Histopathologic changes include clusters of chondrocytes surrounded by fibrous capsules and zones containing degenerated chondrocytes and copious amounts of metachromatic material in the epiphyses and basal zone of the growth plate (1,9). Multinucleated giant cells may be scattered throughout the resting cartilage (12,13,15); however, they are not specific for the disorder (11,15).

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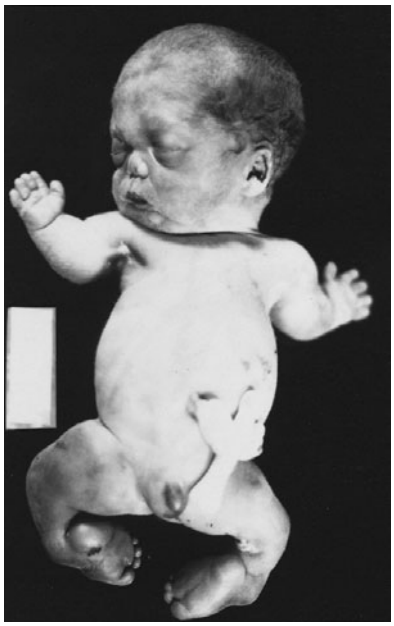

Fig. 7–19. *Atelosteogenesis*, *type I.* Low nasal bridge, rhizomelic shortness, and severe talipes equinovarus. (From SS Yang et al, Am J Med Genet 15:615, 1983.)

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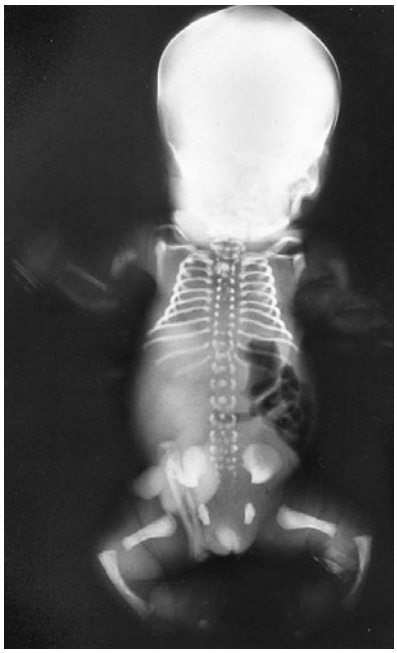
Fig. 7–20. *Atelosteogenesis, type I.* Severe ossification deficiency of vertebral bodies, eleven pairs of ribs, and agenesis of fibulae. Humeri and femora are shortened, with rounded proximal and tapered distal ends. (From SS Yang et al, Am J Med Genet 15:615, 1983.)



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Atelosteogenesis type II (De la Chapelle syndrome)

In 1972, De la Chapelle described a pair of sibs with a distinctive form of short-limb dwarfism, deficient ossification of different parts of the skeleton, cleft palate, and neonatal death (2). Whitley et al (13) reported another affected sib from the original family and a solitary case, and coined the term "De la Chapelle dysplasia," which was subsequently replaced by "atelosteogenesis type II" (11). Twenty cases have been described (2,5,6,8,10–13; RCM Hennekam, unpublished observations). Reviews were provided by Schrander-Stumpel (10), Sillence (12), and Newbury-Ecob (7). Inheritance is autosomal recessive (2). Chromosomal studies have yielded normal results. Mutations in the ubiquitously expressed sulphate transporter *DTDST*, located on chromosome 5q, and found to be responsible for diastrophic dysplasia and achondrogenesis type 1B were found in atelosteogenesis type II (3). For further discussion of the *DTDST* gene, the reader is referred to the diastrophic dysplasia section (below).

The facies is characterized by frontal bossing, flat nasal bridge, and short neck. About 50% of patients have cleft palate. The trunk and limbs are markedly shortened and incurved, the abdomen is protuberant. The thumbs and halluces are radially deviated ("hitchhiker" position) and the halluces and second toes are widely separated. Feet are held in the equinovarus position (Fig. 7–21A,B). Omphaloceles have been reported (12).

Radiographically, the vertebral bodies are moderately flattened. Some infants have mild scoliosis, but there is marked kyphosis of the cervical spine with hypoplastic/dysplastic changes and horizontal sacrum. The iliac bones are rounded with shortened sacrosciatic notches and flat acetabular roofs, sometimes with medial spiculae. The ischial and pubic bones are usually well formed with additional ossification centers. The limb bones are short, particularly proximally, with metaphyseal flaring. The end of the distal humerus manifests a U- or V-shaped depression and the distal femur can be rounded. The radius and tibia are particularly bowed. The distal ulna is often hypoplastic and the proximal ulna can be broad. The second and/or third metacarpals and the first and second metatarsals are usually larger than the remaining bones of the hand or foot. Some of the middle phalanges have double ossification centers (Fig. 7–21D–F). Bronchial rings are irregular in contour and, in some areas, there is increased perichondral fibrous tissue. The reserve zone of the cartilage can be attenuated with many cystic areas containing only radiating threads of matrix (Fig. 7–21C) (5).

Because of the "hitchhiker thumb and hallux," *diastrophic dysplasia* must be excluded (3,9). *Atelosteogenesis type I* can be excluded on histopathologic and radiologic grounds (Table 7–4). An unusual variant was reported by Herzberg et al (4), but because of the gestational age, adequate evaluation is difficult. A still different type was described by Brodie et al (1), which included mesomelia and distal tapering of the humerus, but with different histology and ultrastructural findings.

References [Atelosteogenesis type II (De la Chapelle syndrome)]

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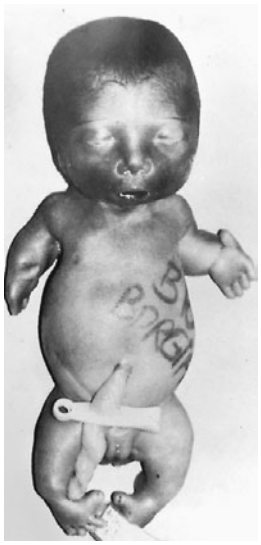

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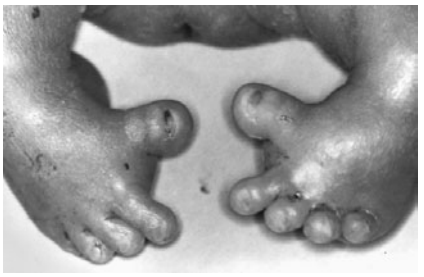

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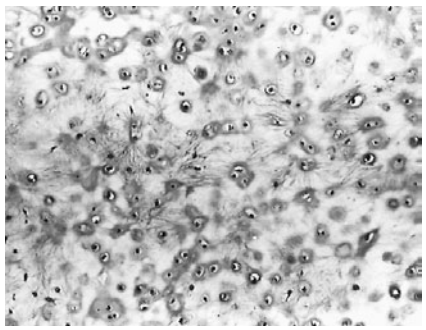

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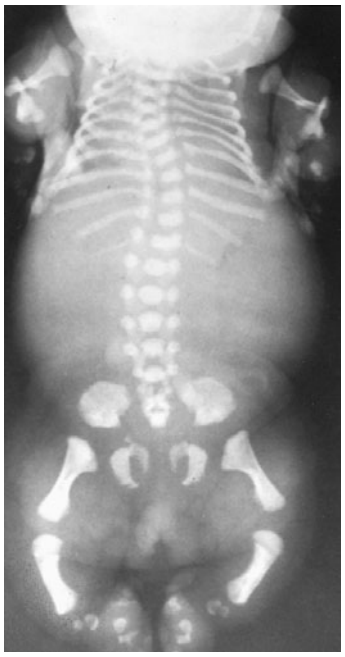

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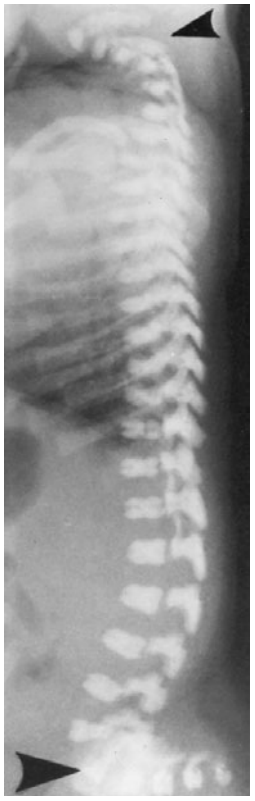

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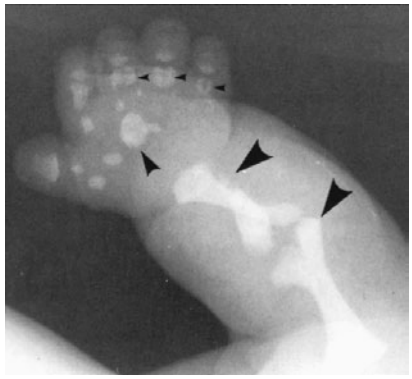

F

Fig. 7–21. *Atelosteogenesis, type II.* (A,B) Short-limbed dysplasia with hitchhiker thumbs and toes, ulnar deviation of fingers, talipes equinovarus, and wide separation between halluces and second toes. (C) Cartilage matrix showing cystic changes and thread-like attenuations of matrix. H&E, ×150. (D,E) Short ribs, rounded ilia, additional ossification centers at ischial and pubic bones, moderate scoliosis, platyspondyly, cervical kyphosis with dysplastic vertebrae, and horizontal sacrum. (F) Large third metacarpal, small remaining metacarpals, and double ossification centers of some phalanges (small arrows) are apparent as are hypoplastic distal ulna and V-shaped distal humerus (large arrows). (From DO Sillence et al, Pediatr Radiol 17:112, 1987.)

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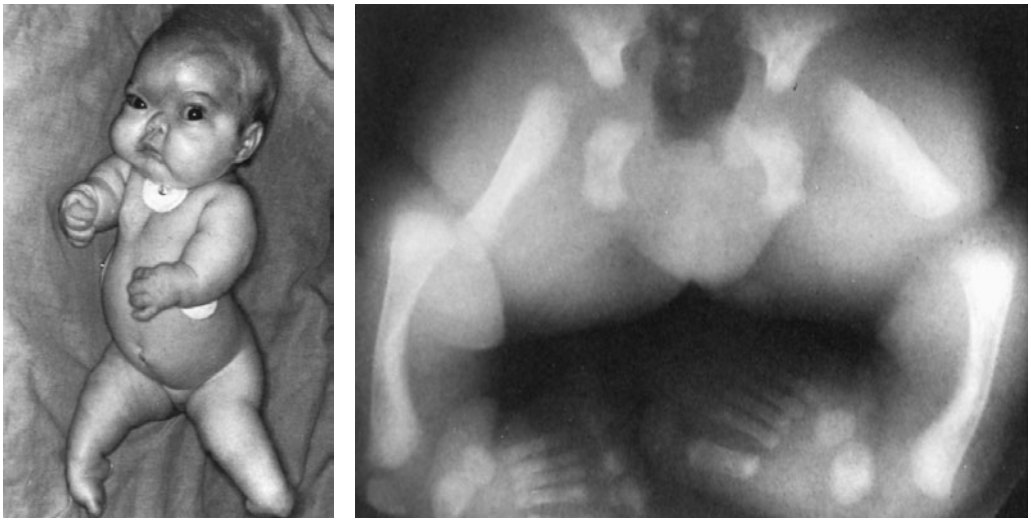
Atelosteogenesis type III

Stern et al (5) delineated a milder, usually nonlethal disorder with features overlapping those of atelosteogenesis type I and type II (Table 7–4). Several other cases have been reported (1–4). All were singletons, with males and females being equally affected, and no consanguinity was reported. There may be overlap with Larsen syndrome, with which it is possibly allelic (4). There is some suggestion of autosomal dominant inheritance (3).

The forehead is broad, the eyes are widely spaced, and the midface and especially the nose are hypoplastic (Fig. 7–22A). The nasal bridge is flat. Half of the patients have cleft palate. Laryngeal hypoplasia is common.



A B

Fig. 7–22. *Atelosteogenesis, type III*. (A) Broad forehead, widely spaced eyes, hypoplastic midface, especially the nose, and short limbs. (B) Marked shortness of femora, multiple joint dislocations, and talipes. (From HJ Stern et al, Am J Med Genet 36:183, 1990.)

Patients with atelosteogenesis type III show a short-limb dwarfism with prominent shortness of the humerus and femora, multiple joint dislocations, camptodactyly, ulnar deviation of fingers, and talipes (Fig. 7–22B). The tips of the fingers are broad, the nails are wide. Polydactyly has been reported (5). There may be cutaneous syndactyly of the second and third toes.

Radiologically, the calvaria is normal, and platyspondyly, scoliosis, coronal and sagittal clefting, and cervical segmentation defects are evident. The clavicles may be wavy or elongated. Both femurs and humeri show distal tapering. The tibia, radius, and ulna are bowed, and ossification of the fibula is absent. Metatarsals are short, proximal phalanges are squared, the middle phalanges are rounded, and the distal phalanges are widened. Histopathological studies did not show giant multinucleated chondrocytes, but only hypocellularity.

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Lethal skeletal dysplasia with gracile bones (osteocraniostenosis)

In 1988, Maroteaux et al (6) described a lethal condition characterized by thin brittle bones. To date, about 15 cases of this possibly heterogeneous condition have been reported (1,1a,2,5–10). The sibs described by Dennis et al (3,4) probably represent another condition.

Although almost all cases have been sporadic, in some cases, there has been parental consanguinity (6), and siblings have been reported by Costa et al (2). Perhaps this represents somatic mosaicism.

Radiographic findings suggest two phenotypes. Type I is characterized by narrow metaphyses, mildly reduced mineralization of the calvaria, and deformed hands and feet. Type II exhibits relative flaring of the metaphyses, poor mineralization of the calvaria, and, rarely, cloverleaf skull, small mouth, small nose, hypoplastic supraorbital ridges, and asplenia/hyposplenia. Cases 1–4 of Maroteaux et al (6) and cases 1–3 of Verloes et al (10) are type II.

References [Lethal skeletal dysplasia with gracile bones (osteocraniostenosis)]

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Boomerang dysplasia

The term "boomerang dysplasia" was coined by Tenconi et al (12) to describe a lethal short-limbed dwarfism. The name is reflective of the shape of the femur, ulna, and tibia (Figs. 7–23 and 7–24). Another example was reported earlier (5). In total, at least 10 patients have been reported (5–6,8–13). In four other cases, differentiation from atelosteogenesis type I (3,4) (Table 7–4), otopalatodigital syndrome type II (7), or Piepkorn syndrome (1) remains difficult. In describing a unique but related entity, Oostra et al (9) suggested that atelosteogenesis type I, Piepkorn dysplasia, and boomerang dysplasia constitute a family of skeletal dysplasias. It had been suggested earlier that the (female) infant with Piepkorn syndrome had, in fact, boomerang dysplasia (13). All but one were male, and all were isolated cases, except the male and his maternal

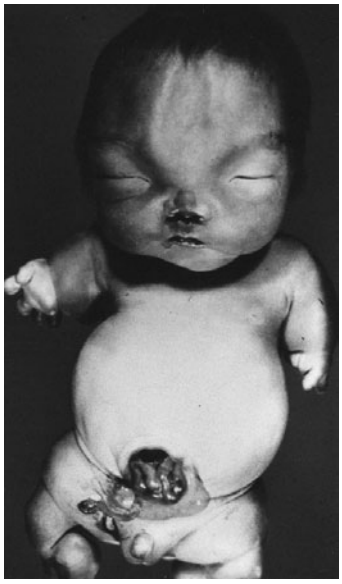


Fig. 7–23. *Boomerang dysplasia.* Facies similar to that seen in frontonasal malformation. In addition to short extremities, note four digits on each hand. (Courtesy of Y Sugiura, Nagoya, Japan.)

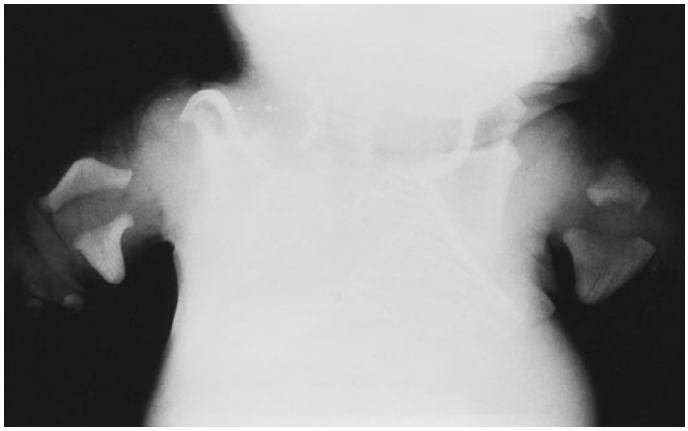
uncle reported in an abstract by Slaney et al (11), who suggested X-linked recessive inheritance.

Head circumference is large, the eyes hyperteloric, and the forehead is full. One patient had frontal encephalocele (13). The nasal root is broad, the nose small, the nostrils anteverted. The nasal septum and lateral cartilages are severely hypoplastic. The philtrum is prominent. The palate was cleft in one infant. Malar hypoplasia and micrognathia are present. The trunk is short, the abdomen prominent. Two patients had omphalocele. The limbs, particularly the upper limbs, exhibit rhizo- and mesomelic shortening with limited joint movement. The lower limbs are bowed anteriorly. The feet are in a calcaneovalgus position. Soft tissue syndactyly of the third and fourth fingers, hypoplasia of thumb nails, and partial duplication of the terminal phalanx of the index fingers are also found.

Radiographically, the radii and fibulae are missing, the ossification centers of the humeri are hypoplastic or missing, and the ulnae, femora, and tibiae are boomerang in shape. The metapodial bones are abnormal in form and the phalanges are not well ossified (Fig. 7–24B,C).

The bodies of the ilia are poorly formed and the pubic bones are absent. There are 13 pairs of ribs. Giant chondrocytes have been described (6,10).

Carpenter and Hunter (2) described a similar but nonetheless different case, which we find difficult to classify.



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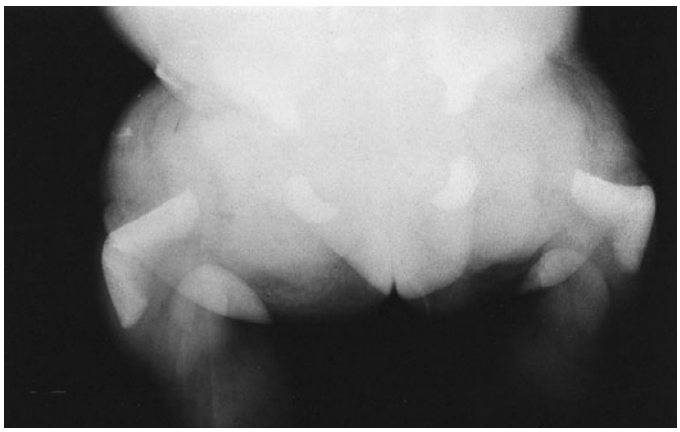

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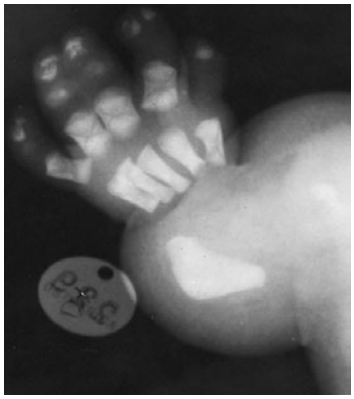

C

Fig. 7–24. *Boomerang dysplasia.* (A,B) Absent radii and fibulae with boomerang shaped ulnae, femora, and tibiae. The body of the ilia is poorly formed and pubic bones are absent. (C) Abnormal metapodial bones and poorly ossified phalanges. (A,B courtesy of Y Sugiura, Nagoya, Japan. C from K Kozlowski et al, Br J Radiol 58:369, 1985.)

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Fig. 7–25. *Burton syndrome.* Note pursed lips. (From BK Burton et al, J Pediatr 109:642, 1986.)

Burton syndrome

In 1986, Burton et al (1) reported male and female sibs with a Kniest-like skeletal dysplasia. In addition, there were microstomia, pursed lips, and dislocated lenses (Figs. 7–25 to 7–29). Lo et al (2) described a second, isolated patient without lens dislocation at 2 and 1/2 years.

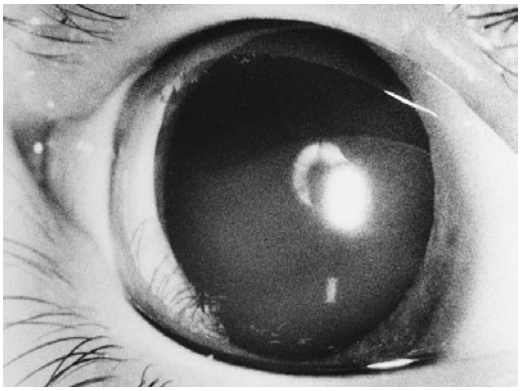
Growth was at the fifth centile. The face, other than having mild exophthalmos and a small mouth with pursed lips, was not distinctive but looked somewhat like the Schwartz-Jampel syndrome facies. In the sibs, bilateral downward subluxation of the lenses was noted at the ages of 11 months and 2 years (Fig. 7–26).

The limbs were short and bowed, and the joints were stiff and enlarged (Fig. 7–27). Radiographically, the long bones were somewhat dumbbell shaped with flared metaphyses and mildly shortened diaphyses (Fig. 7–28). The thoracic and lumbar vertebral bodies were somewhat flattened, and cervical kyphosis and increased lumbosacral angle were also evident. The chest was rather bell shaped and the pelvis exhibited somewhat narrowed sacrosciatic notches with a notched lateral margin of the acetabula and wide ilia (Fig. 7–29).

On iliac crest biopsy the cartilage showed scattered, dense patches within the matrix with disturbed column formation (1). The chondrocytes appeared large and mature rather than degenerated and typically hypertrophic. Within the scattered dense patches there were collagen bundles that were 10–30 times broader than normal.

The condition should be differentiated from *Kniest dysplasia, Freeman-Sheldon syndrome, Schwartz-Jampel syndrome, Larsen syndrome,* and metatropic dysplasia.

Fig. 7–26. *Burton syndrome.* Downward subluxation of lens. (From BK Burton et al, J Pediatr 109:642, 1986.)



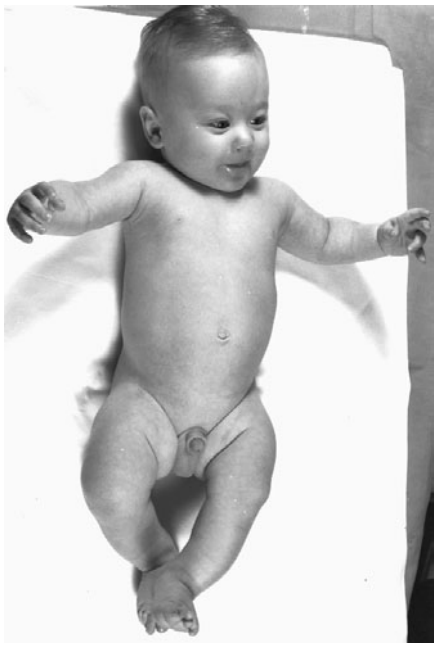


Fig. 7–27. *Burton syndrome.* Note short limbs. (From BK Burton et al, J Pediatr 109:642, 1986.)

References (Burton syndrome)

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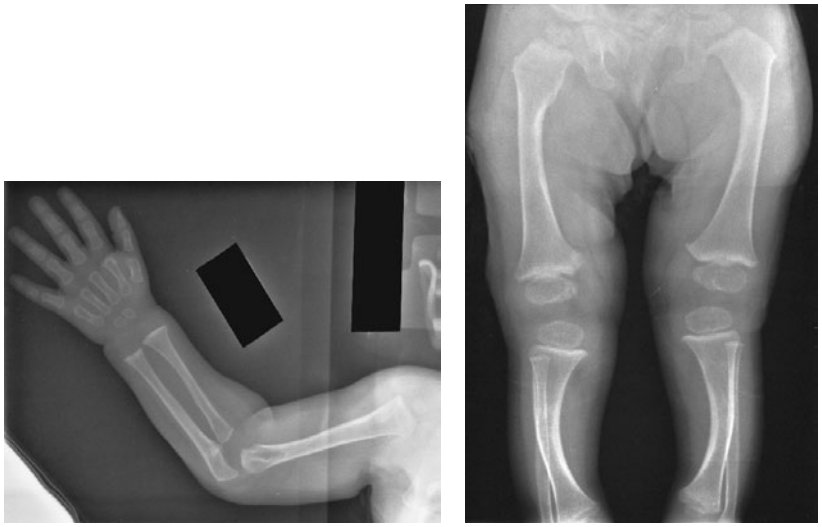
Campomelic dysplasia

Although described earlier by a number of authors (3,7,36), campomelic dysplasia (Figs. 7–30 and 7–31) was first recognized as an entity by Spranger et al (54) in 1970 and Maroteaux et al (35) in 1971. The name is derived from the Greek word "campto," meaning bent. Excellent reviews are available by Hall and Spranger (21), Beluffi and Fraccaro (6), Houston et al (24), and Mansour et al (33). Prevalence has been estimated from 1/100,000 births (55) to as high as 1.6/10,000 (44). At least 200 cases have been documented.

Early reports had assumed an autosomal recessive pattern of inheritance (13,15,21), mainly because of a slightly increased consanguinity rate and affected sibs (2,13,24,36,52,60,62,66). However, the number of affected sib pairs observed has been less than would be expected with an autosomal recessive condition (23,33); some patients were born to mildly affected parents (32,59), and affected half sibs have been born to apparently normal parents (64), all of which points to autosomal dominant inheritance. The chromosomal sex ratio is 1:1, and the phenotypic sex ratio is 3 F:1 M because of sex reversal in males (21,33). Sex-reversed infants are H-Y antigen negative (23,25,46).

There have been several reports of patients with a translocation or inversion involving chromosome 17q23.3–25.1 (33,34,43,61,68). Campomelic patients with a chromosome anomaly appear to have a much milder phenotype with less bowing. Location of the gene on 17q24.3 was favored by mutations that were detected in *SOX9* (8,28,37,57,63). The *SOX9* gene is a homolog of *SRY,* the mammalian Y-linked sex determining gene. *SOX9* is a transcription factor (67) expressed during chondrogenesis together with *COL2A1* (5,67) and during gonadal development (41). Complete deletion of the *SOX9* gene has been reported (45). Campomelic dysplasia without campomelia also maps to the *SOX9* gene (18,52a).

In about 50% of the cases, the child is either born dead or dies within the first 24 hr. Nearly all have succumbed by 10 months of age. A few have lived for many years (19,24,33). Hearing loss and mental retardation are common in all those that survive (24). At least 85% to 95% exhibit



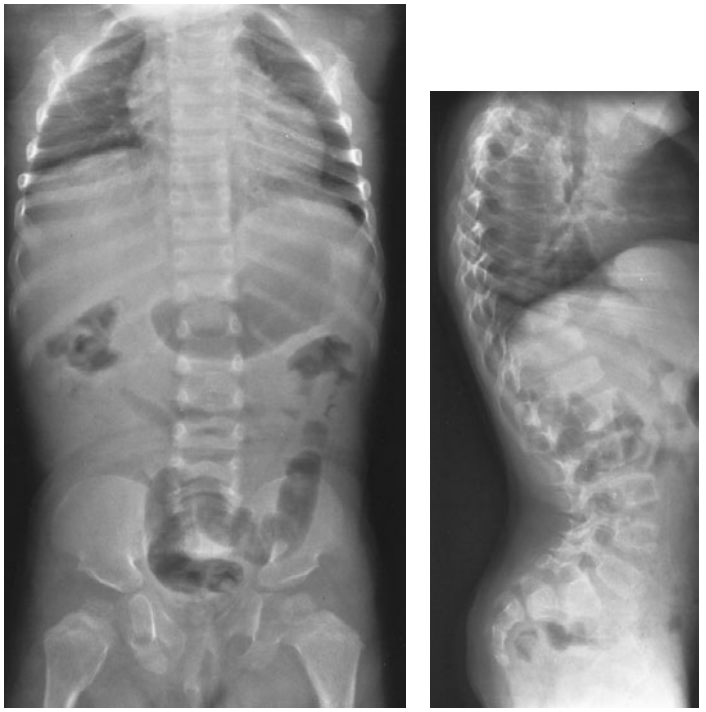
A B

Fig. 7–28. *Burton syndrome.* (A,B) Long bones are somewhat dumbbell shaped with flared metaphyses and mildly shortened diaphyses. (From BK Burton et al, J Pediatr 109:642, 1986.)

respiratory distress as a result of small thoracic cage, narrow larynx, hypoplastic trachea, and, possibly, CNS–based hypotonia. Polyhydramnios, beginning at about 32 weeks, is common.

Frequent craniofacial features are macrocephaly, dolichocephaly, large anterior fontanel and sutures, disproportionately small face, short narrow palpebral fissures, apparent hypertelorism, flat nasal bridge, low-set cartilage-poor pinnae, small nose with anteverted nostrils, long philtrum, small mouth, retroglossia, micrognathia, and short neck with redundant skin (39) (Fig. 7–30) (Table 7–5). Cleft palate is present in 65% to 80% of patients (6,33).

Fig. 7–29. *Burton syndrome.* (A,B) Thoracic and lumbar vertebral bodies are somewhat flattened. The chest is rather bell shaped and the pelvis exhibits somewhat narrowed sacrosciatic notches with notched lateral margin of acetabula and wide ilia. Note increased lumbosacral angle. (From BK Burton et al, J Pediatr 109:642, 1986.)



A B

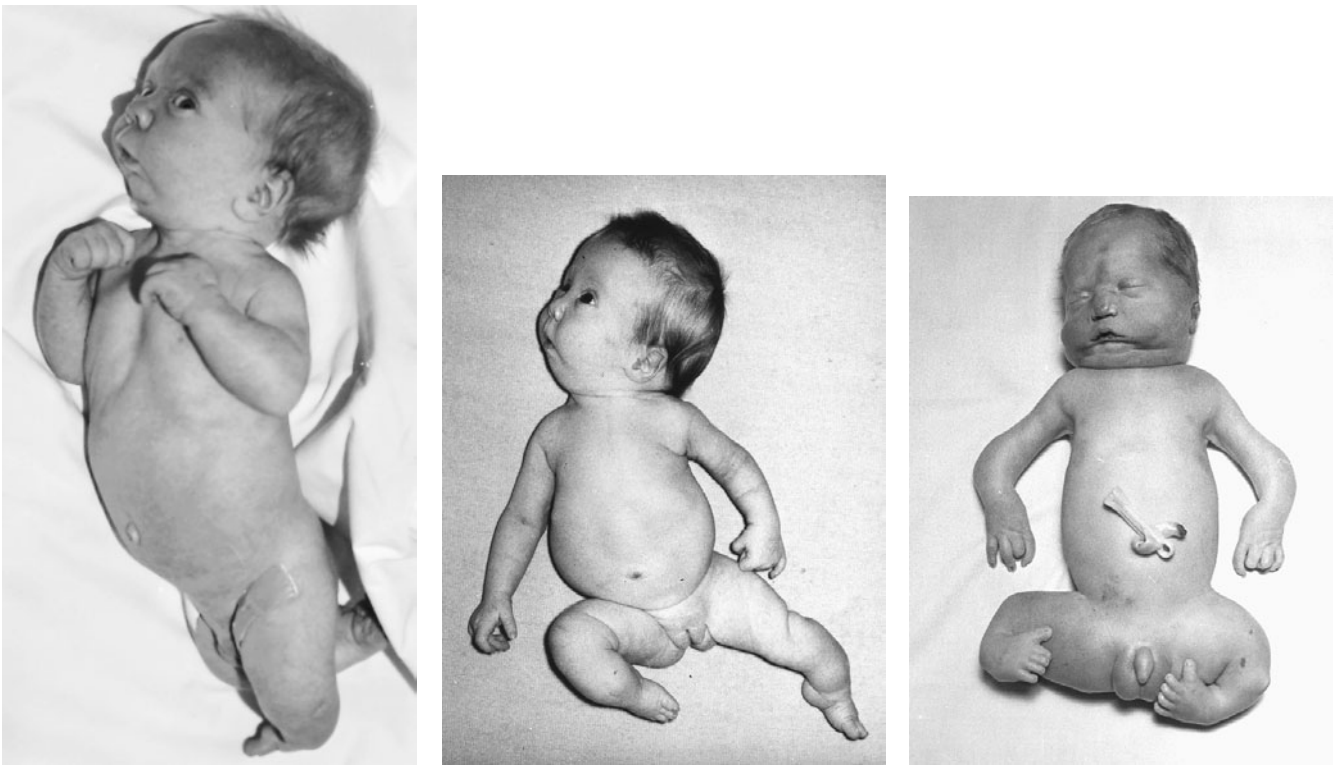
The long bones of the lower extremities are bent, but to varied degrees. Cases without campomelia have been published (14,15,18,20,30,32, 43,69). The genesis of bowing and shortening of the lower limbs has been discussed by Lazjuk et al (29) and Pazzaglia and Beluffi (47). The bones of the upper extremities are mildly bowed in 20% to 25%. The elbows may be dislocated. Pretibial skin dimples over the most convex site are found in about 90%. Talipes equinovarus is a very common feature. There is often a wide space between the hallux and the second toe.

Radiographic changes include tall narrow orbits (70%–90%), hypoplastic bladeless scapulae (90%), small bell-shaped chest (70%–80%), nonmineralized sternum (80%), slender ribs (60%–85%), 11 ribs (55%–70%), and abnormal vertebral bodies (particularly cervical) with nonmineralized pedicles (80%). The mandible may be cleft (1). Bowed shortened tibias and femurs, hypoplastic fibulas, narrow iliac wings with increased acetabular angles, late developing pubic bones, vertical and widely spaced ischia, and dislocated hips are very common (Fig. 7–31). The proximal tibial and distal femoral epiphyses are absent in 80%–95% of patients. The talus is nonmineralized in 80%. The hands exhibit

Table 7–5. Frequency (%) of findings in campomelic dysplasia

Clinical findings	
Macrocephaly	87
Flat nasal bridge	90
Low-set ears	88
Cleft palate	66
Micrognathia	93
Congenital hip dislocation	82
Bowed femora	69
Bowed tibia	91
Pretibial skin dimples	88
Talipes equinovarus	94
Radiologic findings	
Hypoplastic facial bones	70
Hypoplastic scapulae	92
Small, bell-shaped chest	72
Slender ribs	61
Abnormal cervical vertebrae	77
Vertically narrow iliac wings	93
Dislocated hips	85
Bowed femora	90
Bowed tibiae	82
Delayed ossification of distal femoral epiphysis	81
Absent ossification of talus	81

Adapted from S Mansour et al, J Med Genet 32:415, 1995.



A B C

Fig. 7–30. *Campomelic dysplasia.* (A–C) Note bent femora and tibiae, and micrognathia. The upper limbs are curved and there is a gap between the great toe and second toe in C. (A courtesy of JM Opitz, Helena, Montana. B courtesy of J Lindsten, Stockholm, Sweden. C courtesy of RE Stevenson, Greenwood, South Carolina.)

clinodactyly, brachydactyly, and small middle phalanges in 70% (6,21,33). Several cases of campomelic dysplasia without bowing (acampomelic) have been described (14,15,17,18,20,43,69).

Autopsy findings may show absence or hypoplasia of olfactory tracts or bulbs (25%), hydrocephalus (10%–25%), variable congenital heart anomalies [(VSD, ASD, PDA, tetralogy of Fallot, stenosis of aortic isthmus (20%–30%)], deficiency of laryngeal and tracheobronchial cartilages (30%–40%), and hydroureter and hydronephrosis (20%–30%) (50). Renal hypoplasia is also found. Sex reversal is frequent but not always completely so (10); some have ambiguous genitalia (46). Vascular anomalies, especially marked deficiency of the anterior tibial artery, have been described (48). The inner ears show no cartilage cells in the otic capsule and the ossicles are malformed (59).

Differential diagnosis. Kozlowski et al (27) described a few disorders with bent bones, but Hall and Spranger (22) listed almost 30 conditions having congenital bowing of long bones. Campomelic dysplasia must be distinguished from kyphomelic dysplasia and several other unusual conditions (49,51). Kyphomelic dysplasia is a somewhat heterogeneous group of disorders characterized by short, thick, and bent bones, generalized osteopenia, brown–green teeth, normal sclerae, and minimal fractures. In two cases, there was polyhydramnios. The changes resolve with time (22,49). Yet another autosomal recessively inherited disorder was described by Stüve and Wiedemann (9,12,26,53,56,58,65). The radiographic findings are different, and the feet are abnormally positioned. There is respiratory distress and recurrent periods of unexplained hyperthermia occur. In two patients, decreased activity of complexes I and IV of the mitochondrial respiratory chain was found (9). Several authors pointed to the have overlap between Stüve-Wiedemann syndrome and Schwartz-Jampel syndrome type 2 (12,53,58). Nakamura et al (42) described seven cases, including two sibs with congenital bowing of long bones of both upper and lower extremities, that improved with age. In addition, there were inconspicuous skin creases on the flexor side of elbows and knees and advanced bone age. Finally, there is another group of disorders that has scaphomacrocephaly, impaired CNS function, thin bones, bending limited to the femora, talipes, and, frequently, cleft palate (22). This form most closely resembles campomelic syndrome. A condition described by Stevenson (personal communication) (Figs. 7–30C and 7–31) may be a severe form of campomelic dysplasia.

Laboratory findings. The disorder has been diagnosed prenatally (4,11,66).

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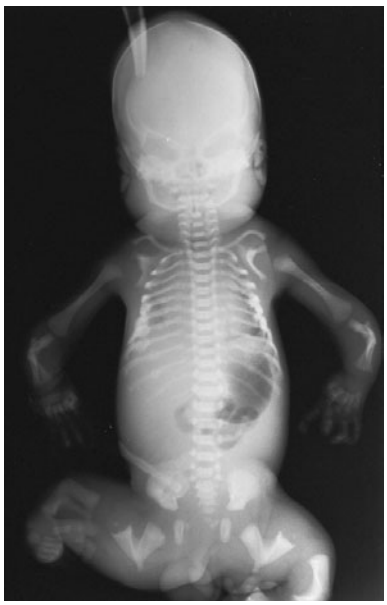

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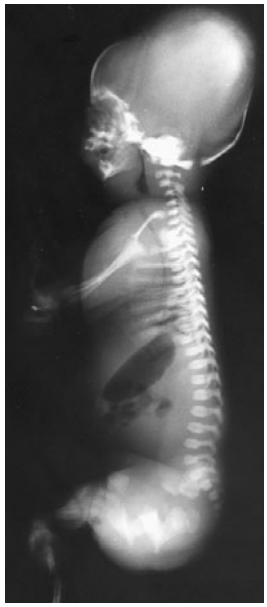

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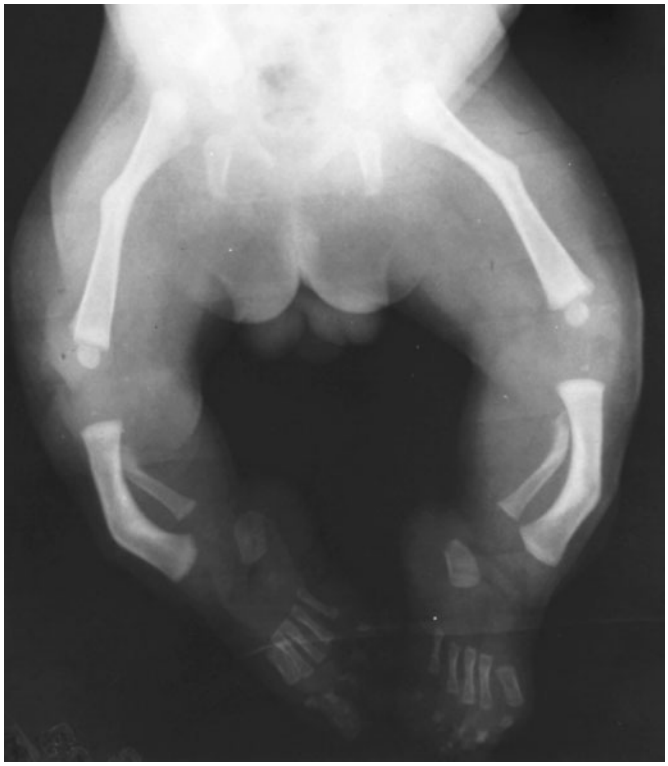

C

Fig. 7–31. *Campomelic dysplasia.* (A,B) Dolichocephaly, bowing of long bones, hypoplastic scapulae, small, bell-shaped chest, flattened vertebral bodies, narrow iliac wings with increased acetabular angles, and talipes equinovarus. (C) Radiograph showing campomelia. (A,B courtesy of RE Stevenson, Greenwood, South Carolina. C courtesy of JM Opitz, Helena, Montana.)

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Cartilage-hair hypoplasia (McKusick-type metaphyseal dysplasia)

In 1964–1965, McKusick et al (46,47) described a syndrome in the Old-Order Amish that was characterized by short-limbed dwarfism and fine, sparse, light-colored hair. Subsequently, non-Amish patients with the disorder were reported (1,17,33,73). An increased birth prevalence has been reported in Finland (32,35,52). The incidence among the Old-Order Amish is estimated to be 1–2/1000 (carrier frequency 1:10) (47) and 1/23,000 in Finland (carrier frequency 1:76) (35). Less than 50 patients have been described among other populations (41).

Autosomal recessive inheritance has been established (47). However, the observed number of affected individuals is significantly less than would be expected on the basis of a recessive hypothesis, even when infant deaths are excluded (35,47). Considerable variability in expression has been noted, even within Amish kindreds (46). Some homozygotes may be so mildly affected that they are presumed to be healthy; this remains unproven, however (68,71).

The gene was assigned to chromosome 9p13 by linkage analysis (68). There is no evidence for genetic heterogeneity among Old-Order Amish, the Finns, or patients of other ethnic backgrounds (69). Single ancestral mutations probably account for the majority of patients among the Amish and Finns (41). Uniparental disomy was found in two families, and may explain the significant deficiency of affected family members (71). The gene itself remains unknown at present.

There are several excellent reviews, most notably those by Van der Burgt et al (73) and Mäkitie et al (40,41). Diagnosis may be very difficult in infancy (31).

Growth. Growth was studied in 108 Finnish patients (44). Mean male birth length was 45.8 ± 2.8 cm and mean female birth length was 44.8 ± 2.7 cm. Birth weight was 3360 ± 410 g for males and 3190 ±430 g for females. Final height attainment was 131 cm for males and 122.5 cm for females.

Facies and hair. The head is of normal size. The hair is blond, brittle, fine, silky, and sparse on the scalp and elsewhere on the body (40,46). About 15% of affected individuals are bald. Eyebrows, eyelashes, and beard are also sparse (Fig. 7–32). The diameter of the hair shaft is 50%–65% that of normal hair and there is no central pigment core (10,12,17, 30,34,46,47,79), although the latter finding is not a constant feature (76).

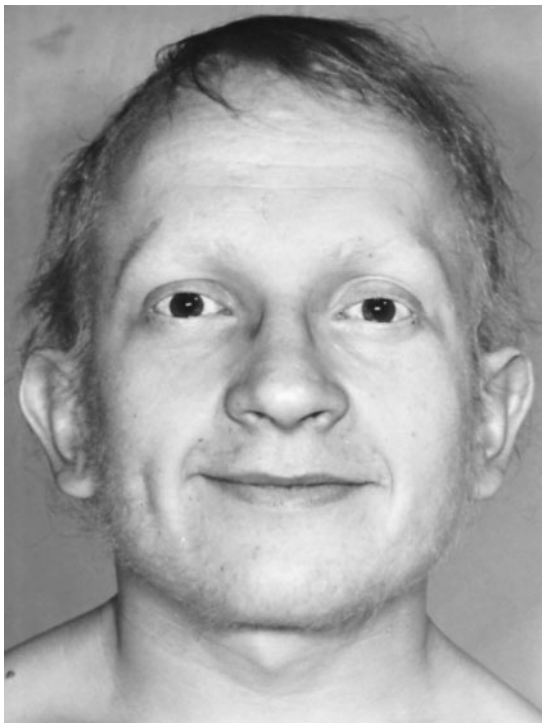
Skeletal alterations. The legs are relatively short, and the femurs are mildly bowed (Fig. 7–32B). The hands are short and pudgy (Fig. 7–33), and the fingernails and toenails are small (73). Some patients have marked hyperextensibility of joints, particularly of the hands, wrists, and feet. However, most are unable to fully extend their elbows. Several patients were noted to have been "floppy" babies (47). A narrow chest, increased lumbar lordosis, and mild scoliosis are common (40,73). Some patients have bowed legs, necessitating surgical correction (40).

Radiologically, irregularly scalloped metaphyses with sclerotic margins are noted (33) (Fig. 7–34). The metaphyseal changes are most pronounced in the knees and ankles; the irregularities disappear after closure of the epiphyses. Small, cloudy, cystic radiolucencies may be scattered throughout the metaphyses, particularly at the distal femoral metaphyses (Fig. 7–34B) (37,38,63). Epiphyses tend to be flattened or cone shaped (19a). There is often less expressed caudal widening of interpediculate distances, and about one-third of patients have mild odontoid hypoplasia. In general, spinal changes are minor. There is mild flaring of the lower rib cage. The sternum is prominent proximally and anteriorly angulated (19b). Vertebral height may be increased and mild lumbar lordosis may be found. The tibia is characteristically shorter than the fibula (Fig. 7–34). Cephalometric studies have not demonstrated striking abnormalities (57). The metacarpophalangeal pattern has been reported to be variable (73).

On microscopic examination of the costochondral junction, few cartilage cells are found; those present do not form orderly columns (47).

Infections. An important clinical feature of severe cartilage-hair hypoplasia is the unexplained susceptibility to severe varicella and other infections (1,25,28,40,46,47,73). Several patients have died from severe infections (40). The increased infection rate is mainly found in infancy and childhood. Despite persistently impaired cellular immunity, adults do not suffer from unusual infections. Chronic noncyclic neutropenia with maturation arrest has also been reported (1,8,34,40,47,73). Immunologic investigations in two children revealed persistent lymphopenia, diminished skin hypersensitivity, diminished responsiveness of their lymphocytes to phytohemagglutinin in vitro, and, in one child, delayed rejection of a skin allograft. Serum immunoglobulin levels were normal or elevated (34). Patients have not been able to synthesize antibodies to a variety of viral and bacterial antigens. It has been suggested that these persons have a distinct form of cellular immune defect that is responsible for their unusual susceptibility to varicella infection. Trojak et al (72), using mixed lymphocyte culture studies and mitogen-induced stimulation studies, found significant defects in several T-lymphocyte functions in Old-Order Amish patients. Similar abnormalities have been found in Finnish patients (42,55). These investigators concluded that impairment of cellular immunity was an integral part of the syndrome. Polmar and Pierce (54) found a defect in T-lymphocyte proliferation and concluded that it was not caused by excess suppressor cell activity or impaired accessory cell function. Defective proliferation was also found in B cells and fibroblasts. They also noted that individuals with the disorder had marked impairment of proliferation-dependent cytotoxic mechanism, whereas proliferation-independent natural killer cell activity was normal of even above normal. In two patients, bone narrow transplantation corrected the immune deficiency but not the skeletal dysplasia (5,24).

Smallpox vaccination and live polio vaccine should be avoided (60,73). In case of varicella infection, adequate therapeutic schemes are available (80).



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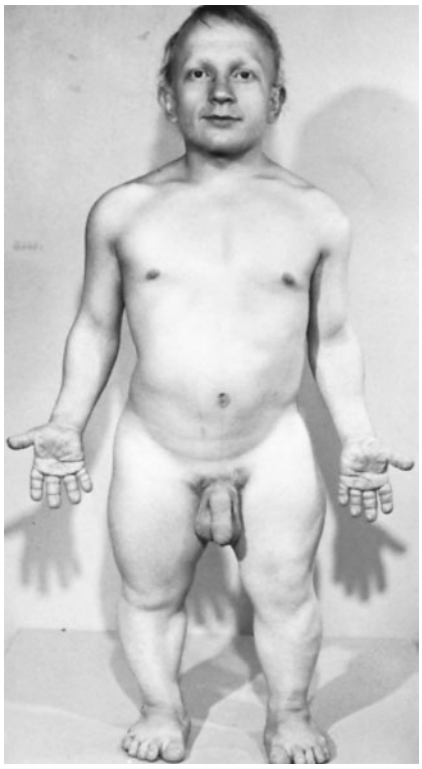


B

Fig. 7–32. *Cartilage-hair hypoplasia.* (A) Note sparse blond hair and deficiency of eyebrows and eyelashes. (B) Marked shortening of extremities.

Malignancy. Among 110 patients, about 10% had one of the following malignancies: Hodgkin's disease, non-Hodgkin lymphomas, skin neoplasms, eye cancer, liver cancer, or leukemia (18,43,56). Other investigators have reported incidence of Hodgkin's disease (20,41), skin neoplasms, testicular tumor, and lymphosarcoma (41). Cases of anemia, varying from mild with spontaneous recovery to severe and with fatal outcome, have been reported (18,39,40,54,73).

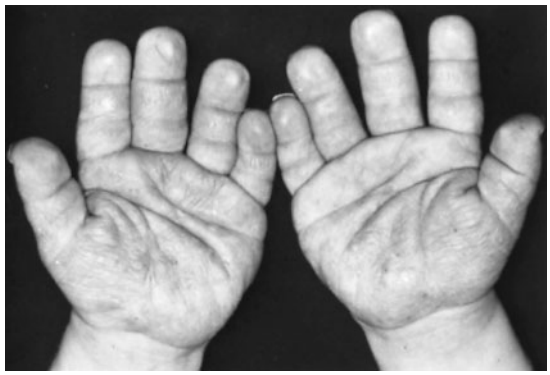


Fig. 7–33. *Cartilage-hair hypoplasia.* Note short hands.

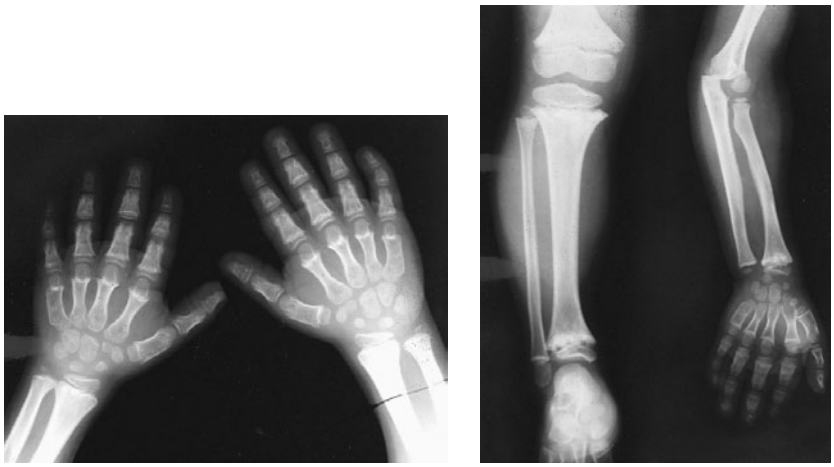
Other findings. Cesarean section is necessary for childbirth. Hirschsprung disease has been reported repeatedly in these patients (2,7,25,33,46,47,73); in the Finnish series, it was found in 7% of the patients (40). Both short-segment and total colon aganglionosis occur. Intestinal malabsorption was first thought to be very common, but further studies concluded that the malabsorption was likely secondary to gastrointestinal infections (34,40,47,73). Other rare symptoms include aseptic coxitis (2,40), esophageal atresia (40), unilateral facial nerve palsy with rudimentary ear (40), anosmia (40), and seizures (40).

Differential diagnosis. Fine blond hair may be seen in hypohidrotic ectodermal dysplasia (as well as in many other ectodermal dysplasia syndromes).

Disorders in which chondroosseous dysplasia is associated with abnormalities of immune function may be distinguished from cartilage-hair hypoplasia by radiologic examination (24,52). One of these disorders is the syndrome of chondroosseous dysplasia, adenosine deaminase deficiency, and severe combined immunodeficiency. (9,48). In cartilage-hair hypoplasia, adenosine deaminase levels have been reported to be normal (29) or increased (59). Gatti and associates (19) described a syndrome of lymphopenic agammaglobulinemia, short-limbed dwarfism, cutis laxa, alopecia of scalp, ichthyosiform erythroderma, and absence of hair and eyebrows. The disorder probably has autosomal recessive inheritance. Patients reported by McKusick and Cross (45) in an Old-Order Amish family had a skeletal dysplasia, ataxia telangiectasia, and Swiss-type agammaglobulinemia. The Schwachmann-Diamond syndrome (66,73) is characterized by metaphyseal chondrodysplasia, malabsorption, pancreatic insufficiency, and neutropenia. Blackfan-Diamond anemia has been described in cartilage-hair hypoplasia (22). Nezelof (51) described patients with T-cell deficiency and little or no abnormality of gamma globulin; the defect may be limited to the thymus. Some patients with the disorder (16) had metaphyseal dysostosis.

Achondroplasia and *hypophosphatasia* may be easily distinguished from cartilage-hair dysplasia on skeletal radiographs. In addition, patients with hypophosphatasia prematurely exfoliate deciduous teeth, mainly incisors and canines, during the first few years of life (6). Metaphyseal irregularities in cartilage-hair dysplasia are sharp, in contrast to the frayed and indistinct metaphyses in vitamin D–resistant rickets.

Cartilage-hair hypoplasia should be differentiated from other metaphyseal dysplasias. *Metaphyseal dysplasia, Jansen type*, is characterized by mental and motor retardation, abnormally shaped skull, hypertelorism, flexion deformities of many joints, beading at costochondral junctions, and gross metaphyseal widening (21,26,31,64). The immune system is normal. The pattern of inheritance is autosomal dominant. The mutated gene was found to be a PTH-PTHr8 receptor (61). Schmid-type metaphyseal dysplasia is characterized by normal face, mild growth retardation, and metaphyseal irregularities and widening that diminishes with age (11,32,58,62). In childhood, the capital femoral epiphysis is especially enlarged. The Schmid type is caused by mutations in type X collagen (13,77). Inheritance is autosomal dominant. Spahr-type metaphyseal dysplasia is an autosomal recessive entity with moderately short stature, bowed legs, waddling gate, increased lordosis, and metaphyseal widening (15,65). The capital femoral epiphyses are small.



A B

Fig. 7–34. *Cartilage-hair hypoplasia.* (A) Radiograph of hands showing scalloped metaphyses with sclerotic margins and flattened epiphyses. (B) Radiograph of long bones. Note metaphyseal irregularities. The tibia is characteristically shorter than the fibula.

Verloes et al (74) described six patients with similar bone changes but no hypotrichosis. Perhaps this is an allelic disorder.

Bellini et al (4) and Verloes et al (75) described two families with affected sibs with developmental delay, short stature, prominent forehead, hypoplastic midface with a broad nasal root and anteverted nares, and short fingers and toes. Radiographs showed distinctive widening of the metaphyses and epimetaphyseal fusion leading to V-shaped epiphyses. The hands and feet showed a picture similar to acrodysostosis. They suggested the name "acroscyphodysplasia" (75).

Bellini and Bardare (3) and Jequier et al (27) reported a metaphyseal chondrodysplasia with cone-shaped epiphyses and cupped metaphyses in tubular bones and in hands and feet, abnormally shaped vertebral bodies, odontoid hypoplasia, and alopecia. There was early growth but premature closure of epiphyses. Wiedemann and Spranger (78) described a similar metaphyseal dysplasia. Maroteaux et al (44) reported an entity with slight shortness and varus deformity of the lower limbs, and radiographically hypoplastic femoral necks and metaphyseal dysplasia. Stature was not affected. Because the symptoms regressed spontaneously, the authors called the entity "metaphyseal anadysplasia." Spranger (66) has described other metaphyseal dysplasias.

Laboratory aids. Steffensen and Østergaard (67), Van der Burgt et al (73), and others (53,55,72,76) have demonstrated selective dysfunction of cell-mediated immunity and inverted ratio of T-helper/T-suppressor cells. Prenatal diagnosis is discussed by Dungan et al (14) and Sulisalo et al (70).

References [Cartilage-hair hypoplasia (McKusick-type metaphyseal dysplasia)]

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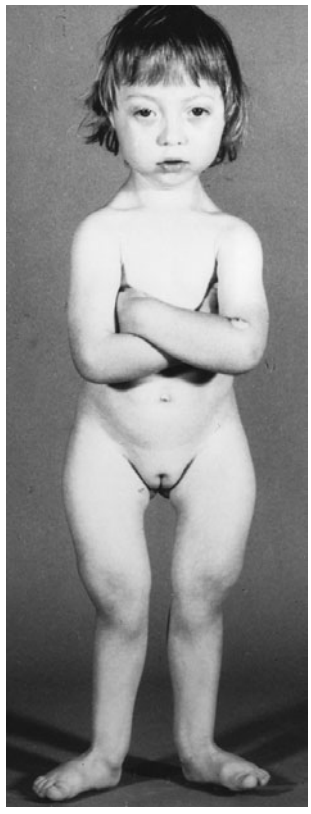
Metaphyseal dysplasia, type Jansen

The Jansen type of metaphyseal dysplasia is a rare form of growth disorder showing progressive changes reminiscent of rickets or primary hyperparathyroidism. Reported for the first time by Jansen (9) in 1934, at least 16 cases have been subsequently reported (1–8,10–18).

Clinical findings have included severe short stature of postnatal onset, para-articular widening, short bowed limbs, ape-like stance, waddling gait, normal intelligence, and clinodactyly. The facies is characterized by prominent frontonasal and supraorbital ridges and zygomata. The eyes are often prominent in infancy. The mandible is markedly reduced in size (Fig. 7–35).

Fig. 7–35. *Metaphyseal dysplasia, type Jansen.* (A) Mother and daughter exhibiting extreme short stature. (B) Note short, bowed limbs.

A



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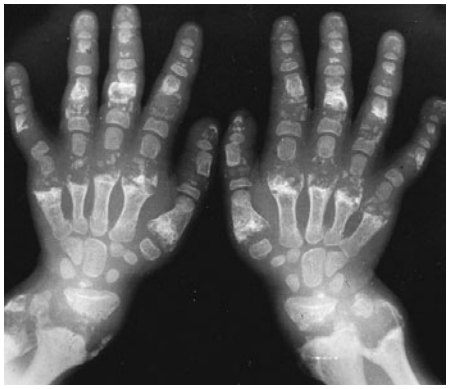

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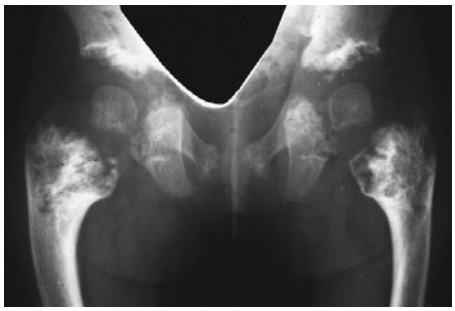

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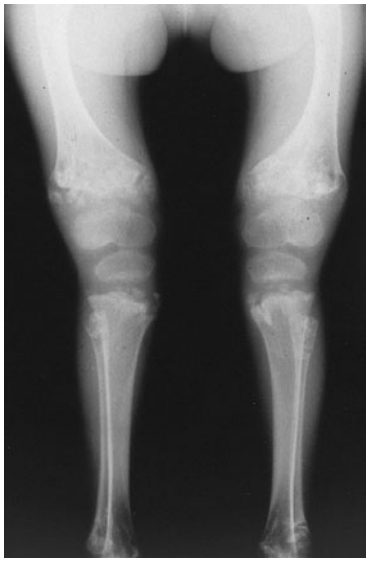

C

Fig. 7–36. *Metaphyseal dysplasia, type Jansen.* (A–C) Short tubular bones, gross metaphyseal widening, enlarged epiphyseal centers of distal metacarpals, and irregular ossification. Knees show splaying and fragmentation of metaphyses and irregular ossification. The pelvis shows metaphyseal widening and irregularity, normal epiphyses, and bowing of femora. (From K Kruse and C Schutz, Eur J Pediatr 152:912, 1993.)

Radiographic alterations change with time. During infancy, there are diffuse demineralization and rickets-like findings in the metaphyses, cortical erosions, and increased subperiosteal bone formation. The epiphyses and diaphyses are normal. During childhood, the tubular bones are short and curved with wide, chaotically frayed and cupped metaphyses (Fig. 7–36). The fingers may be short and clubbed. Rib fractures have been documented. The long bones exhibit increased density. The calvaria and skull base are hyperostosed. The cranial sutures are wide in infancy and there may be choanal stenosis.

Inheritance is autosomal dominant, but most cases represent new mutations (3). Mutations involve a PTH-PTHrP receptor gene (15a).

Laboratory changes consist of hypercalcemia, hypercalciuria, elevated urinary phosphate, and cyclic AMP (2,4,6,7,9,13,17). There is no increased serum 1,25–dehydroxyvitamin D despite low to normal levels of parathormone (PTH) and PTH-related peptide. The parathyroid glands appear normal (6,7,17).

References (Metaphyseal dysplasia, type Jansen)

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Table 7–6. Features of the three major forms of chondrodysplasia punctata

	X-linked dominant type	X-linked recessive type	Rhizomelic type
Head circumference	Normal for age	Mild microcephaly	Small for age
Nose	Hypoplastic	Hypoplastic	Hypoplastic
Cataracts	65%, often unilateral and asymmetric	In some cases, bilateral	65% bilateral and symmetric
Skin changes	Congenital ichthyosiform erythroderma; ichthyosis in older child; systematic atrophoderma, pseudopelade, coarse twisted scalp hair	Mild ichthyosis as neonate; sparse unruly hair	Dry scaly rash in 25%, hair normal
Contractures	Mild in 25%	Mild	Frequent, severe
Skeletal changes	Asymmetric limb shortening, usually femur and humerus; scoliosis after first year	Distal phalanx hypoplasia; carriers have broad wrists and short arms	Severe bilateral shortening of femur and/or humerus with severe metaphyseal changes
Stippling	Asymmetric involvement of long bones: paravertebral, laryngeal, tracheal	Bilateral symmetric involvement of long bones; paravertebral, laryngeal, tracheal	Proximal and distal humeri and femora, knee; no paravertebral stippling
Mental retardation	Normal to mildly retarded	Delay; hyperactivity, behavioral problems	Severely retarded; hypotonia
Prognosis	Good; lethal in males	Relatively good	Lethal, usually in first year
Inheritance	XLD	XLR	AR

Chondrodysplasia punctata (general)

Chondrodysplasia punctata is a term used for a heterogeneous group of skeletal dysplasias characterized by the radiographic appearance of punctate or stippled calcifications at long bone epiphyses during infancy. Thus, chondrodysplasia punctata is not a specific disease designation but is a radiographic sign evoking consideration of a spectrum of genetic and teratogen-induced disorders.

First described by Conradi (2) in 1914 and by Hünermann (4) in 1931, chondrodysplasia punctata was later split into two categories by Spranger et al (7), who differentiated the relatively mild and presumably autosomal dominant Conradi-Hünermann disease from lethal chondrodysplasia punctata, rhizomelic type. Burck (1) distinguished a hitherto sporadic form characterized by mesomelic shortening of the limbs and Sheffield et al (6) described a large series with an unusually mild picture. More recently, Curry et al (3) proposed an X-linked recessive chondrodysplasia punctata that may present as a chromosome microdeletion syndrome.

Thus, three major and at least two less frequent clinical entities have been distinguished on the basis of degree of skeletal aberration, presence of cataracts, and skin involvement (Table 7–6). Although these attempts to differentiate clinical phenotypes appear justified, there is uncertainty as to whether all phenotypic differences represent true genetic heterogeneity or are merely gradations in the variable expression of a single X-linked gene or gene complex. The heritable phenotypes must be further differentiated from the teratogenic effects of anticoagulant therapy with vitamin K antagonists (e.g., *Warfarin embryopathy*) and a number of other conditions in which transient epiphyseal stippling may occur.

Kelley et al (5) found abnormal sterol metabolism in some cases of chondrodysplasia punctata.

References [Chondrodysplasia punctata (general)]

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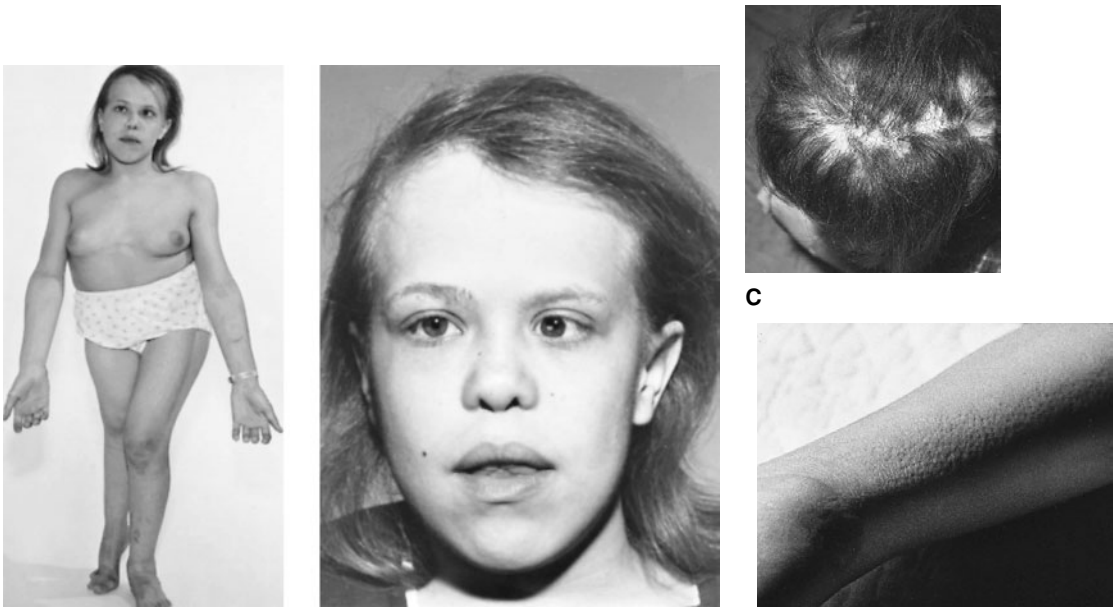
Conradi-Hünermann disease: X-linked dominant type. The eponym Conradi-Hünermann disease is frequently indiscriminately used for the group of chondrodysplasia punctatas, but it should be employed only for the X-linked dominant form (Figs. 7–37 and 7–38), which was first recognized by Happle et al (18,21) to be limited to females. The mother of an affected daughter may have mild manifestations, such as short stature or skin changes or cataracts (2,9,20,26,27,33,41). It has been proposed that this form accounts for at least 25% of cases (32), but our review suggests that all reported cases of Conradi-Hünermann syndrome, including the "autosomal dominant" cases, actually represent the X-linked dominant condition. The disorder occurs exclusively in females, because the underlying gene defect is lethal in hemizygous males (11). A stillborn male infant has been noted (3). A family with the X-linked dominant type has been reported in which an affected male was found to have XXY Klinefelter syndrome (41). The rare occurrence of the X-linked dominant type in males (18,47) can be best explained by a postzygotic mutation or a half-chromatid mutation, as first proposed by Lenz for incontinentia pigmenti (29). Other familial observations have been reported (2,10,16,32,39).

Following discovery of peroxisomal enzyme deficiencies in the rhizomelic type (23), similar abnormalities were reported in the X-linked dominant type (13,24,34). Already in 1983, Happle (20) suggested that the X-linked dominant type may have a murine homologue in the mouse mutant Bare Patches (*Bpa*). The name was derived from the skin abnormalities found in female mice of a particular strain after multiple doses of X-irradiation (30). The gene was mapped within Xq27–28 (22,30). The fact that peroxisomal anomalies were also found in Bpa mice (13) further suggested that the human *Bpa* gene was responsible for the X-linked dominant type. This has been echoed by Wilson and Aftimos (49). However, Traupe et al (45) excluded the region in three smaller families. They suggested the existence of an unstable premutation that can become silent in males (45). Kelley et al (28) found increased levels of 8-dehydrocholesterol, suggesting a sterol-Δ^8-isomerase deficiency as cause for the disorder. In 1999, Braverman et al (4) found that mutations in the gene encoding 3β-hydroxysteroid Δ^8, Δ^7-isomerase cause X-linked dominant Conradi-Hünerman syndrome. The gene is at Xp11.22–p11.23. Mosaicism has been reported (21).

The disorder is intermediate in severity with a good prognosis. Intelligence appears to be normal, although performance on specific tests may be impaired by poor vision and skeletal limitations on motor skills (32).

Facies. Frontal bossing is common, with macrocephaly being noted in several patients (7,12,14,16,21,25,40) (Fig. 7–37A,B). The nasal root is flat and broad (7,12). The face is often asymmetric because of hypoplasia of one side (14,21,33,39). The neck may be short (10,21,40).



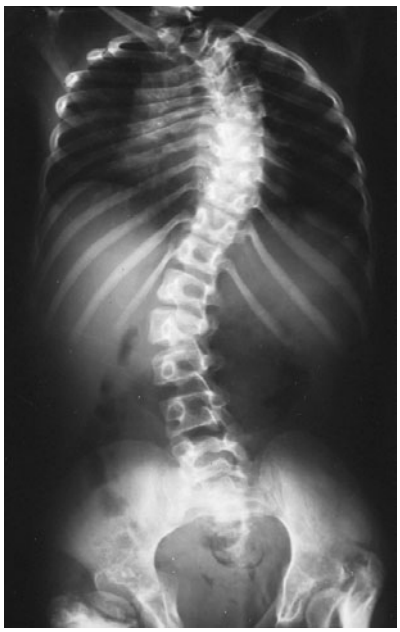
A B C D

Fig. 7–37. *Chondrodysplasia punctata*, *X-linked dominant* (*Conradi-Hünermann*) *type.* (A) Height is reduced. Note disproportionate limb length and scoliosis. (B) Sparse hair, flat midface, anteverted nostrils, and cataract. (C) Patchy alopecia on scalp. (D) Skin changes. (From D Comings et al, J Pediatr 72:63, 1968.)

Eyes. Congenital diffuse cataracts have been observed in about 65% of patients. The cataracts may be unilateral (35%) or bilateral, often with asymmetric intensity (19) (Fig. 7–37B). Happle (19) pointed out that this exception to the general rule that hereditary cataracts tend to be bilateral and symmetrical is probably caused by lyonization. Microphthalmia and microcornea have also been reported (26,39).

Skin. Newborn patients exhibit ichthyosiform erythroderma with thick, adherent scales arrayed in a linear, blotchy pattern, presumably reflecting lyonization (26). The hyperkeratotic eruption is followed by systematized atrophoderma distributed in a mosaic pattern leaving patchy linear areas of alopecia on the scalp (Fig. 7–37C,D). A linear pattern of hyperpigmentation, which is not congruent with the pattern of hairlessness, has been observed and compared to incontinentia pigmenti (10). The nail plates are often flattened (12). Microscopic sections of the skin show a thin stratum granulosum. These skin changes can be distinguished from other forms of ichthyosis on the basis of histologic and ultrastructural criteria (6,13,17).

Fig. 7–38. *Chondrodysplasia punctata*, *X-linked dominant* (*Conradi-Hünermann*) *type.* Note severe scoliosis.



Musculoskeletal alterations. In infancy, punctate calcifications are scattered throughout the spinal column, costal cartilages, sternum, clavicles, scapulae, and in the epiphyseal centers of the extremities. Loss of the characteristic stippled epiphyses with time makes diagnosis difficult. In some individuals there is true dysplasia of vertebral bodies (7,10). Stature is usually reduced (1,40). Scoliosis or kyphoscoliosis with asymmetric shortening of limb bones, particularly the femur and humerus, is common (Fig. 7–38). Shortening of the limbs is asymmetrical. Flexion contractures involving the hip or knee joints (16), elbow (26,36), or fingers (10,20,33) and hip dysplasia (1,9,10,25,33,39) have been reported. Metapodial bones may also be involved (19,26). Some patients have exhibited postaxial supernumerary digits of the hands (19,32,36,38,39). Talipes is not uncommon (14,16,26).

Other manifestations. Mental retardation has been described (10) but is rare. Congenital paraplegia resulting from uncharacteristic maldevelopment of the spinal cord has been reported (9). Cardiovascular disorders, including peripheral pulmonary arterial stenosis (47), have been rarely mentioned (25,40).

Laboratory aids. Intrauterine radiographic examination of a pregnancy at 16 weeks failed to show diagnostic features, although the characteristic extensive calcifications in sites of endochondral bone formation were apparent by radiographic examination of the abortus. Prenatal sonographic diagnosis has been accomplished (37,48).

References (Conradi-Hünermann disease: X-linked dominant type)

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Chondrodysplasia punctata, rhizomelic type. This type, the most severe form of chondrodysplasia punctata, leads to death usually before the second year of life (Figs. 7–39 and 7–40), although much longer survival can occur (30). Familial occurrence has been reported (10,19,26,30), both sexes are equally affected, and parental consanguinity has been estimated at 8%–10%; all of these features point to autosomal recessive inheritance. Biochemical studies have indicated that this type results from a disorder of peroxisomal metabolism (14).

Patients exhibit profound deficiency of plasmalogen synthesis, the presence of unprocessed peroxisomal thiolase in the liver, reduced alkyldehydroxyacetone phosphate synthase activity in fibroblasts, and elevated phytanic acid levels in plasma and liver, indicating a reduction of phytanic acid oxidation to 1%–5% of controls (1,16,23). Other peroxisomal functions are normal. Additional information has been gained by complementation studies (13,16,20,23,25), in which fibroblasts from two different patients, both deficient in a peroxisomal process, are fused and the resulting multinucleated cells are examined. Restoration of activity can occur only if each cell line complements the gene product defective in the other. Moser et al (20) found at least 11 different groups, of which the rhizomelic type was one. Patients showed a homogeneous clinical picture, although a more mild picture does occur (2,20,22,26). Patients with isolated deficiency of alkyldihydroacetone phosphate synthase deficiency have the classic rhizomelic-type phenotype (29).

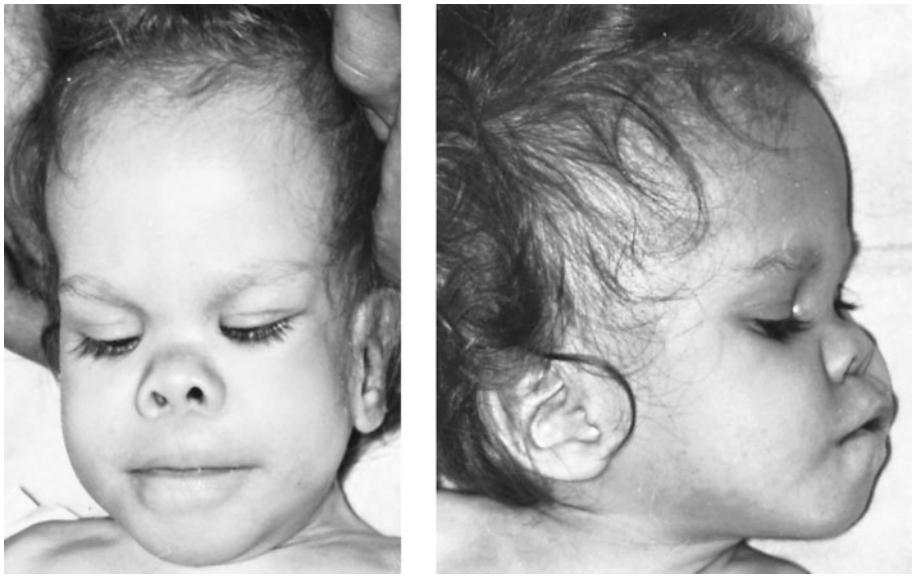
Three groups (3,21,24) have independently proven that the disorder is caused by mutations in one of the peroxisomal assembly proteins (peroxins), PEX7, located at 6q22–24. The *PEX* genes are required for import of matrix proteins into peroxisomes by peroxisome targeting signals (PTS) (3). *PEX7* encodes the receptor for one of these signals, PTS2. Different mutations in *PEX7* have been found in patients with the classic rhizomelic type (3,21,24). A founder effect and the structure of the gene have been dealt with at length (3a).

Facies. The face is symmetric, but notable for frontal bossing, flat nasal bridge, and small nares (Fig. 7–39).

Eyes. Cataracts observed in about two-thirds of the cases are usually bilateral and of equal density (25). Other lens abnormalities can occur (9).

Skin. At least 25% of patients have ichthyosis, which develops shortly after birth.

Musculoskeletal alterations. In contrast to the other types of chondrodysplasia punctata, there is severe congenital rhizomelic shortening of the extremities. Small head circumference tends to be present at birth and is a constant finding in older infants and children. Contractures have been noted in over 60% and foot deformities in about 10% of patients.



A B

Fig. 7–39. *Chondrodysplasia punctata*, *rhizomelic type.* Autosomal recessive form. (A) Flat midface and small upturned nose. (B) Deficient midface and posteriorly angulated ears.

Radiographic skeletal abnormalities include severe shortening, metaphyseal cupping, splaying, and disturbed ossification of the humerus and/or femur (Fig. 7–40). Epiphyseal and extraepiphyseal calcifications are usually severe (Fig. 7–41). Lateral views of the spine show a coronal cleft of the vertebral bodies (26). There are marked degenerative changes in resting chondrocytes (23).

Oral manifestations. Cleft palate (4,6,7,10,18,23,26) and submucous palatal cleft (1) have been noted in the rhizomelic type. There is one report of a patient with laryngeal atresia (27).

Other. Hearing loss (30), hypospadias (30), and magnetic resonance imaging (MRI) anomalies of the brain (31) have been described.

Laboratory aids. Prenatal diagnosis of the rhizomelic type is possible by sonography (30), peroxisomal investigations (12,15), and probably also by molecular study of *PEX7*, although this has not been reported yet.

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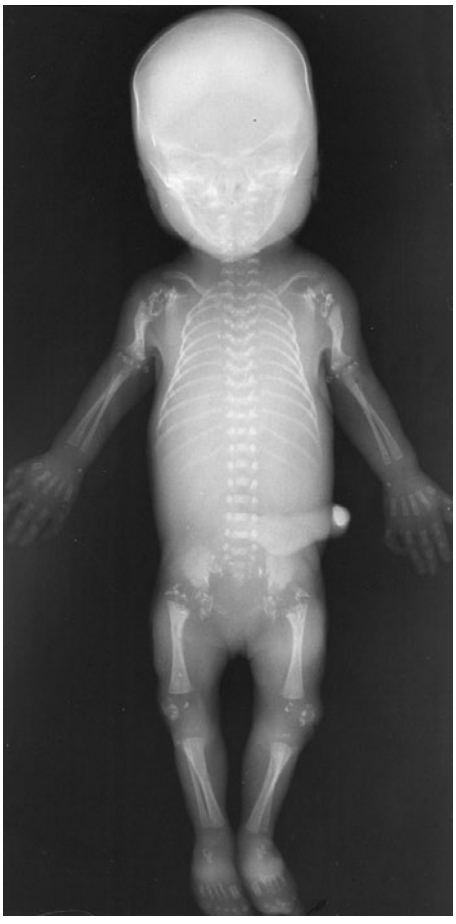
Fig. 7–40. *Chondrodysplasia punctata*, *rhizomelic type.* Note abbreviation of humeri and femora with stippling at proximal and distal ends. (From JM Connor et al, Am J Med Genet 22:243, 1985.)



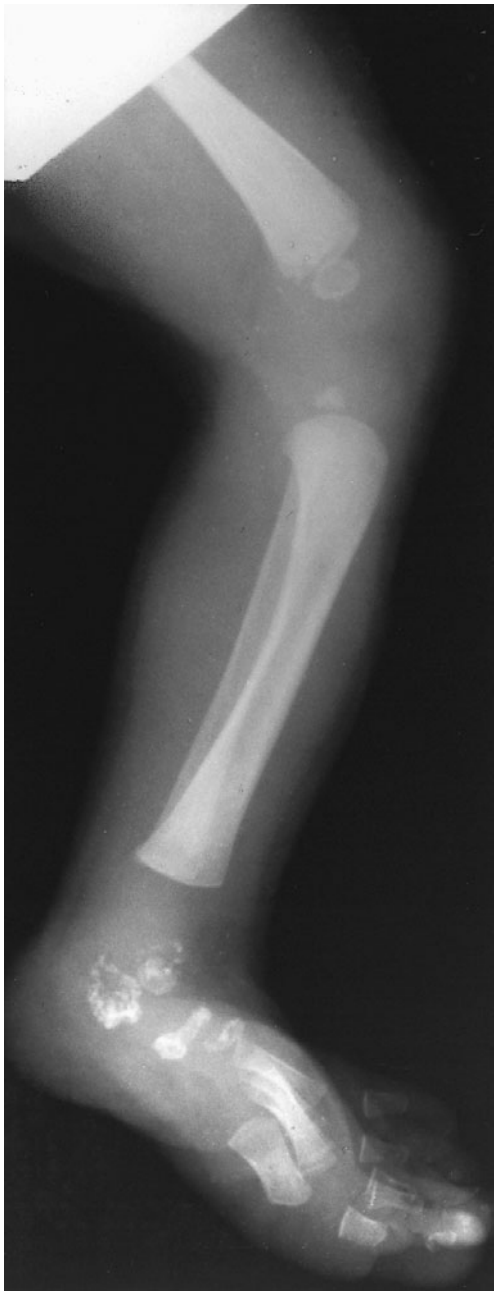


Fig. 7–41. *Chondrodysplasia punctata*, *rhizomelic type.* Note stippling of heel.

the rhizomelic form of chondrodysplasia punctata. A complementation study. Hum Genet 89:439–444, 1992.

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Chondrodysplasia punctata, X-linked recessive type. An X-linked recessive disorder with chondrodysplasia punctata, ichthyosis, and mental retardation was reported by Curry et al (6). Cytogenetic studies revealed a small deletion at Xp22.32 in four affected males and in 11 of 25 apparently normal related females. Several other patients with interstitial deletion (3,4,13,14,16) or X-Y translocation involving Xp (1,2,13,21) have been reported. The presence of ichthyosis in affected males prompted biochemical studies that demonstrated functional deletion of three genes previously mapped in this region of the X chromosome, which corresponded to the observed deleted (steroid) sulfatase; Xg^a; and the M1C2X locus for expression of 12E7 antigen (2,6). Hence, it is a truly contiguous gene syndrome (3). It has been suggested that extensive calcification of blood vessels may play an important role in the pathology of this form (10). A genotype-phenotype study has been carried out (18). Heterozygous female carriers are clinically normal but, as a group, are slightly shorter, with broad wrists and short arms, in comparison to non-carrier relatives (1,2,6,20). After further refinement of the locus (7,11,12,14), Franco et al (8) were able to isolate the causative gene, *ARSE,* through positional cloning. It is an arylsulfatase enzyme that shows high sequence homology with steroid sulfatase. Point mutations were found in 5 of 27 patients by Franco et al (8). Parenti et al (15) described another mutation. It remains uncertain whether other genes in the critical region for the X-linked recessive type of chondrodysplasia punctata, named *ARSD* and *ARSF,* are also in part responsible for the symptoms in patients nullisomic for Xp22.3.

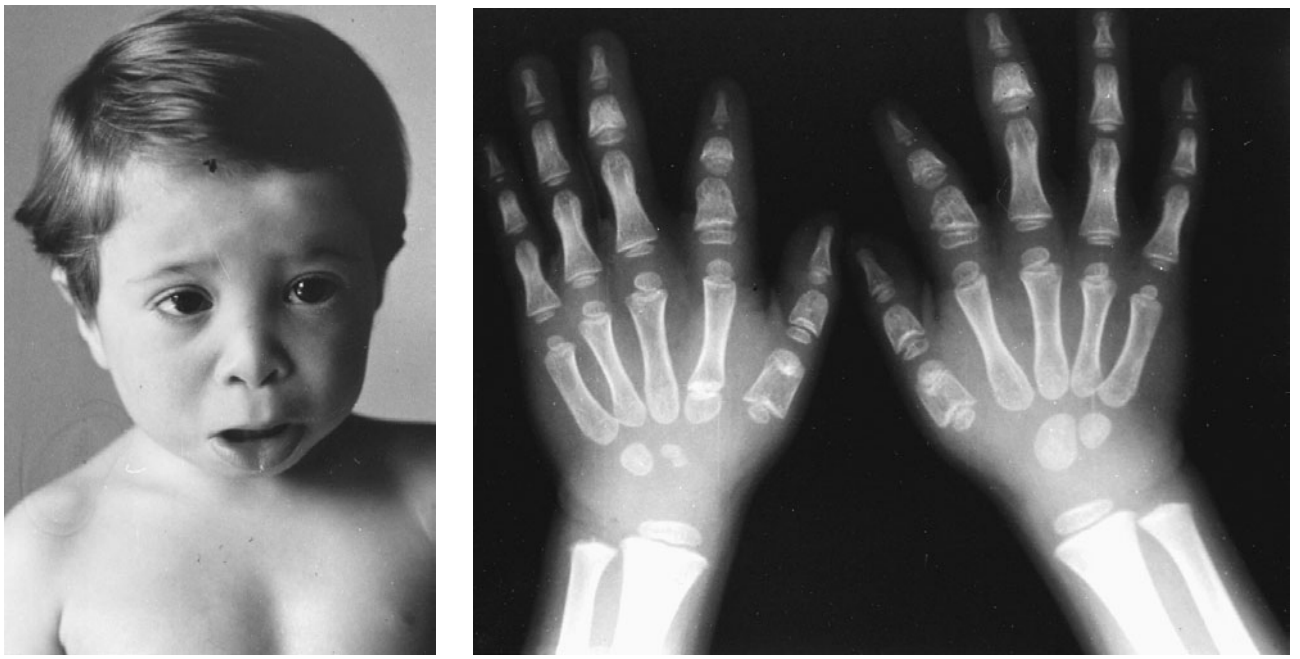
Chondrodysplasia punctata, Sheffield type may be in part caused by mutations in *ARSE*. As this latter entity is undoubtedly heterogeneous and the exact relationship between *ARSE* mutations and clinical picture remains uncertain, it is described separately.

Facies. Nasal hypoplasia was present in all children with some tendency toward improvement in later childhood (Fig. 7–42A). Sensorineural hearing loss may occur (4,6,15).

Eyes. Bilateral cataracts have been observed in some patients. One patient had optic nerve hypoplasia (16).

Skin. All patients had sparse and unruly hair with mild ichthyosis particularly over the chest, back of legs, neck, and axillae.

Musculoskeletal alterations. Bilaterally symmetric punctate stippling of multiple epiphyseal centers is characteristic, including the paravertebral epiphyses and those of the larynx, trachea, and long bones; these disappear relatively rapidly with age (17). Hypoplasia of the distal phalanges (brachytelephalangia) is common (Fig. 7–42B).



A B

Fig. 7–42. *Chondrodysplasia punctata*, *X-linked recessive type.* (A) Five-year-old boy with prominent forehead, underdeveloped flat nose, short columella, and long philtrum. (B) Note short first metacarpals, cone-shaped epiphyses, and short first and second proximal and middle phalanges. (From G Parenti et al, Am J Med Genet 73:139, 1997.)

Other. Mild mental retardation (1,2,4,13,16,21), hydronephrosis with multiple small cysts (4,21), and choanal atresia (4) have been reported.

Laboratory aids. Prenatal diagnosis has been accomplished (5).

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Chondrodysplasia punctata, Sheffield type (and brachytelephalangic type). In 1976, Sheffield et al (7) described a series of 23 patients with an unusual mild type of chondrodysplasia punctata, characterized by failure to thrive, apparent developmental delay, Binder-like facial features, and punctate calcifications in the calcaneus and sometimes elsewhere. It seems very likely that this group of patients was heterogeneous. Norman et al (5) described another case. The so-called brachytelephalangic type of chondrodysplasia punctata (1,3,4) is probably the same entity. It has been suggested that some patients with Binder phenotype may in fact have chondrodysplasia punctata, Sheffield type (2,6).

The difference between the Sheffield and the X-linked recessive types can be difficult to determine. Indeed, in one case reported by Maroteaux (4), a mutation in the *ARSE* gene was found, as can be found in the X-linked recessive type. The X-linked recessive type is usually characterized by microdeletion at Xp22.3; the influences on the phenotype by nullisomy of other genes at Xp22.3 is uncertain. Therefore, it is prudent to keep the Sheffield type separate from the X-linked recessive type. In some patients of the Sheffield type, an autosomal recessive pattern of inheritance was suggested (5,8).

Most patients have low–normal birth weight. Growth velocity is mildly impaired thereafter. The nose is already characteristic at birth, showing a tip flattened by a shortened columella and depressed nasal bridge. The inadequate nasal airway can produce respiratory problems in the neonatal period. The nasal bridge fills out at a later age, but plastic surgery may still be warranted. Otherwise, the face is usually normal, although proptosis (3), nystagmus (7), and other usually mild dysmorphias (1) occur. The limbs can be normal, but brachydactyly with somewhat bulbous thumbs is not uncommon. Several patients had postaxial polydactyly (7).

Radiologically, fine stippling at birth is especially frequent in the calcaneus in a lateral view of the foot. Other sites can be tarsals, toes, sacrum, other vertebrae, proximal femora, proximal humeri, and laryngeal cartilages. Within 2 to 4 years most stippling is no longer visible. Sagittal clefts of the vertebral bodies and very small distal phalanges of all fingers can be found. The other phalanges and metacarpals can be shortened to a lesser extent (1,3,4).

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Chondrodysplasia punctata, tibia-metacarpal type. In 1982, Burck (3) described two unrelated girls with a form of chondrodysplasia punctata characterized by marked mesomelic shortening of limbs, mild localized punctate epiphyseal calcifications, dislocation of radial heads and patellae, and characteristic face. In retrospect, the patients reported by Asanti and Heikel (1) and Haynes and Wangner (5) likely had the same entity. Several other patients have been reported (2,4,6–8), although the case described by Borochowitz (2) and by Fryburg and Kelly (4) had rhizomelic shortening instead of mesomelic shortening. Further related cases have been discussed (3,7); all have been sporadic. The symmetry and consistency of the symptoms make a genetic origin more likely. Peroxisomal studies were reportedly normal (4,8).

Patients show shortened limbs at birth, often more pronounced in the arms. With time, the shortening becomes more apparent. Facial features include flat face, flat nasal bridge, small nose, relatively long philtrum, small mouth, and micrognathia. Some patients have hypertelorism (3,7), thin vermilion borders of the lips (2,7), and cleft palate (7) or highly arched palate (2,7). No patient has had cataracts, one patient had atrophic facial skin changes (7). There is often bowing of upper or lower arms, which diminishes with age. A mild pectus excavatum, hyperlordosis, and mild hypomobility of the large joints have been described. The growth is moderately diminished (2–4 standard deviations below the mean); no adult height has been reported. Mental development is normal. No internal anomalies have been recorded.

Radiologically, the major symptoms are shortening of the tibiae and, to a lesser extent, the radii. In two cases, the shortening was more pronounced in the humeri. Distal ulnae may be hypoplastic and the fibulae very long. The metacarpals are short and show calcific stippling, especially the fourth. The distal phalanges may be short. The cervical vertebral bodies are underossified neonatally. Otherwise, the spine shows a coronal cleft indicating insufficient fusion of the anterior and posterior ossification centers. The ribs and pelvis are usually normal. Punctate calcifications are most prominent in the sacrum, metacarpals, carpals, and tarsals; this state appears with age. In some patients stippling was more widespread (4,5). Dislocations of patellae (3,8) and radii (3,7,8) have been recorded.

References (Chondrodysplasia punctata, tibia-metacarpal type)

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Other disorders with stippled epiphyses. Epiphyseal stippling in infancy is a nonspecific sign and may be seen in a variety of other disorders including Zellweger syndrome, different forms of adrenoleukodystrophy, other peroxisomal disorders (23), Blomstrand syndrome, cerebro-costo-mandibular syndrome (3), multiple epiphyseal dysplasia, kyphomelic dysplasia, acrodysostosis (22), Astley-Kendall syndrome (15), alcohol embryopathy, hydantoin embryopathy, coumarin embryopathy (7,13,24), maternal lupus erythematosus (2,6,20), chondritis secondary to bacteremia, I-cell disease, infantile sialic acid storage disease, G_{M1}-gangliosidosis, Smith-Lemli-Opitz syndrome, Keutel syndrome (5,14a), trisomy 18, trisomy 21, mosaic trisomy 9 (1), duplication of distal 16pter (9), deletion of 7q11 (16), and congenital hypothyroidism. Stippled epiphyses may be found in single digits (12) and in CHILD (*c*ongenital *h*emidysplasia, *i*chthyosiform erythroderma, *l*imb *d*efects) syndrome (8). Kozlowski and Majewski (10) have described a separate form of chondrodysplasia punctata (acrospondylar type) with mainly irregular calcifications at the base of metacarpals and metatarsals, and poorly ossified vertebrae with stippling, especially cervically. Toriello et al (21) reported a form with stippling of proximal humoral epiphyses, retarded bone age, coloboma of iris, some unusual facial features (brachycephaly, small nose, anteverted nares), and developmental delay. Ciske et al (4) reported a similar patient who had, in addition, an atrioventricular canal, coarctation of aorta, partial absence of the callosal body, small vermis, and enlarged ventricles. Refetoff et al (17) reported a family with the combination of stippled epiphyses, goiter with elevated protein-bound iodine (PBI), severe deafness, and mild dysmorphic features. Another form of epiphyseal stippling of especially the thorax, carpals, sacrum, proximal femoral epiphyses, and tarsals, together with osteoclastic hyperplasia, was reported by Shohat et al (18). Dappled diaphyseal dysplasia combines multifocal ossification of long bones of limbs, ribs, and pelvis with lethal short-limbed dwarfism (19). Mortier et al (14) reported stippled epiphyses with some similarity to the brachytelephalangic X-linked form. The child had cleft lip/palate, telecanthus, and aplasia cutis congenita of the scalp.

References (Other disorders with stippled epiphyses)

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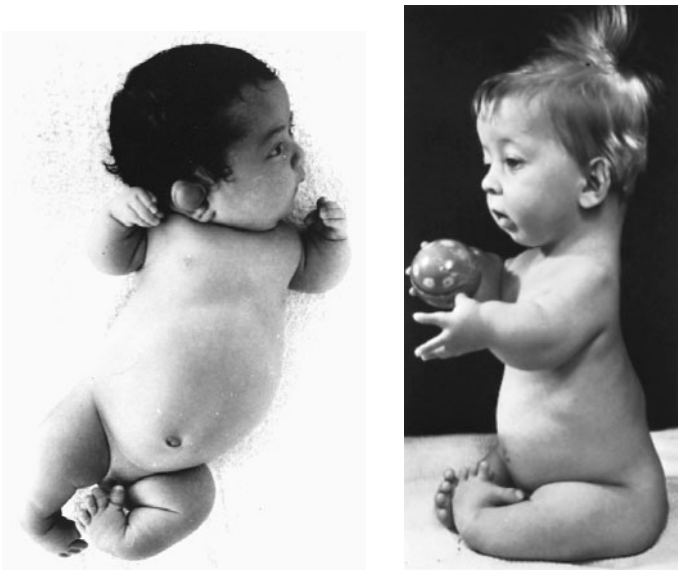
Diastrophic dysplasia

In 1960, Lamy and Maroteaux (27) used the term "diastrophic dwarfism" to describe a syndrome consisting of micromelic dwarfism, progressive scoliosis, bilateral talipes equinovarus, and various deformities of digits, hip dysplasia, characteristic external ear deformities, and, frequently, cleft palate (Figs. 7–43 to 7–45). Over 400 cases have been described, with over 150 of these coming from Finland (10,36). The incidence in Finland is estimated to be 1 in every 30,000 newborns (10). The syndrome has autosomal recessive inheritance (1). There is a founder effect in Finland (12a). Both sexes are equally affected. Prior to its delineation, cases in infants were generally classified as examples of "achondroplasia with clubbed feet," and in adults, as Morquio syndrome (5,24). Early examples are those of Arraga in 1897 [republished, see (29)], Schenk (38) in 1910, and Duken (5) in 1921.

The so-called diastrophic variant is presently considered to be a mild form of diastrophic dysplasia, reflecting the wide variability in phenotypic expression of this condition (9,15,26). Gustavson et al (8) have suggested that there are lethal and nonlethal forms, with the lethal form exhibiting lower birth weight, overlapping joints, dislocation of cervical spine, and, frequently, congenital heart disease. Fertility seems to be reduced (43).



A B

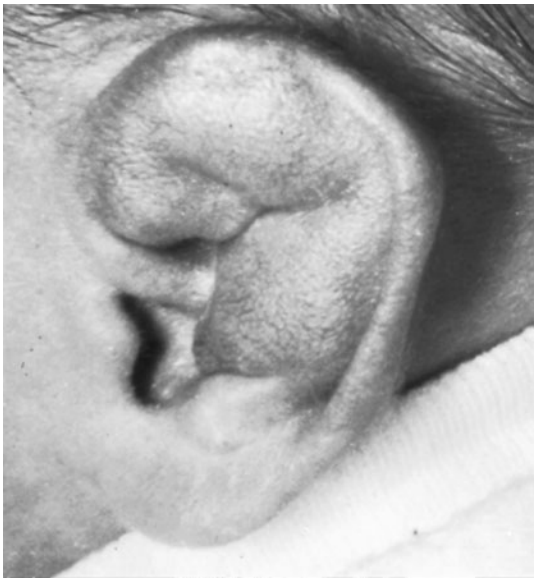
Fig. 7–43. *Diastrophic dysplasia.* (A) Micromelia, talipes equinovarus, and cystic ear. (B) Micromelic dwarfism, scoliosis, bilateral talipes equinovarus, and deviated thumbs and halluces. (A courtesy of C Gonzales, Sao Paulo, Brazil. In: MM Cohen Jr, The Child with Multiple Birth Defects, Raven Press, New York, 1982, p 104. B from J Spranger and H Gerken, Z Kinderheilkd 98:227, 1967.)

For a long time, the basic defect was considered to be a metabolic abnormality of the chondrocyte that induces cell death and/or defect in the synthesis of collagen or proteoglycan (16). Through work within the Finnish population, Hastbacka and co-workers (10) mapped the syndrome to chromosome 5q32. The same group of investigators cloned and sequenced the gene, which was named "diastrophic dysplasia sulfate transporter" (*DTDST*) (12). When mutated, sulfate uptake across the cell membrane is insufficient, leading to undersulfation of proteoglycans in cartilage. Mutations were found in patients with diastrophic dysplasia, achondrogenesis type 1B, and atelosteogenesis type 2 (40), thus constituting a separate bone dysplasia family. The severity of the phenotype within this bone dysplasia family correlates well with the predicted effect of mutations in *DTDST* (40). Rossi et al (37) described patients heterozygous for transporter gene mutations who showed features of both diastrophic dysplasia and atelosteogenesis type 2. A novel mutation for a broad bone variant has been found (31a).

About 25% of patients die in infancy of aspiration pneumonia or respiratory distress (glossoptosis, tracheomalacia). The somewhat hoarse cry, noted in several infants, may be related to abnormal laryngeal cartilages that may, in turn, reflect poor prognosis (43).

Facies. The face tends to be round with narrow nasal bridge, broad midnose, flared nostrils, and circumoral fullness (31,43) (Fig. 7–43). Bilateral but, at times, asymmetric deformity of the pinnae has been noted in over 80% of patients (43). It may be evident within the first few days or weeks of life as a cystic swelling from which serosanguineous fluid may be extracted (24,43) (Fig. 7–44). This resolves within a month, but the architecture of the pinnae becomes distorted with calcification of the cartilage. The external auditory canals may be narrowed. Cephalometric analysis has been performed (20–22).

Musculoskeletal alterations. Mesomelic dwarfism is a constant feature. Mean birth length is about 42 cm. Horton et al (17) and Mäkitie and Kaitila (30) established growth curves. Mean adult height in Finnish males is 136 cm (129–160 cm) and in females, 129 cm (90–143 cm); the Horton study showed height in males ranging from 86 to 127 cm and in females from 104 to 122 cm (17,30). The variability in growth failure was great even within sibships. Growth delay was aggravated



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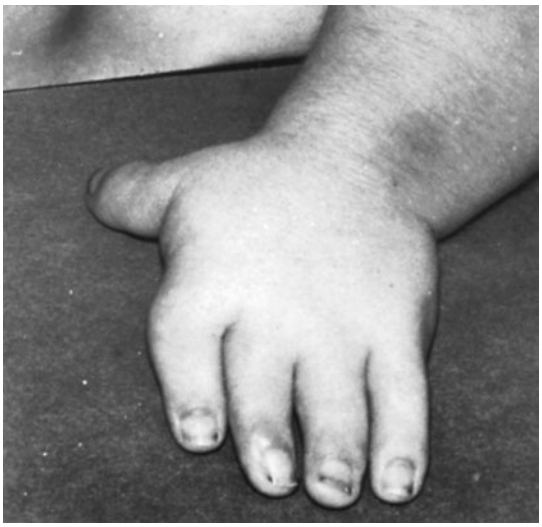

B

Fig. 7–44. *Diastrophic dysplasia.* (A) Cystic ear during hemorrhagic phase, which later resolves, leaving pinna calcified and distorted in form. (B) Hand and fingers are short, with thumb proximally placed.

in puberty by weak or absent pubertal growth spurt. There is shortening of all limbs (Fig. 7–43). Bilateral talipes equinovarus is severe, becomes worse with age, is resistant to treatment, and tends to recur after therapy. The patients bear their weight on their toes; thus walking is limited.

The thumbs are proximally inserted, hypermobile, and laterally displaced (hitchhiker's thumb) (14). The broad hands and shortened fingers often exhibit ulnar deviation. Frequent webbing, contractures, and fixation of the interphalangeal finger joints occur (Fig. 7–45). The metacarpophalangeal profile pattern has been discussed by Butler et al (3).

Scoliosis is not present at birth but is progressive, particularly in preadolescent years. It tends to become severe and rigid with a large rotary component (2,4,13,14,23,33). Kyphosis is occasionally associated. Lordosis is frequent and is not progressive (8). All patients reported by Herring (13) and Bethem et al (2) presented spina bifida occulta in the cervical spine. Flexion contracture and/or subluxation or dislocation, particularly of the hips and knees and, to a lesser extent, of the shoulders, are common and progressive, further reducing height (43). Inguinal hernia has also been described (42,43).

Radiographic changes include shortening and thickening of nearly all tubular bones. The epiphyses have delayed appearance and are flattened and distorted. With time, the metaphyses become widened, irregular, and deformed. The humerus is less shortened than the radius and ulna. The thumb is proximally placed, and the first metacarpal is small and rounded (Fig. 7–45A,B). Synostosis of the proximal interphalangeal joints is a constant feature. Carpal development is accelerated, but secondary centers for the metacarpals, metatarsals, and phalanges are retarded in appearance. The metacarpals are broader at the distal end than at the proximal end. The first metatarsal is broader and wider than the others (1,4,28,41,44) (Fig. 7–45C).

Dislocation or subluxation of hips and coxa vara are associated with flattening of the acetabular roof and delayed appearance and poor development of the capital femoral epiphysis. The patella is often subluxated. Progressive kyphosis of the cervical region of the spine, with subluxation of the second and third cervical vertebrae, is frequent and may result in spinal cord compression (2,13,25,28). The interpediculate distance tends to narrow below the third lumbar vertebra (2) (Fig. 7–45C–F). Death later in life results from progressive cervical kyphosis with medullary compression (25) (Fig. 7–45F). Intelligence is normal.

Precocious ossification of costal cartilages and calcification of pinnal cartilage occur in at least 80% of patients. Intracranial calcification has also been described (43).

Currarino (3a) pointed out that 50% of children have a double-layered manubrium sternum.

Histopathologic study has shown a generalized degenerative disorder of cartilage, with focal death of cells followed by matrix dissolution, cyst formation, fibrovascular scarring, and dystrophic ossification (34). Characteristic histopathologic findings include degeneration of chondrocytes, abnormal distribution of collagen in resting cartilage, and large cystic lesions in the resting cartilage which exhibits intracartilaginous ossification (16). Similar findings have been reported in fetuses (31).

Oral manifestations. The mouth is full and broad, with the lower lip slightly larger than the upper. Cleft palate has been found in 25%–60% of patients (1,20,28,37,42). Rintala et al (36) reported 43% of their patients with cleft palate and 32% with submucous palatal cleft. Oddly, this latter group did not have nasal speech. They further estimated that 10% had glossoptosis due to micrognathia. These investigators noted at a later time that 12 of 39 cases had cleft palate, and 11 had submucous cleft palate (21). Most patients have some degree of micrognathia. Teeth may be small (19). The abnormal size and shape of the vocal tract lead to hyponasality (22).

Differential diagnosis. The disorder may be confused with a plethora of chondrodysplastic and other disorders, such as arthrogryposis, *achondroplasia*, *atelosteogenesis type I*, and *cartilage-hair hypoplasia* (28,43). *Pseudodiastrophic dysplasia*, a rare recessive bone dysplasia, has a somewhat similar phenotype, but has interphalangeal joint dislocations and platyspondyly. The characteristic degeneration of cartilage is not evident.

Pinnal calcification can rarely be seen in other disorders such as ochronosis, Addison's disease, acromegaly, systemic chondromalacia, familial cold hypersensitivity (43), Nance-Sweeney chondrodysplasia, and *Keutel syndrome*.

Laboratory aids. Prenatal diagnosis has been made by ultrasonography (6,7,18,32) and with polymorphic DNA markers (11). In fetuses, scoliosis and joint contractures are usually absent (33).

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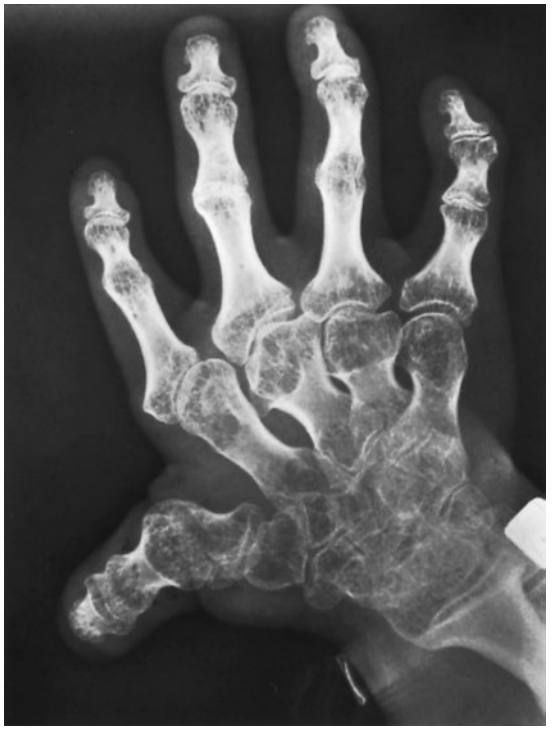

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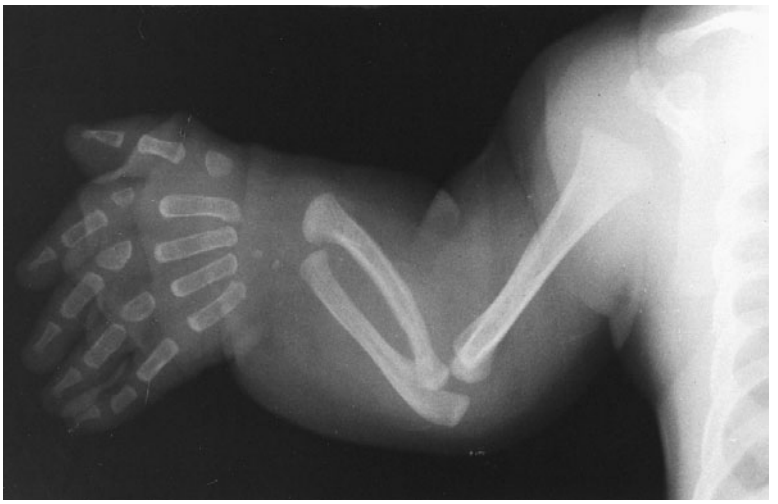

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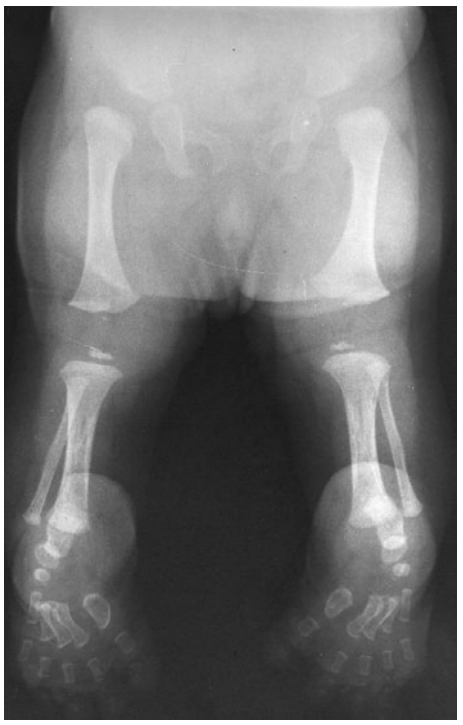

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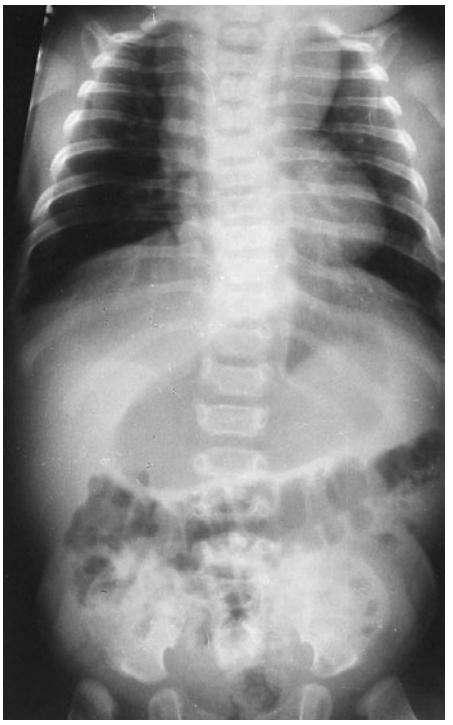

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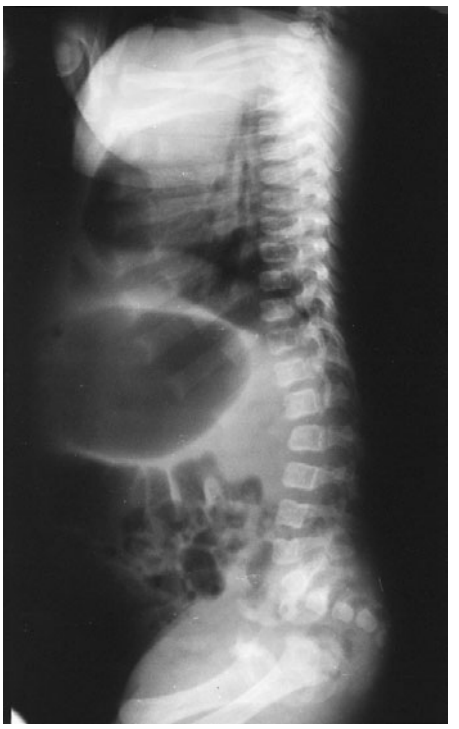
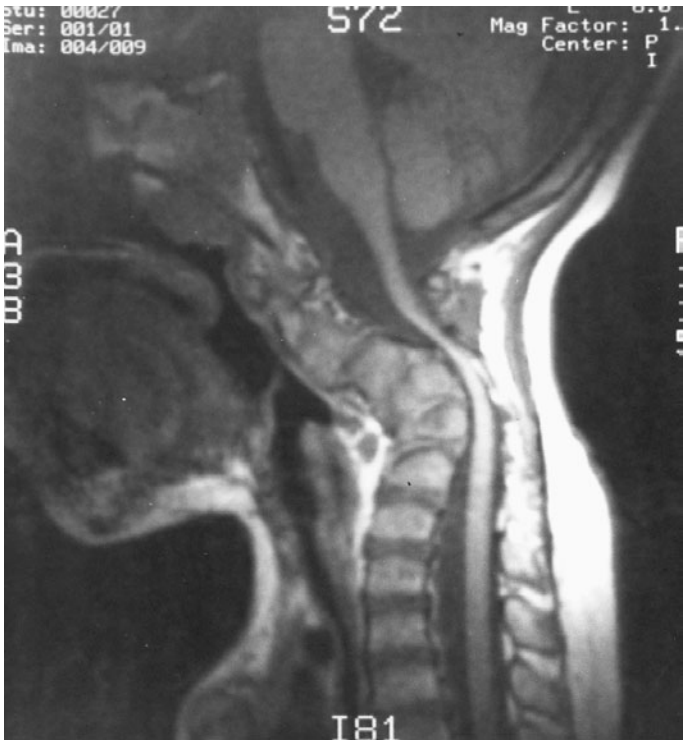


E

Fig. 7–45. *Diastrophic dysplasia.* Radiographs. (A) Short, broad metacarpals with widened metaphyses. The first metacarpal is particularly shortened. Fusion is evident at the proximal interphalangeal joint of the second to fourth fingers. (B–E) Shortening and thickening of tubular bones, proximally placed thumb, talipes, and narrow interpediculate distance below the third lumbar vertebra. (F) Magnetic resonance image showing compression of spinal cord at C4 level. (A from J Spranger and G Gerken, Z Kinderheilkd 98:227, 1967. B–E courtesy of G Aicardi, Genoa. F from J Krecak and RJ Starshak, Pediatr Radiol 17:321, 1987.)



F

Fig. 7–45. (*cont.*)

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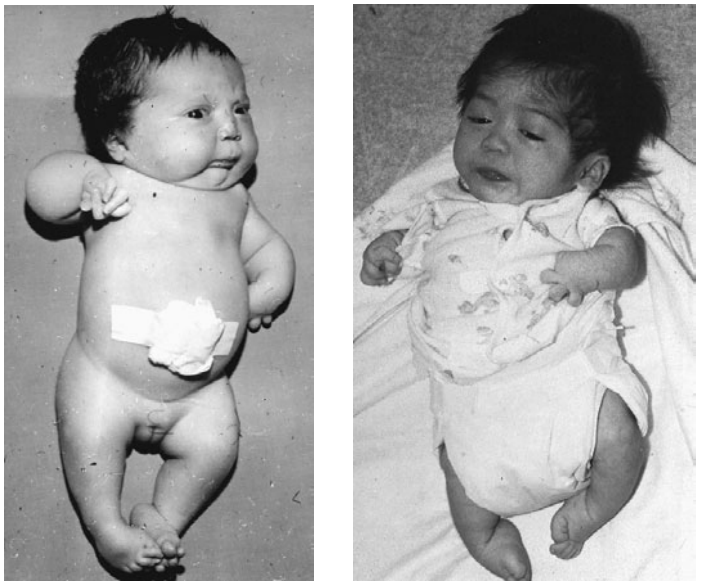
Pseudodiastrophic dysplasia

In 1974, Burgio et al (2) were the first to describe an autosomal recessive condition that they called "pseudodiastrophic dwarfism." Eight additional patients have been reported (1,3,4,6,7). Although the clinical findings are somewhat similar to those of diastrophic dysplasia, distinct radiologic and chondroosseous histologic differences are evident. Furthermore, while diastrophic dysplasia has been shown to be caused by mutations in the diastrophic dysplasia sulfate transporter gene, this gene is not involved in pseudodiastrophic dysplasia (5).

There is rhizomelic shortening of the limbs and severe clubfoot deformity, but no "hitchhiker's thumb" (Figs. 7–46 and 7–47). The patients described by Burgio et al (2), Canki et al (3), Canki-Klain (4) and Fischetto et al (7) died within the first year of life. However, Eteson et al (6) reported two children over the age of 4, one of whom was later reported to be alive at 16 years (5), and Canki-Klain et al (4) described a child of almost 6 years.

Among the ten cases described to date, six had cleft palate. At birth, the cranium is enlarged with midface hypoplasia. The sclerae appear somewhat bluish. There is mild hypertelorism, flat nasal bridge, large malformed earlobes, and folded superior helices, dislocated elbows, interphalangeal dislocations, and clubfeet. Long clavicles, slightly short ribs with anterior flaring, and platyspondyly with scoliosis can be found. The pelvis appears normal with horizontal acetabular roofs and medial and lateral acetabular spikes. Rhizomelic shortening of limbs, elbow dislocations, and interphalangeal joint dislocations of the hands and clubfeet are characteristic. Later, in infancy and early childhood, the vertebral bodies



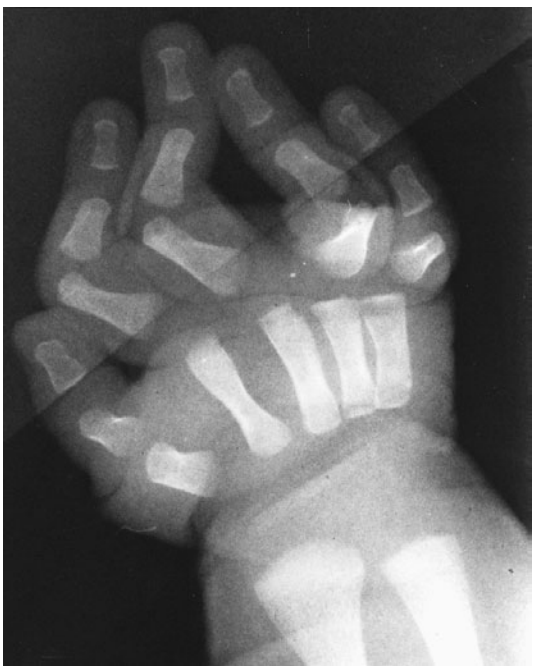
A B

Fig. 7–46. *Pseudodiastrophic dysplasia.* (A,B) Flat nasal bridge, short limbs, finger contractures, and clubfeet. (A from G-R Burgio et al, Arch Fr Paediatr 31:681, 1974. B from DE Eteson et al, J Pediatr 109:635, 1986.)

appear hypoplastic, and platyspondylic scoliosis progressively worsens. The sacrosciatic notches become smaller.

Radiographic features that distinguish the syndrome from that of diastrophic dysplasia are platyspondyly, rhizomelic shortness of limbs, and dislocation of elbow, knee, and proximal interphalangeal joints. The degeneration of cartilage, characteristic of diastrophic dysplasia, is not seen in pseudodiastrophic dysplasia, in which irregular myxoid degeneration with small cystic areas is seen. In pseudodiastrophic dysplasia there is no cystic enlargement of the pinnae.

Fig. 7–47. *Pseudodiastrophic dysplasia.* Radiograph of hand showing multiple interphalangeal and metacarpophalangeal joint dislocations with resultant ulnar and radial deviation of digits. (From DE Eteson et al, J Pediatr 109:635, 1986.)



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Dyggve-Melchior-Clausen syndrome

This syndrome was first defined by Dyggve et al (6) in 1962, although earlier examples appear to have been published (9). It is a disorder of short-trunk dwarfism and mental retardation and has most often been mistaken for Morquio syndrome (Figs. 7–48 to 7–50). About 50 examples have been reported.

There is genetic heterogeneity, with both forms being autosomal recessive. One form is the Dyggve-Melchior-Clausen syndrome, and includes mental retardation (1–4,6,7,9,11,12,15,22–24); the other, which has no mental retardation, is commonly called "Smith-McCort" syndrome (8,10,13,14,16,21,23). X-linked inheritance has been suggested (5,26), but the patients in these reports probably had X-linked spondyloepiphyseal dysplasia, tarda type. Among those patients with mental retardation, several are Lebanese (4,15) or Moroccan (2,20) in origin. The high carrier frequency is probably the explanation for the unexpected recurrence in the son of a brother of affected sibs (RCM Hennekam, unpublished observation). Obligate heterozygotes are clinically normal. There is no clue regarding mapping of the gene.

Neonatal measurements are normal. Life span, apart from the risk of atlantoaxial instability, is normal. A summary of all major findings is provided in Table 7–7.

Facies. The face is coarse with a prominent mandible. Adults often have a receding forehead.

Table 7–7. Dyggve-Melchior-Clausen syndrome findings ($n = 44$)

Clinical findings	
Mental retardation	44/44
Short stature	44/44
Rhizomelia	27/30
Microcephaly	34/37
Short neck	27/29
Prominent sternum	36/39
Short thorax	39/40
Scoliosis	11/29
Increased lumbar lordosis	33/39
Restricted joint mobility	27/29
Genua valga	15/24
Waddling gait	31/33
Radiological findings	
Platyspondyly	43/44
Notched anterior vertebral bodies	37/40
Hypoplastic dens	26/27
Hypoplastic scapulae	27/29
Hypoplastic iliac bones	40/40
Lacy iliac crest	39/42
Dysplastic acetabulum	30/30
Short, broad phalanges	40/42
Delayed ossification of epiphyses	37/37

Adapted from FA Beemer and RCM Hennekam, T Kindergeneeskd 52:103, 1984.

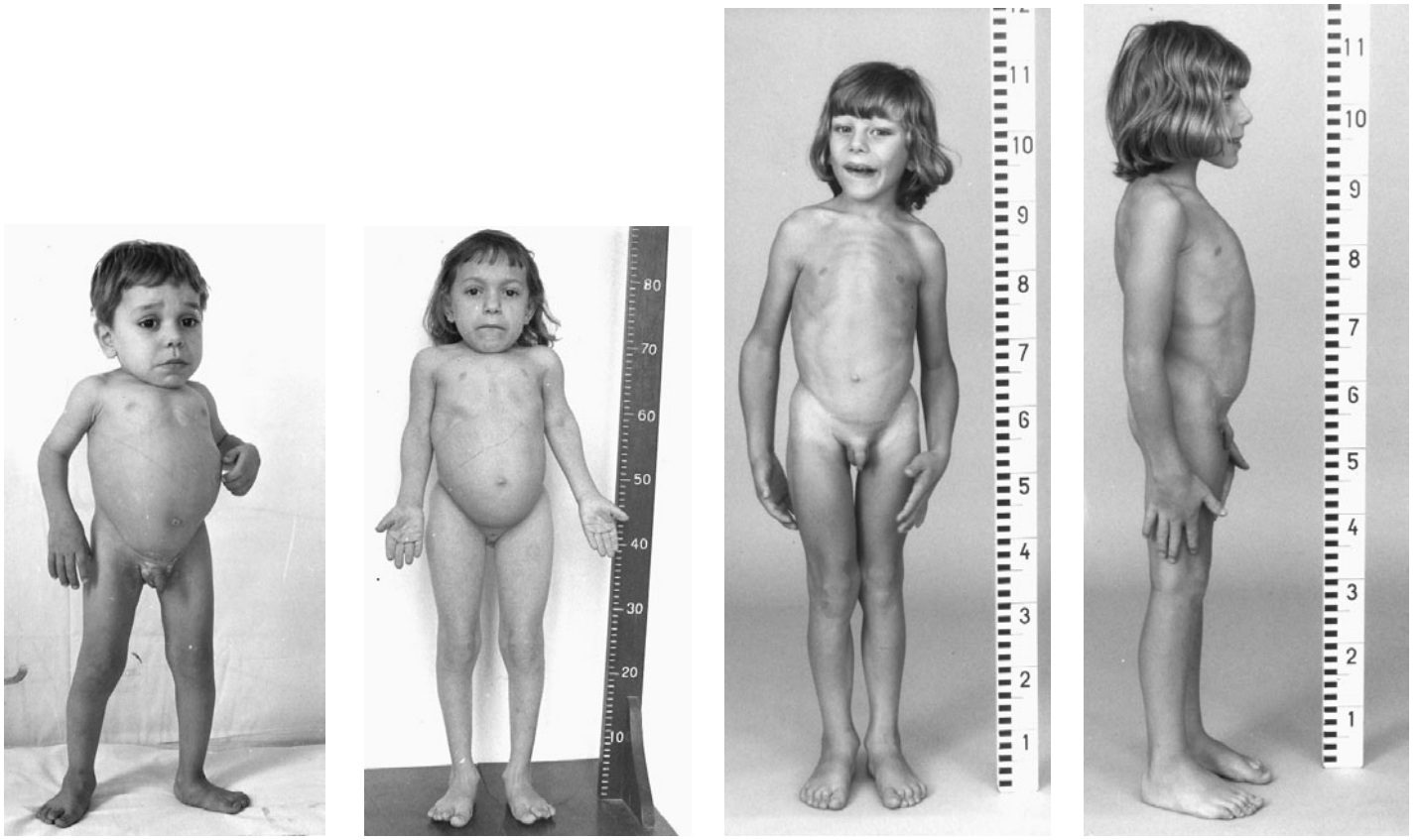


Fig. 7–48. *Dyggve-Melchior-Clausen syndrome.* (A–D) Short-trunk dwarfism. Ten-year-old male in C,D with short stature, protrusion of sternum, and thoracic kyphosis. (A,B from SPA Toledo et al, Am J Med Genet 4:255, 1979. C,D from R Schlaepfer et al, Helv Paediatr Acta 36:543, 1981.)

Fig. 7–49. *Dyggve-Melchior-Clausen syndrome.* (A) Platyspondyly with central indentation and ventral pointing. (B) Marked platyspondyly in older individual. (A from R Schlaepfer et al, Helv Paediatr Acta 36:543, 1981. B from HV Dyggve et al, Neuropadiatrie 8:429, 1977.)

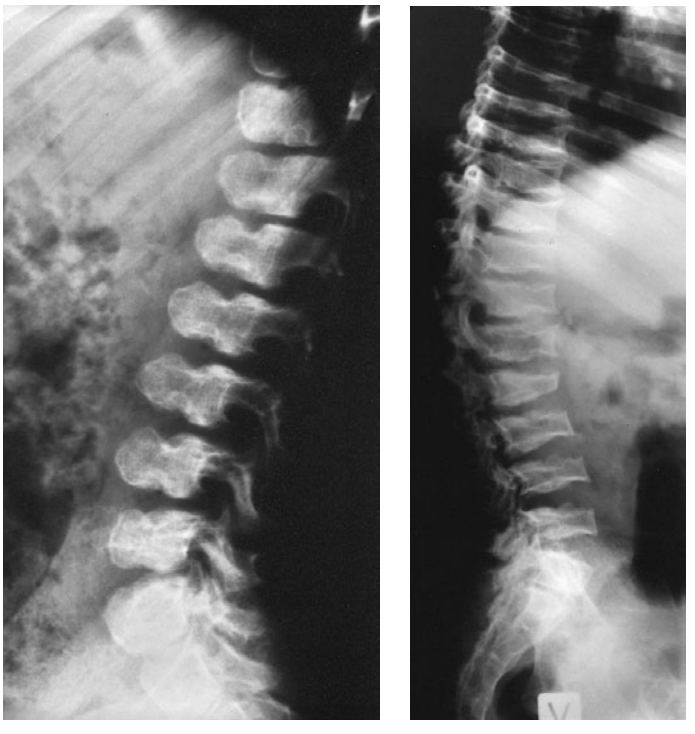
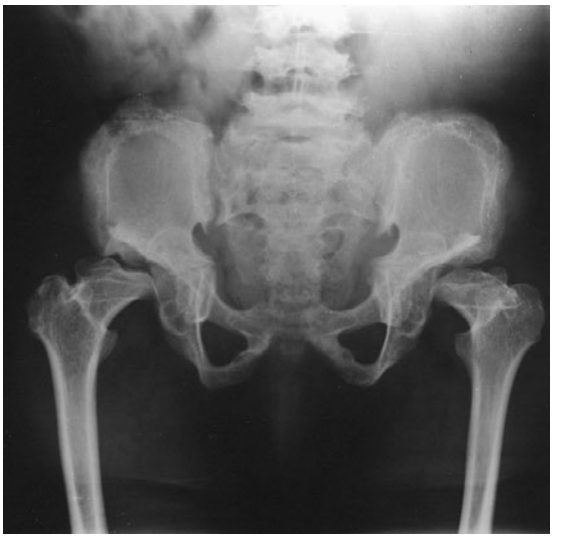


Fig. 7–50. *Dyggve-Melchior-Clausen syndrome.* Short and broad iliac wings with lacy crests. Ischial and pubic bones are somewhat plump with flattened, poorly demarcated acetabula; hypoplasia and shortening of femoral necks are evident. (From HV Dyggve et al, Neuropadiatrie 8:429, 1977.)



Central nervous system. In the Dyggve-Melchior-Clausen form, milestones are delayed and progressive mental deficiency is mild to moderate (IQ 35–65); there is also microcephaly, with the adult head circumference rarely exceeding 47 cm. In the Smith-McCort type, head circumference is only mildly reduced (53–54 cm) and intelligence is normal.

Skeletal changes. Adult height ranges from 98 to 127 cm (mean 119 cm). By age 5–8 years, disproportionate stature becomes evident. The trunk and neck are short, the chest is barrel shaped with a protruding sternum, and thoracic kyphosis and lumbar lordosis occur (Fig. 7–48). Joint mobility is somewhat restricted. Atlantoaxial instability predisposes to spinal cord compression (15). There is rhizomelic limb shortening and genua valga. Most patients assume a crouching stance and walk with a waddling gait. The hands and feet are broad and may show camptodactyly.

Radiographic changes. These changes include disproportionately large facial bones with hyperpneumatization of paranasal sinuses and calvarial thickening in parietal and occipital regions. The vertebrae are flattened with irregular endplates and notching of the anterosuperior bodies in the lumbar region (Fig. 7–49). The odontoid process is often hypoplastic. The ilia are small and irregular with a wide pubic symphysis. The iliac crests have a lacy outline during childhood that becomes a nonspecific irregularity in adulthood (Fig. 7–50). The acetabula are sloping and dysplastic. The femoral heads are small, flattened, and usually dislocated. The shoulder joints are similarly affected. The humoral diaphysis is short and curved with distal metaphyseal flaring. The radial heads and olecranons are dysplastic and the metacarpals are shortened. The proximal row of carpal bones is small. Otherwise, the hand bones are essentially normal. The bones of the lower extremities are less severely affected (2–4,19,20,22,25). Usually patients do not have internal anomalies, although in one patient, valvular aortic stenosis was noted (17).

On light microscopy, resting cartilage cells show lacunae containing clusters of five or more chondrocytes in some areas. The cartilage matrix is very fibrous. Horton and Scott (11) described clusters of degenerating chondrocytes. Electron microscopic studies revealed that the chondrocytes exhibit cisternae of rough endoplasmic reticulum and vesicles coated with a smooth, single-layered membrane (8). Biochemical analysis of cartilage showed increased glucosaminoglycans (8). The findings in Smith-McCort syndrome are similar (16).

Differential diagnosis. In contrast to *Morquio syndrome*, no mucopolysaccharidurias and no corneal clouding occur. Normal hearing and teeth, microcephaly, and mental retardation are characteristic. The skeletal changes are truly different in spite of somewhat similar appearance (e.g., the lacy iliac crest, the eventually normal bones of the hands). There may be resemblance to *spondyloepiphyseal dysplasia*.

Laboratory aids. Some investigators have found elevated chondroitin sulfate-*N*-acetylgalactosamine 6-sulfate sulfatase and reduced aryl sulfatase glycoprotein-AMP metabolism (7). The uptake of radioactive sulfate (22) or results from other proteoglycan degradation studies (3) were normal. The increased pipecolic acid levels (18) were not found in other cases (RCM Hennekam, unpublished observations). Reliable prenatal diagnosis is currently not possible.

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Dyssegmental dysplasia, type Silverman-Handmaker

Apparently, the first illustrated report of this bone dysplasia, which was lethal at birth, was that of Simmonds (15) who, in 1901, was trying to illustrate the value of radiographic diagnosis.

Almost 70 years were to pass before the second case of anisospondylic micromelic dwarfism was described by Silverman (14). There have been about 20 examples published under various terms (1–10,12–17), another possible case being that of Maisonneuve et al (11). Gorlin and Langer (5) described the early history of the disorder. Prabhu et al (13) provide a review. Inheritance is autosomal recessive (2,4,10,13). A defect in the *PAX1* gene should be looked for.

Polyhydramnios has been noted in about 25% of cases. Birth weight is generally normal but birth length is reduced as a result of short spine and curved lower limbs. The infants are either stillborn (40%) or live only a few days, although there are exceptions (2,13). Hydrocephaly and occipital encephalocele have been reported (1,8). In a few cases there was a defect in the occipital bone (1,6). Other CNS anomalies are polymicrogyria (6), Dandy-Walker malformation and cerebellar hypoplasia (1), and arachnoid cyst (13).

The facies is somewhat unusual. There is mild blepharophimosis, flat nasal bridge, hypoplastic supraorbital ridges, and dysplastc ears. The mandible is small and the neck remarkably short (Fig. 7–51). Cleft palate is reported in about one-half of the cases (1,8,12,13–16).

The chest is narrow. Reduced joint mobility is a constant feature. The limbs are short and curved (microcampomelia) with talipes equinovarus (Fig. 7–51). The fingers may wedge and the thumbs may be adducted. Lumbosacral kyphosis may be marked. Hirsutism has been present in about 90% of the cases. Inguinal and/or umbilical hernia have been

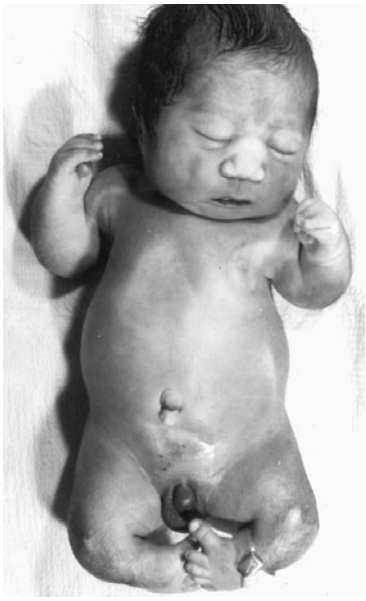

Fig. 7–51. *Dyssegmental dysplasia, type Silverman-Handmaker.* Abbreviated limbs, overlapping fingers with cortical thumbs, flat nose, and hirsutism of lower legs. [From RJ Gorlin and LO Langer Jr, Birth Defects 14 (6B):193, 1978.]

reported (8). In the few cases that have come to autopsy, hydroureter and hydronephrosis have been observed in the more severe examples (1,4,7,8,17). Patent ductus has been found in several patients (1,4,7,8). A longer-surviving patient had subluxated lenses at 6 weeks of age, and showed minimal developmental progress at 8 months (13).

Radiographically, short trunk and narrow thorax are evident. The vertebral bodies are of variable size, thickness, and width (anisospondyly). Most vertebral bodies consist of two or more ossified masses separated by vertical radiolucent clefts in lateral view (Figs. 7–52 and 7–53). The iliac bones have decreased vertical dimension with hypoplasia of the horizontal and inferior margins, giving them a rounded shape. The acetabula are small in comparison to the wide proximal femora. The sacrosciatic notches are narrow and deep. There is severe symmetric shortening of all tubular bones with marked metaphyseal flaring and cupping. The long bones may appear to be somewhat folded upon themselves, particularly the ulnae (Fig. 7–52). The scapulae are small and rounded in comparison to the wide humeral metaphyses. The radius is disproportionately short. The first metacarpals are particularly abbreviated.

Microscopically, a disturbance in enchondral ossification is apparent, including a lack of columnization, ballooning of cartilage cells, mucoid degeneration of resting cartilage, and prominent large, unfused calcospherites in the growth plate and calcifying zones. There is accumulation of acid mucopolysaccharides and no increase in collagen fibers (Fig. 7–54) (6,7). The disorder may have a disturbance in formation of α 1-collagen chains (17).

Differential diagnosis includes *Kniest syndrome and Burton syndrome*. More disturbed chondrocyte columnization is seen in Kniest syndrome, but the same "Swiss cheese" cystic changes are observed. Prenatal diagnosis by ultrasound has been accomplished (2,8,8a,9).

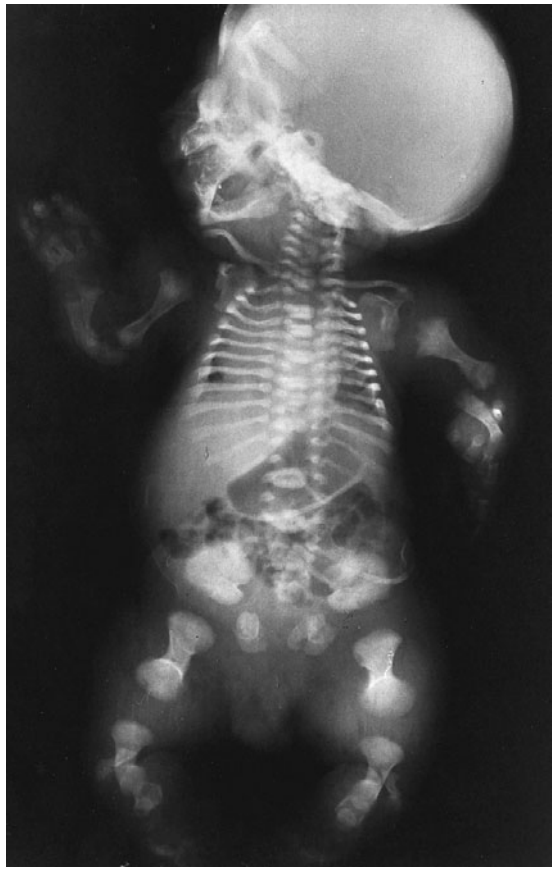

Fig. 7–52. *Dyssegmental dysplasia, type Silverman-Handmaker.* Radiograph showing severe symmetric shortening of all tubular bones with marked metaphyseal flaring and cupping. The ulnae appear to be somewhat folded on themselves. The trunk is short and the thorax narrow. Vertebral bodies are of variable sizes, thickness, and width. The iliac bones have decreased vertical dimensions with hypoplasia of the horizontal and inferior margins, giving them a rounded shape. Acetabula are small in comparison to the wide proximal femora. The sacrosciatic notches are narrow and deep.

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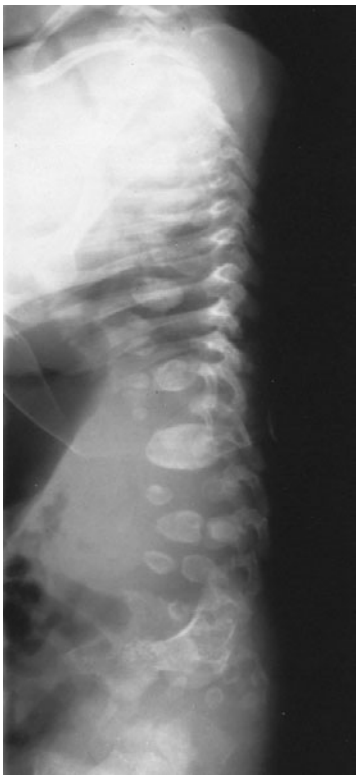

Fig. 7–53. *Dyssegmental dysplasia, type Silverman-Handmaker.* Radiograph showing abnormal vertebral bodies with anisopondyly.

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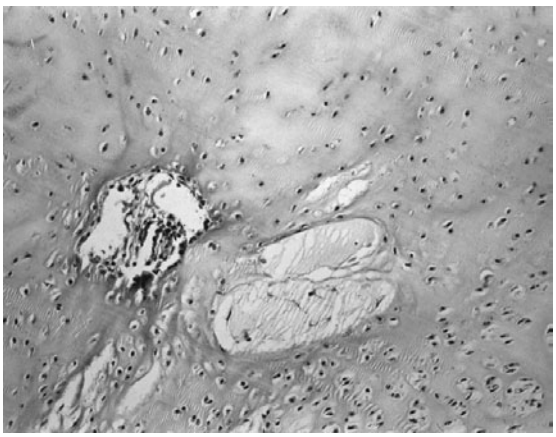
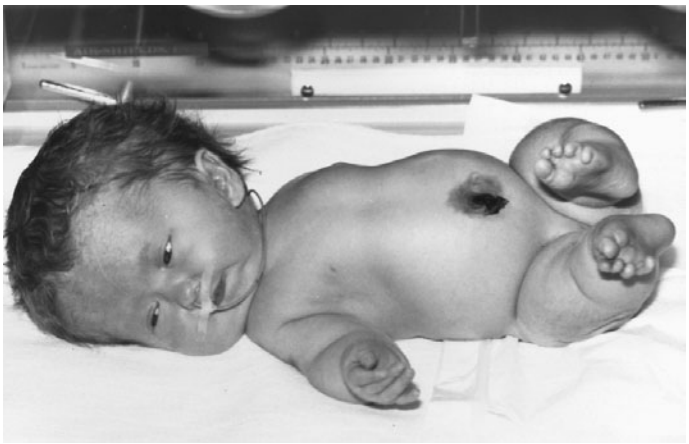
Dyssegmental dysplasia, type Rolland-Desbuquois

In 1972, Rolland et al (12) reported an infant with a short-limbed chondrodysplasia that resembled Kniest syndrome (Figs. 7–55 to 7–58). About 35 examples have been described by other authors (1–4,6). It is considered to be a mild form of dyssegmental dysplasia (1,3,8). The disorder is lethal in about 40% of patients, but many survive past infancy (7,9,10). Inheritance is autosomal recessive (1,3,12). All affected infants exhibit neonatal distress.

Fig. 7–54. *Dyssegmental dysplasia, type Silverman-Handmaker.* Puddle-like spaces in cartilage matrix.





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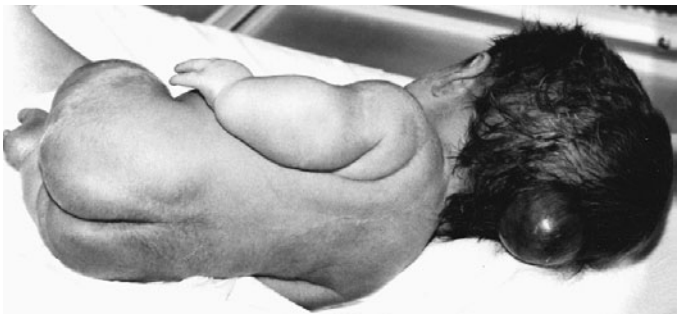

B

Fig. 7–55. *Dyssegmental dysplasia, type Rolland-Desbuquois.* (A,B) Infant with hydrocephaly, occipital encephalocele, and short limbs. (From N Dinno et al, Eur J Pediatr 123:39, 1976.)

The facies is similar to that seen in dyssegmental dysplasia, type Silverman-Handmaker. The orbits are shallow. The face is round and flat with relative micrognathia. One infant manifested an occipital encephalocele (4), another an occipital defect (1), and two had hydrocephalus (4,6). One child had dislocated lenses (6), and two had glaucoma (8). Cleft palate has been found in most cases.

As in the Silverman-Handmaker type, there is microcampomelia, decreased joint mobility, narrow chest, and hirsutism. Hernia is noted in a few infants (1,6,12), but the radiologic changes are less severe. The long bones are short, broad, and bowed with some degree of metaphyseal widening. The pelvis appears essentially normal. Lateral spinal views demonstrate variability in size and shape of the vertebral bodies and prominent coronal clefting, but less than that seen in the Silverman-Handmaker type. There is accelerated carpal bone maturation (6). The ribs are short and flared (Figs. 7–56 to 7–58).

Chondroosseous morphology is characterized by patches of broad collagen fibers. The growth plate is normal but foamy Kniest-like changes may be observed in the resting cartilage cells. *COL2A1* mutations have not been found (8).

The disorder reported by Maroteaux et al (8) had Kniest-like features. Dyssegmental dysplasia, type Rolland-Desbuquois, should not be confused with the Larsen-like disorder that is referred to as "Desbuquois syndrome" (13). Desbuquois syndrome, which also has autosomal recessive inheritance, is characterized by short stature, flat midface, prominent eyes, short neck, narrow thorax, and joint laxity. Radiographic changes include osteoporosis, short long bones with broad metaphyses, prominent lesser trochanter, flat acetabular roof, advanced carpal and tarsal bone age, and supernumerary phalanges (2,5,13).

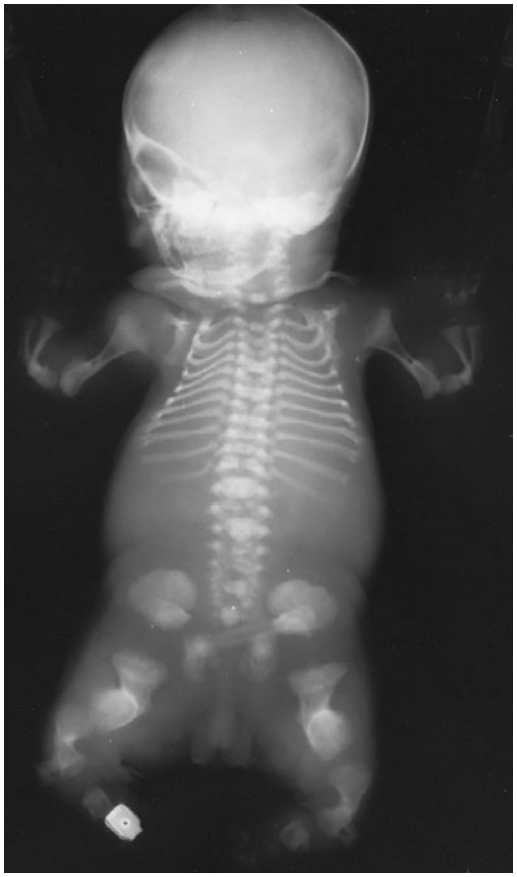

Fig. 7–56. *Dyssegmental dysplasia, type Rolland-Desbuquois.* Radiograph showing short, broad long bones with metaphyseal widening. The chest is narrow and the ribs are short and flared. (Courtesy of LO Langer, Jr, Minneapolis, Minnesota.)

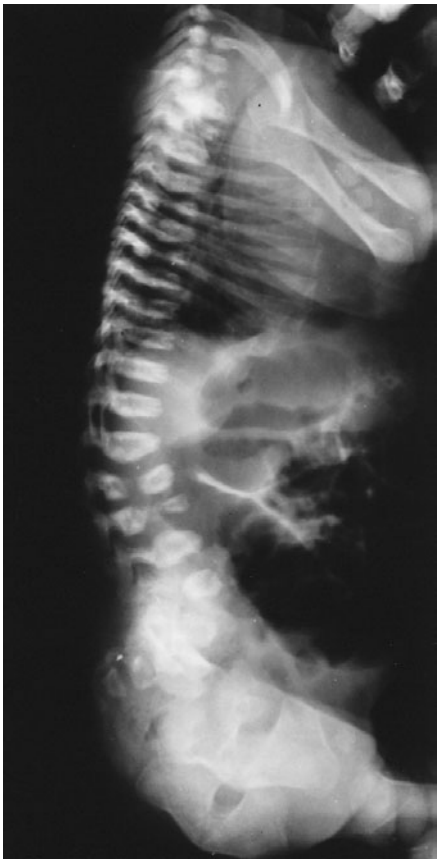

Fig. 7–58. *Dyssegmental dysplasia, type Rolland-Desbuquois.* Lateral spine radiograph showing variability in size and shape of vertebral bodies and prominent coronal clefting. (Courtesy of LO Langer, Jr, Minneapolis, Minnesota.)

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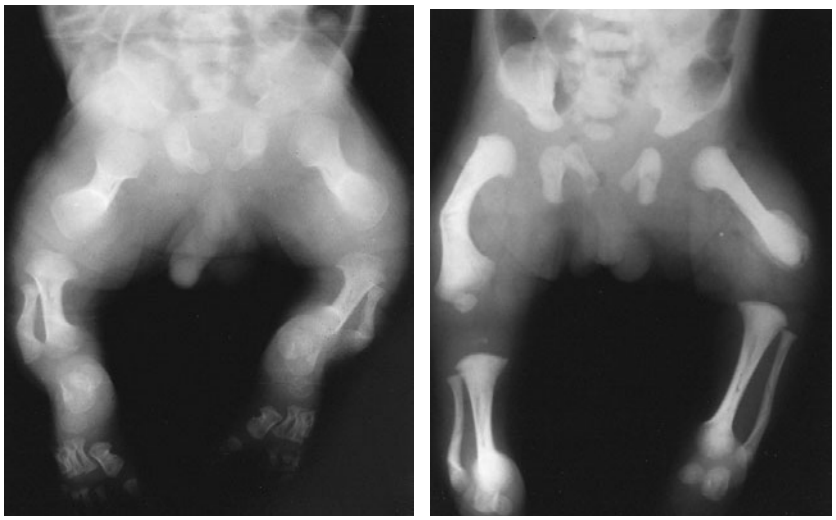

A B

Fig. 7–57. *Dyssegmental dysplasia, type Rolland-Desbuquois.* (A,B) Radiographs of lower limbs at different ages. Long bones are short and broad with some metaphyseal widening. Note bowing in B. (Courtesy of LO Langer, Jr, Minneapolis, Minnesota.)

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Ellis–van Creveld syndrome (chondroectodermal dysplasia)

Credit is given to Ellis and van Creveld (13) for describing the complete syndrome that bears their names and calling it "chondroectodermal dysplasia." The disorder, partially described in several earlier reports (1,4,28,33,52), consists of bilateral postaxial polydactyly of the hands, chondrodysplasia of long bones resulting in acromesomelic dwarfism, ectodermal dysplasia affecting nails and teeth, and congenital heart anomalies. The syndrome has autosomal recessive inheritance (25a,26,27,37). The gene is allelic with that of Weyers acrodental dysostosis (37a). Parental consanguinity has been confirmed in about 30% of cases (9,11,13,19,25a,29,37; RCM Hennekam, unpublished observations). Several authors have suggested that postaxial polydactyly may be a heterozygote manifestation of the syndrome (16,19,41), although this was not found in several other large pedigrees (9,25a,26). Ellis–van Creveld syndrome is the most common type of dwarfism among the Amish (25a,26). McKusick et al (25a,26) found 52 cases in 50 sibships among the Amish isolate of Lancaster County, Pennsylvania. The disorder has been reported in non-Amish populations as well (9,19,24). Birth prevalence has been estimated at 7/1,000,000 (42). There are about 300 reported cases.

The life expectancy is mainly determined by the congenital heart defect and the respiratory problems due to the thoracic cage deformity. The oldest living patient was 82 years of age (9). Nagai et al (30) reported a boy with symptoms fitting both Jeune syndrome (asphyxiating thoracic dysplasia) and Ellis–van Creveld syndrome. Polymeropoulos et al (34) have demonstrated linkage to chromosome 4p16. The gene, *EVC*, is a transcription factor having a leucine zipper (37a). Asphyxiating thoracic dystrophy and the short rib–polydactylies have been excluded from this region (24).

Facies. The facies is not especially characteristic except for a mild defect in the middle of the upper lip, which, although often present, is usually not striking. Some patients have been noted to have hypertelorism (9,43).

Skeletal anomalies. The extremities are often plump and markedly shortened progressively distalward, that is, from the trunk to the phalanges (Fig. 7–59). Bilateral postaxial hexadactyly is frequent (Fig. 7–60) and heptadactyly has also been noted (12). Frequently, the patient cannot make a tight fist. Less frequently there are extra toes (9,21,26,27). A wide space is often present between the hallux and the other toes (40). Genua valga (9,29), curvature of humerus, talipes equinovarus (9,47,49), talipes calcaneovalgus (11), and pectus carinatum with thoracic constriction (12,26,40) have also been reported.

Radiographically, the tubular bones are short and thickened. The diaphyseal ends of the humerus and the femur are plump. Shortening of the radius and ulna is even more marked than that of the humerus. The proximal end of the ulna and the distal end of the radius are unusually large, and the proximal end of the radius and the distal end of the ulna are unusually small (Fig. 7–61A,B). Duplication of the ulnar ossification center may be present in the first year of life (20). The widened end of the tibial shaft is irregular, and the ossification centers in the proximal epiphysis are hypoplastic (Fig. 7–61A,B). There is peaking of the proximal tibia, with a long lateral and a short medial slope, resulting in genua valga after the age of 6 years (26). The fibula is most severely shortened, being only about 50% of normal length (12). Syncarpalism (hamate and capitate), synmetacarpalism, and polymetacarpalism are frequent (5,9,21,26,29,31) (Fig. 7–61C,D). Cone-shaped epiphyses of the hands (type 37 of Giedion) are pathognomonic for the syndrome (18) (Fig. 7–61C).

In infancy, the pelvis is dysplastic with low iliac wings and hook-like downward projection of the medial acetabulum. The capital femoral epiphysis may ossify prematurely. In childhood, the pelvic shape normalizes. Histopathologic studies in three fetuses showed chondrocytic disorganization in the physeal growth zone, both in the long bones and vertebrae (36).

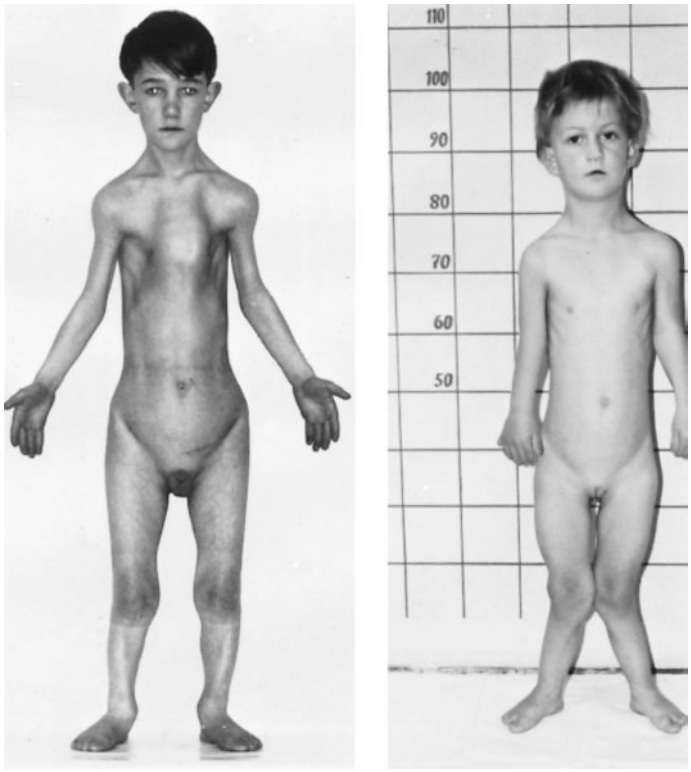
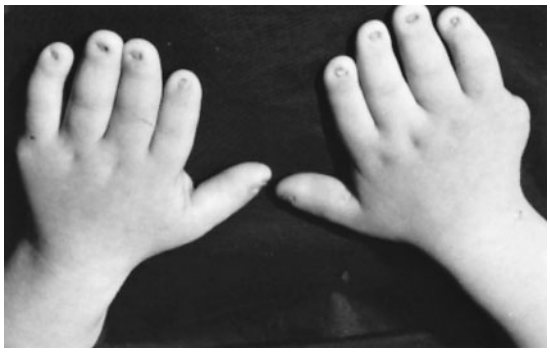


Fig. 7–59. *Ellis-van Creveld syndrome.* (A) Long thorax with pectus carinatum; mesomelia of lower extremities. (B) Compare phenotype with A. (A from GB Winter and M Geddes, Br Dent J 122:103, 1967. B from HO Bützler et al, Fortschr Geb Roentgenstr Neuen Bildgeb Verfahr Erganzungsbd 118:537, 1973.)

Fig. 7–60. *Ellis-van Creveld syndrome.* Digits are abbreviated, with hypoplastic nails. Note that digits have been amputated on ulnar side. (Courtesy of DH Altman, Miami, Florida.)



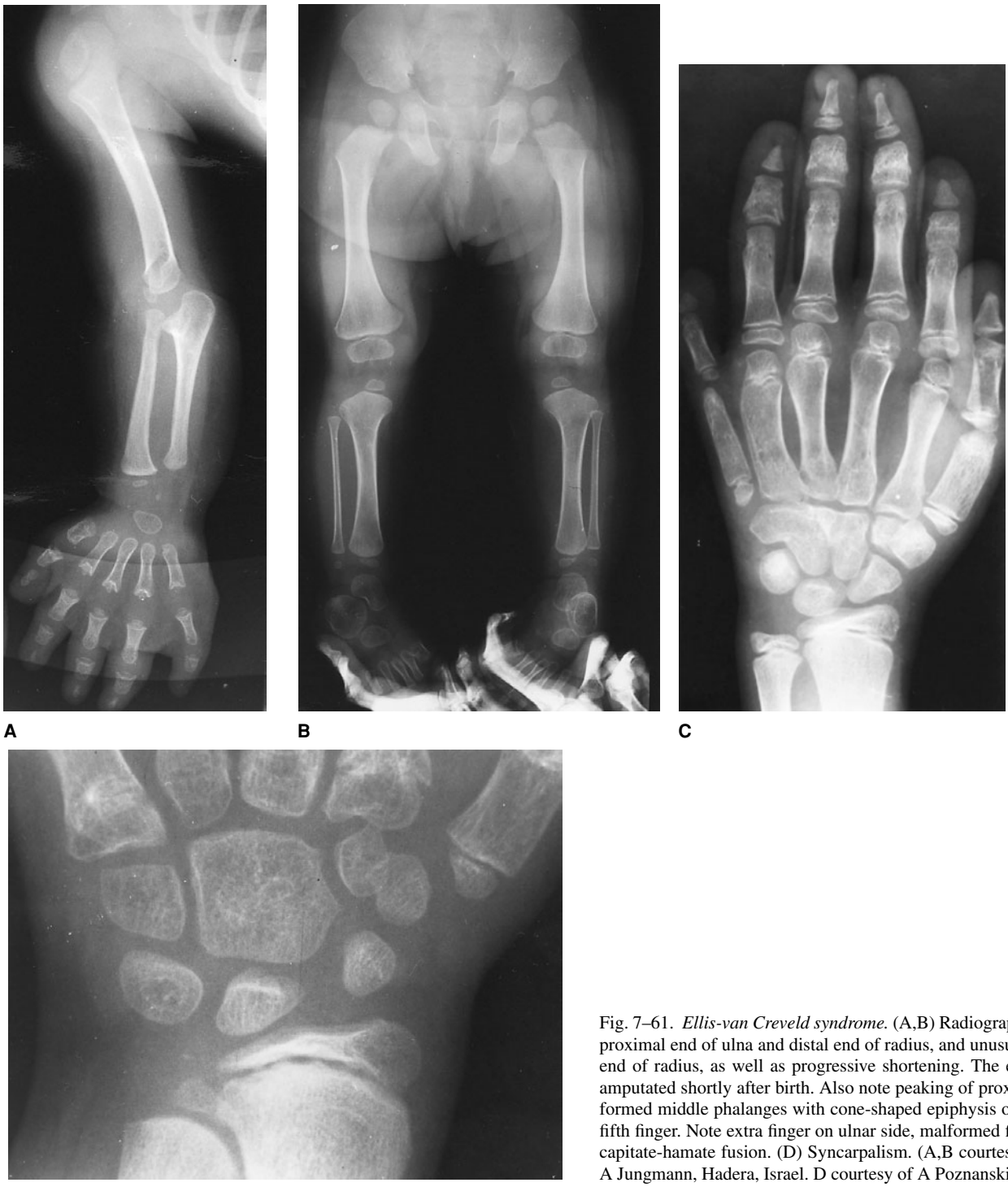


Fig. 7–61. *Ellis-van Creveld syndrome.* (A,B) Radiographs. Unusually large proximal end of ulna and distal end of radius, and unusually small proximal end of radius, as well as progressive shortening. The extra digit had been amputated shortly after birth. Also note peaking of proximal tibia. (C) Malformed middle phalanges with cone-shaped epiphysis of middle phalanx of fifth finger. Note extra finger on ulnar side, malformed fifth metacarpal, and capitate-hamate fusion. (D) Syncarpalism. (A,B courtesy of D Gutman and A Jungmann, Hadera, Israel. D courtesy of A Poznanski, Chicago, Illinois.)

Heart. Congenital heart defects are found in 50%–60% of patients (9,24), the most frequent defects being single atrium (40%) and endocardial cushion defect (14). Some patients have cor triloculare (29), atrioventricular canal (10,36), or even cor biloculare (40). Lynch et al (24) have reviewed the heart anomalies comprehensively.

Hair and nails. The hair, particularly the eyebrows and pubic hair, has been stated to be thin and sparse (13,21,26,29,50). However, RJ Gorlin has not been impressed that this is a feature. Nearly all patients have severe dystrophy of the fingernails, which are markedly hypoplastic, thin, and often wrinkled or spoon shaped (Fig. 7–60). Dermatoglyphic studies have shown an increased number of whorls (9).

Eyes. The eyes are usually normal, but esotropia (29) and congenital cataract (21,27) have been occasionally observed.

Genitourinary system. About one-third of male patients have genital anomalies. These anomalies have included cryptorchidism (13), mild epispadias (26,27), and hypospadias (26,48). Miscellaneous abnormalities of the urinary system have been reviewed by Rosemberg et al (37).

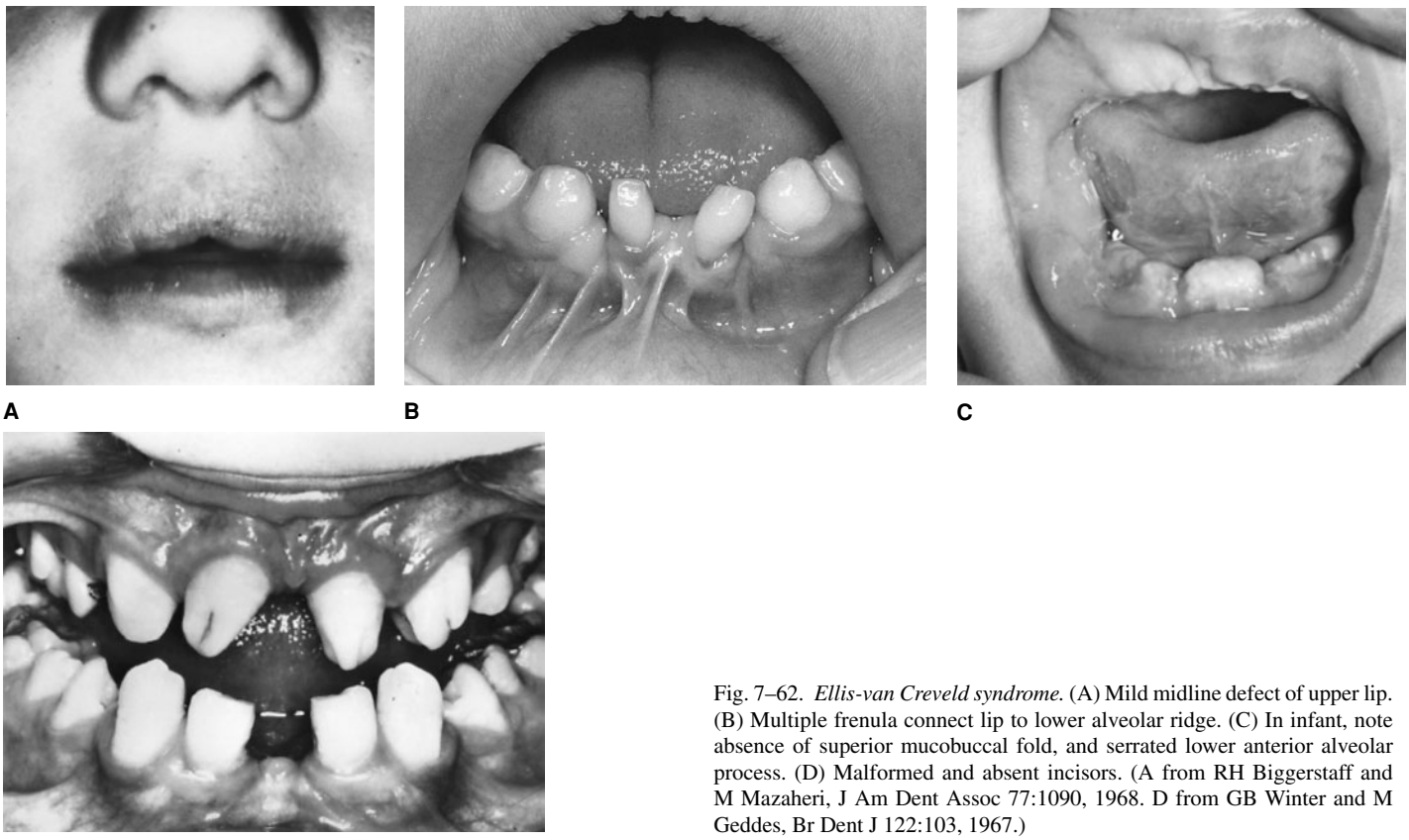


Fig. 7–62. *Ellis-van Creveld syndrome.* (A) Mild midline defect of upper lip. (B) Multiple frenula connect lip to lower alveolar ridge. (C) In infant, note absence of superior mucobuccal fold, and serrated lower anterior alveolar process. (D) Malformed and absent incisors. (A from RH Biggerstaff and M Mazaheri, J Am Dent Assoc 77:1090, 1968. D from GB Winter and M Geddes, Br Dent J 122:103, 1967.)

Central nervous system. Some patients are mentally retarded (32,48), but McKusick et al (26) have suggested that retardation is not an integral part of the disorder. Hydrocephaly has been noted is several instances (3,15). Other CNS anomalies have been reviewed by Rosemberg et al (37). Dandy-Walker malformation has been described (3,8,55).

Oral manifestations. The most striking and constant finding is fusion of the middle portion of the upper lip to the maxillary gingival margin so that no mucobuccal fold or sulcus is present anteriorly (2,9,11, 13,21,27,29,35,50). The middle portion of the upper lip appears to have a notch (2) (Fig. 7–62A). Natal teeth have been observed in at least 25% of patients and may be more frequent than reported. Congenitally missing teeth are also a constant finding, particularly in the mandibular anterior region (2,9,14,27,28,35,38,48) where the alveolar ridge is often serrated (2,11,13,40,47,54) (Fig. 7–62B,D). Notching of the lower alveolar process may represent continuation of the normal serrated condition of the gingiva from the third to the seventh month in utero (51) (Fig. 7–62C). Erupted teeth are usually small (2,27), have conical crowns, (2,9,12,13,28,53), and are irregularly spaced (2,13,14,28,53). Teeth that are not conical are somewhat bicuspid in form, with accentuated cuspal height and deep fissures (Fig. 7–62D). Supernumerary teeth have also been noted on occasion (21,35,38,53).

Differential diagnosis. It may be almost impossible to differentiate radiographically the Ellis-van Creveld syndrome from asphyxiating thoracic dystrophy (6,30,31). Patients may have identical changes in the hands, pelvis, and long bones. Differential diagnosis is based on the following clinical changes present in the Ellis-van Creveld syndrome: cardiac anomalies, nail hypoplasia, fusion of upper lip and gingiva, and, when present, neonatal teeth. Later in life, genua valga in Ellis-van Creveld syndrome and renal failure with hypertension in asphyxiating thoracic dystrophy help distinguish the two disorders.

The Ellis-van Creveld syndrome is differentiated from other chondrodystrophies such as achondroplasia, chondrodysplasia punctata, Morquio syndrome, and cartilage-hair dysplasia by its distinctive radiographic features. Fryns and Moerman (17) reported a newborn with an acromesomelic form of dwarfism that resembled the Ellis-van Creveld syndrome. Their case had in addition extensive vertebral segmentation defects.

Polydactyly and hypodontia or other dental anomalies have been seen in several generations without other apparent stigmata (46) and in association with acrodental dysostosis (Weyers) and trisomy 13. Postaxial polydactyly is also seen as a component of *Bardet-Biedl syndrome* (39). In combination with congenital heart defects and mucometrocolpos, the differentiation from McKusick-Kaufman syndrome may be difficult (54). An autosomal dominantly inherited disorder resembling both Ellis-van Creveld syndrome and *Weyers acrodental dysostosis* was mapped to chromosome 4p16. It was independently shown that Weyers acrodental dysostosis represents the heterozygous expression of the gene causing Ellis-van Creveld syndrome (22,37a).

Partial fusion of the upper lip as a result of hyperplastic frenula is seen in the *oro-facial-digital syndromes*. Natal teeth are observed in *pachyonychia congenita* and *Hallermann-Streiff syndrome*. Natal teeth may also occur alone and may, in some instances, be familial (23,44).

Laboratory aids. The disorder has been diagnosed prenatally by ultrasound and fetoscopy (7,15,25).

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Fibrochondrogenesis

In 1978 and 1979, Lazzaroni-Fossati (8,9) described a neonatal lethal form of short-limb dwarfism, abnormally developed vertebrae, and abnormal facial appearance (Figs. 7–63 to 7–65). Nine additional examples have been reported (1–6,10,12). Inheritance is clearly autosomal recessive (1,2,8,12). Al-Gazali et al (1) provide an excellent review.

The face is round and flat with prominent eyes and anteverted nares. The mouth is often small. Cleft palate has been present in two patients (8,9,11) and in one case a severe micrognathia and bifid tongue were found (6). There is a narrow chest, moderately severe micromelia, and markedly enlarged joints. The head and trunk are proportionate. One patient had omphalocele.

Radiographically, the skull is relatively large with a large anterior fontanelle and hypoplastic facial bones. The clavicles are long and thin, the scapulae small. The ribs are short with wide, cupped anterior ends. The tubular bones are short and dumbbell shaped with metaphyseal flare and peripheral spurs. The vertebral bodies are flattened and project a diagnostic pear-shaped silhouette on lateral view. Two cases had ectopic extra-articular calcifications (1,5).

The ilia are small with narrow sacrosciatic notches and a medial acetabular spike. The ischia and pubic bones are short and relatively broad and the fibulae are short.

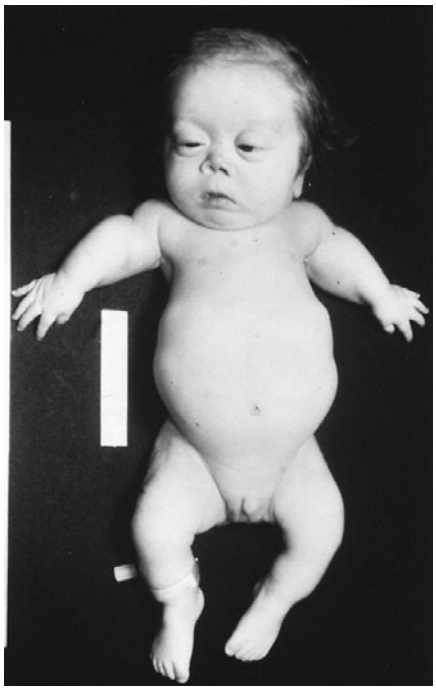
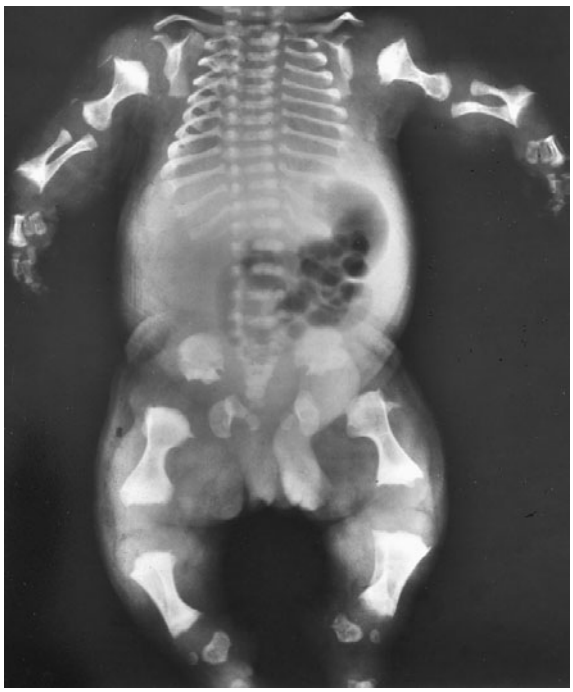


Fig. 7–63. *Fibrochondrogenesis.* Note round face, protuberant eyes, flat nasal root, anteverted nares, short neck, rhizomelic shortening of limbs, proportionate head, and trunk length. (From CB Whitley et al, Am J Med Genet 19:265, 1984.)

Fig. 7–64. *Fibrochondrogenesis.* Short ribs with flared and cupped anterior ends, small scapular bodies, platyspondyly, sagittal cleft in upper and mid-thoracic bodies, and small iliac bones with narrow sacrosciatic notches. Long tubular bones are short and broad with metaphyseal spurs. Proximal and distal ends of humeri and proximal ends of femora and tibiae are convex. (From CB Whitley et al, Am J Med Genet 19:265, 1984.)



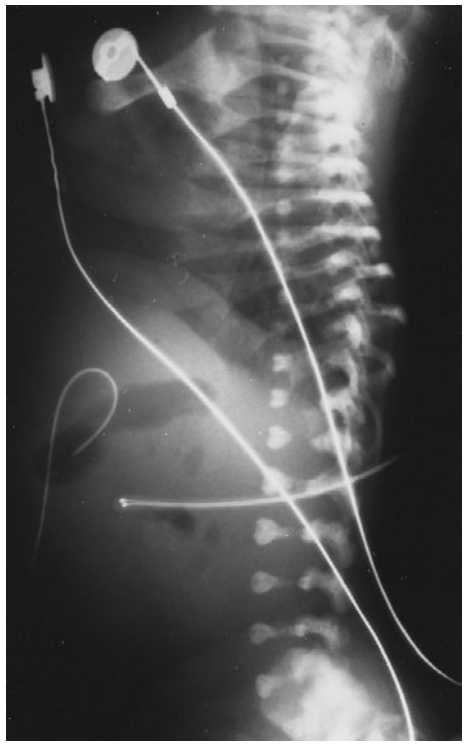


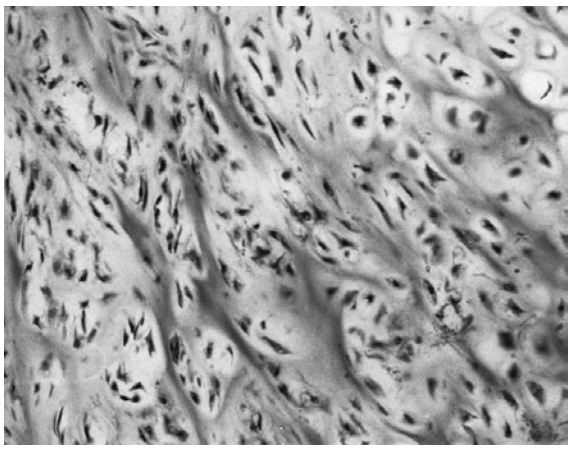
Fig. 7–65. *Fibrochondrogenesis.* Lateral spine showing pear-shaped silhouette due to ossification of only upper and mid-thoracic bodies. (From CB Whitley et al, Am J Med Genet 19:265, 1984.)

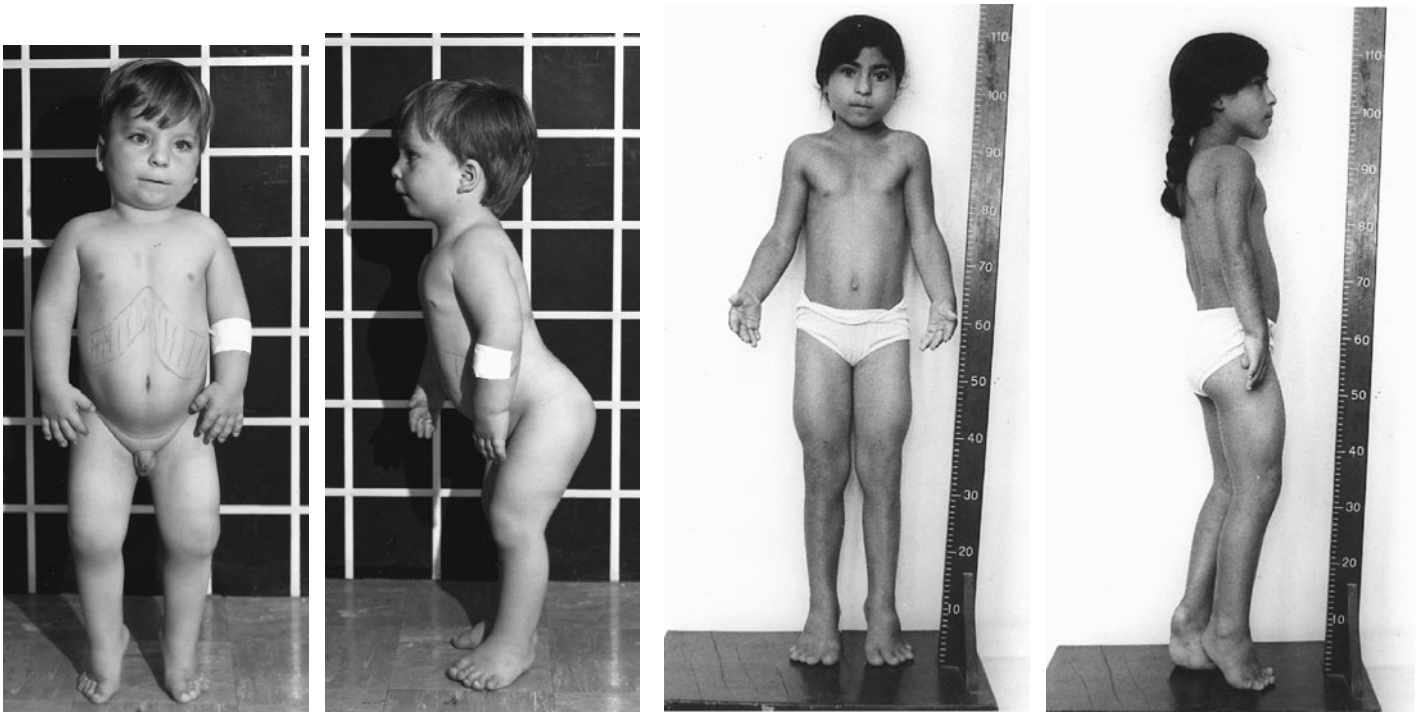
Cartilage histopathology is distinctive (6,10,12) (Fig. 7–66). The growth plate is disorganized with fibroblastic dysplasia of chondrocytes that are often clustered two to four cells per lacuna. Characteristic extracellular densely fibrous collagenic septa are evident. Ultrastructural studies show a paucity of endoplasmic reticulum in chondrocytes.

Fibrochondrogenesis should be differentiated from other perinatally lethal bone dysplasias, especially *Schneckenbecken dysplasia* and *Raine syndrome* (7). The latter syndrome has a similar external appearance, but radiologically shows a generalized sclerosis of long bones, ribs, and cranial base.

Prenatal diagnosis has been accomplished ultrasonographically (11).

Fig. 7–66. *Fibrochondrogenesis.* Columnar alignment of hypertrophic cells is distorted. Resting cartilage is composed of hypercellular, often spindle-shaped cells with hyperchromatic nuclei. (From CB Whitley et al, Am J Med Genet 19:265, 1984.)





A B C D

Fig. 7–67. *Geleophysic dysplasia.* (A,B) Short stature, short arms, joint limitation, and tip-toe gait due to pes equinovarus. (C,D) Compare phenotype with patient shown in A and B. (A,B from JW Spranger et al, Am J Med Genet 19:489, 1984. C,D from CP Koiffmann et al, Am J Med Genet 19:483, 1984.)

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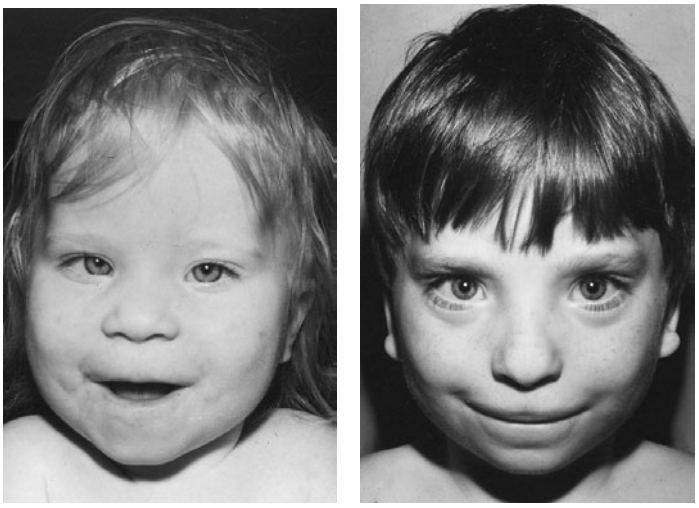
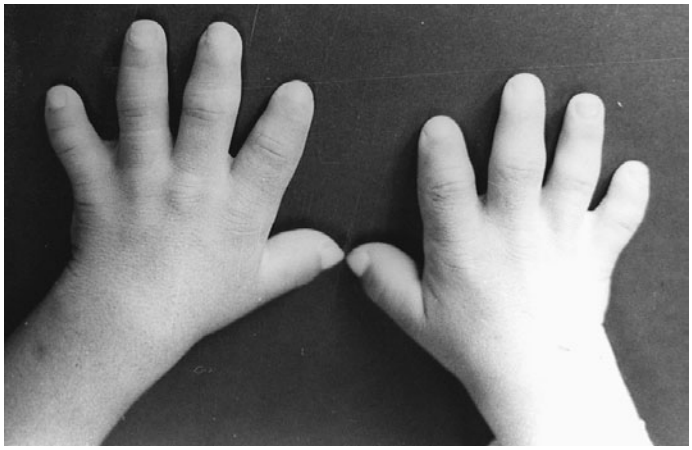
Geleophysic dysplasia

In 1971, Spranger et al (13) reported a skeletal disorder characterized by a happy-natured (geleophysic) face, short stature, and short hands and feet (Figs. 7–67 to 7–69). An early example is that of Vanace et al (17). At least 25 additional cases have been reported (4–12,14,16–18; RCM Hennekam, unpublished observation). Children with similar findings but with an unhappy face have also been noted (11,15). Inheritance is autosomal recessive (4,8,10,12,14,16). Shohat et al (12) found lysosomal vacuoles in skin epithelial cells and postulated a lysosomal storage disease. Death has occurred in several children under the age of 5 years (14,17).

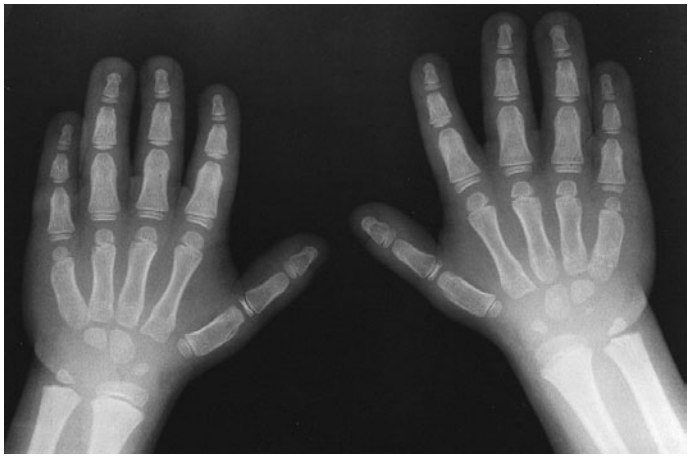
Fig. 7–68. *Geleophysic dysplasia.* (A,B) Up-slanting palpebral fissures, full cheeks, long philtrum, and thin vermilion of upper lip resulting in pleasant facies. (A,B from JW Spranger et al, Am J Med Genet 19:489, 1984.)



A B



A



B

Fig. 7–69. *Geleophysic dysplasia.* (A) Brachydactyly. Note decreased finger extension. (B) Radiograph showing somewhat short and plump tubular bones. Shafts of first and fifth metacarpals and proximal and middle phalanges are widened. (A from CP Koiffmann et al, Am J Med Genet 19:483, 1984. B from JW Spranger et al, Am J Med Genet 19:489, 1984.)

The facies is indeed pleasant. The palpebral fissures are narrow and upward slanting, the cheeks full, and the philtrum long and flat. There is thin vermilion of the upper lip that, in most cases, is upturned. The mouth may be wide, and the neck is somewhat short (Fig. 7–68).

Height is usually far below the third centile, but a few authors have reported normal stature (8,11). The arms are somewhat short (Fig. 7–69A). There is joint limitation at the elbows, hips, and knees and decreased finger extension. All manifest a tiptoe gait as a result of pes equinovarus.

Progressive thickening of cardiac valves (70%) usually starts in late infancy or in childhood. Hepatomegaly and a thickened doughy skin are also characteristic (14). Tracheal narrowing has occurred in three cases (12,14,16).

Radiographically, tubular bones are somewhat short and plump, capital femoral epiphyses are short and irregular, and shafts of the first and fifth metacarpals and proximal and middle phalanges are widened (Fig. 7–69B). One patient developed Perthes disease (10).

Light microscopically, on iliac crest biopsy, the ground substance showed a reduction in mucopolysaccharides and incomplete modeling of the growth plate (8). Transmission electron microscopy showed numerous lysosomal-like storage vacuoles, several of which contained lamellar structures. These vacuoles were also found in skin fibroblasts (8,12). Metabolic studies have repeatedly given normal results.

Motor (4,12,14,17) and speech (4,10,13) delay are common. Late in infancy, recurrent respiratory and middle ear infections (50%) become more frequent. The liver is nearly always enlarged, with the hepatocytes having a vacuolated cytoplasm. There are umbilical and inguinal hernias (14). Death may result from infiltration of the mitral and aortic valves with an abnormal glycoprotein (14).

Prenatal diagnosis may be difficult, as limb shortening is sonographically detectable only after 28 weeks of gestation (9,10).

Acromicric dysplasia should be excluded from the diagnosis. In geleophysic dysplasia, the facial appearance is different. The liver is usually enlarged with some type of storage material (5,8,12,14,18), there is progressive thickening of heart valves with poor prognosis, and inheritance is autosomal recessive (2,5,10). Figuera (1,7) pointed to resemblance with Myhre syndrome and Hennekam et al (2) to similarity with Moore-Federman syndrome. Hopkin et al (3) described three unrelated cases with short stature, joint hypomobility, and short hands and feet, who facially resembled geleophysic dysplasia, but who had severe laryngeotracheal stenosis and no cardiac or hepatic enlargement.

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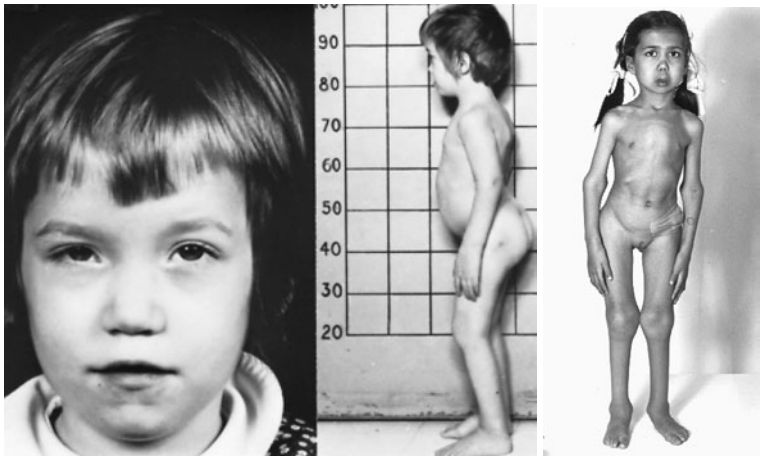
Kniest dysplasia (metatropic dysplasia, type II)

The disorder described by Kniest (11) in 1952 is a form of generalized spondyloepimetaphyseal bone dysplasia with disproportionate dwarfism. Most patients have been isolated examples but several authors (7,10,15,16) have noted the disorder in two generations. Identical twins have been described (27). A lethal variant (30) and an autosomal recessive Kniest-like syndrome have been reported (26). Poole et al (22) demonstrated that the C-propeptide is missing in type II collagen. Indeed, *COL2A1* gene mutations were found in patients with Kniest syndrome



A B C

Fig. 7–70. *Kniest dysplasia.* (A,B) Five-year-old girl with flat midface, myopia, and cleft palate. At birth, legs were noted to be abnormally short and hips were stiff. Umbilical and inguinal hernia were repaired. (C) Six-year-old with short stature, protruding sternum, and large joints. Hips and knees flexed due to contractures. Note more severely affected face than in A. Patient also had myopia and cleft palate. (Courtesy of J Spranger, Mainz, Germany.)

(34,35). Collagen type II is a molecule that forms trimeric fibrils and has a large, central triple-helical domain. The gene is located at chromosome 12q13–14. Most cases of Kniest dysplasia are caused by small deletions in the *COL2A1* gene, especially in exon 12 (4,33,36). This causes incorporation of shortened chains into the fibrils and, therefore, malalignment of cross-linking sites. Mutations in the *COL2A1* gene may cause a spectrum of phenotypes, varying from achondrogenesis to Stickler syndrome (4). Mosaicism for a dominantly acting mutation may manifest as Stickler syndrome or mild spondyloepiphyseal dysplasia (31), which may be important for counseling parents of a child with Kniest dysplasia. An excellent review of the molecular findings is that of Faber et al (2a).

Several authors (14,15) have confused the condition with metatropic dysplasia, type I. Spranger et al (32) gave a historical view, a follow-up of the original patient, and described the molecular defect in that patient.

Facies. The face is round, the midface is flat, and the nasal bridge depressed, giving the eyes a somewhat exophthalmic appearance (Fig. 7–70). The nostrils may be anteverted. The neck is usually short. The head appears to sit on the thorax. Severe myopia and lattice degeneration with or without retinal detachment and/or cataract formation have been present in about 40% of cases, as has cleft palate (2,10,25,28). A large series was studied by Maumenee and Traboulsi (17). Mawn et al (18) reviewed all skeletal dysplasias that manifest congenital glaucoma. Conduction and/or sensorineural hearing loss, a frequent finding, may develop before puberty. Recurrent otitis media and respiratory infections are common.

Musculoskeletal alterations. At birth, cleft palate, clubfoot, and prominent knees may be noted (2,5,21,28,29). Lordosis, dorsal kyphosis, and tibial bowing usually develop within the first few years of life. The child may not sit and walk until ages 2 and 3, respectively. By that time, most joints become progressively enlarged and stiff. The gait is waddling. Movement at the metacarpophalangeal joint is normal, but the child cannot make a fist. The fifth fingers are generally not involved. The palms may have a violaceous hue. The elbows, wrists, and knees become particularly enlarged, and flexion and extension of most joints become progressively reduced. The feet are flat and turned out. Hernia is frequent. Adult height ranges between 105 and 145 cm.

Radiographically, the neurocranium is large in comparison with the facial skeleton. The anterior fontanel is late to close. The cranial base angle is flattened and the sella turcica is anteriorly displaced. The odontoid is short and wide (5,10,27). Occipitoatlantal instability may occur (19). Platyspondyly, particularly of the upper thoracic part of the spine, is severe. The vertebrae exhibit vertical clefts. The long bones are somewhat short, slightly bowed, and have flared metaphyses. The epiphyses are large (20), irregular, and punctate. The hands show epiphyseal and carpal retardation with generalized osteopenia. Later, the carpal bones assume bizarre shapes and sizes. The iliac bones are small, particularly in relation to the large capital femoral epiphysis and proximal femoral metaphysis. The pubic rami are poorly ossified. The femoral capital epiphysis forms late, the neck is wide and short with a poorly osssified central area, and there may be coxa vara. The trochanter is prominent (12,13) (Fig. 7–71).

Histopathologic examination of the bones has shown that the soft, crumbly cartilage contains large chondrocytes that lie in a very loosely woven matrix containing numerous empty spaces ("Swiss cheese cartilage") (Fig. 7–72) (2,3,6,23,24). Ultrastructural studies of cartilage cells have shown dilated cisternae of endoplastic reticulum, a finding noted in other skeletal dysplasias. Vacuolar degeneration of extralacunar matrix is found in the area of the resting cartilage adjacent to the growth plate (8). The collagen fibrils are fragmented and disintegrated, resulting in a web-like pattern and large, open, cyst-like spaces (6).

In differential diagnosis, *dyssegmental dysplasia, type Rolland-Desbuquois, spondyloepiphyseal dysplasia congenita,* and *Burton syndrome* should be excluded. Type II collagenopathies include achondrogenesis, type II, hypochondrogenesis, spondyloepiphyseal dysplasia congenita, Kniest dysplasia, Stickler syndrome, spondylometaphyseal dysplasia of the Strudwick type, and AD spondyloarthropathy. The nature of the mutations and their location determine the phenotypic differences. Premature stop codons leading to less type II collagen are milder, whereas point mutations that involve folding and mutations near the carboxy-terminal end result in severe phenotypes (4).

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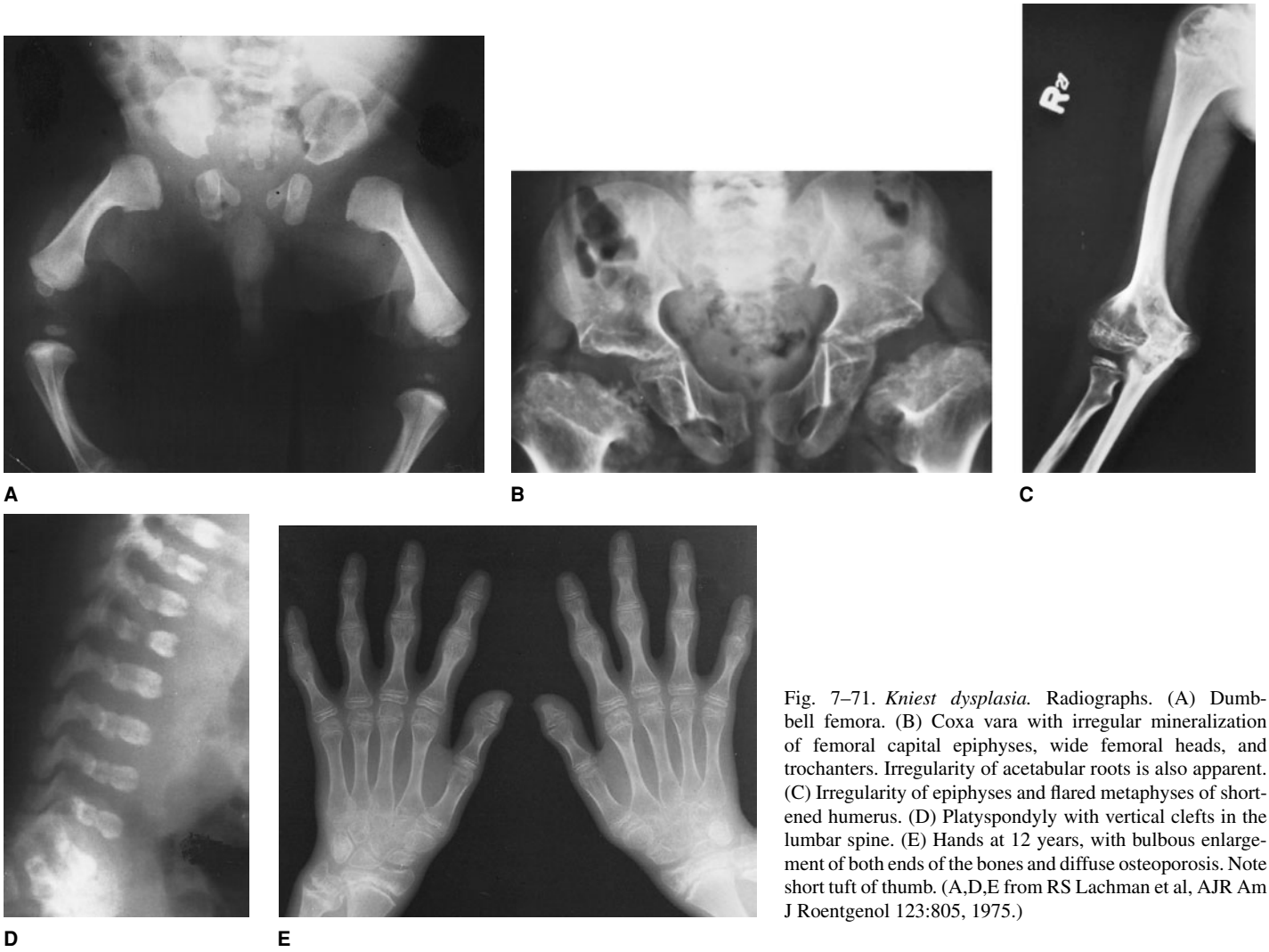
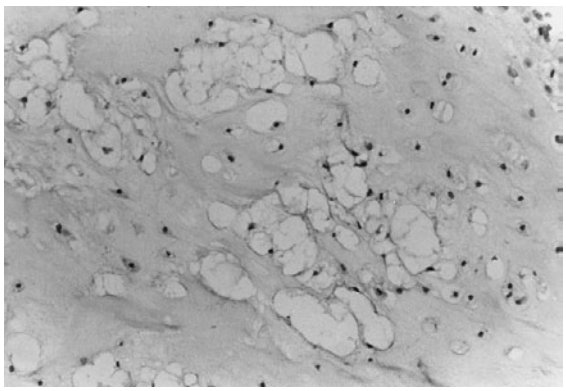


Fig. 7–71. *Kniest dysplasia.* Radiographs. (A) Dumbbell femora. (B) Coxa vara with irregular mineralization of femoral capital epiphyses, wide femoral heads, and trochanters. Irregularity of acetabular roots is also apparent. (C) Irregularity of epiphyses and flared metaphyses of shortened humerus. (D) Platyspondyly with vertical clefts in the lumbar spine. (E) Hands at 12 years, with bulbous enlargement of both ends of the bones and diffuse osteoporosis. Note short tuft of thumb. (A,D,E from RS Lachman et al, AJR Am J Roentgenol 123:805, 1975.)

Fig. 7–72. *Kneist dysplasia.* "Swiss-cheese" cartilage. (From RS Lachman et al, AJR Am J Roentgenol 123:805, 1975.)



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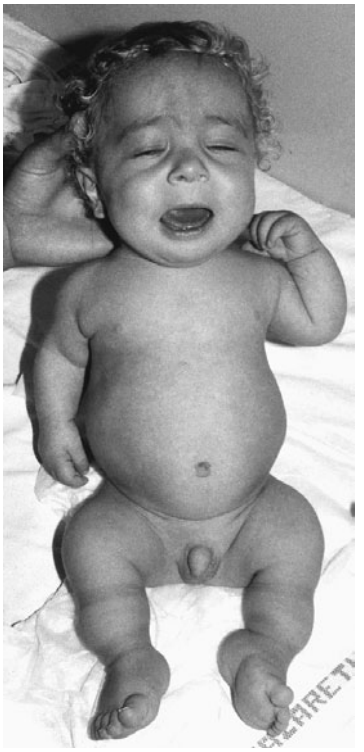


Fig. 7–73. *Kyphomelic dysplasia.* Note long philtrum, small chin, small limbs and trunk, and bowed femora. (From PD Turnpenny et al, J Med Genet 27:269, 1990.)

Kyphomelic dysplasia

Kyphomelic dysplasia was first described by Hall and Spranger (5) and Khajavi et al (7) in 1975–76 as a variant of campomelic dysplasia. In 1983, Maclean et al (9) recognized it to be a distinct entity and proposed the name "kyphomelic dysplasia" (the Greek word "kyphos" means bent forward). Fourteen patients are known (1–5,7,9,10,13,15–18; RCM Hennekam, unpublished observation). Because of four affected sib pairs (1,3,13,15) and no vertical transmission, autosomal recessive inheritance is likely. However, there is a 10 M:1 F sex predilection. An adult has been reported (13a). In one family, a mother had brachydactyly type E (1). Chromosomes have been normal. A type I collagen defect has been found (N. Robin, personal communication, 2000).

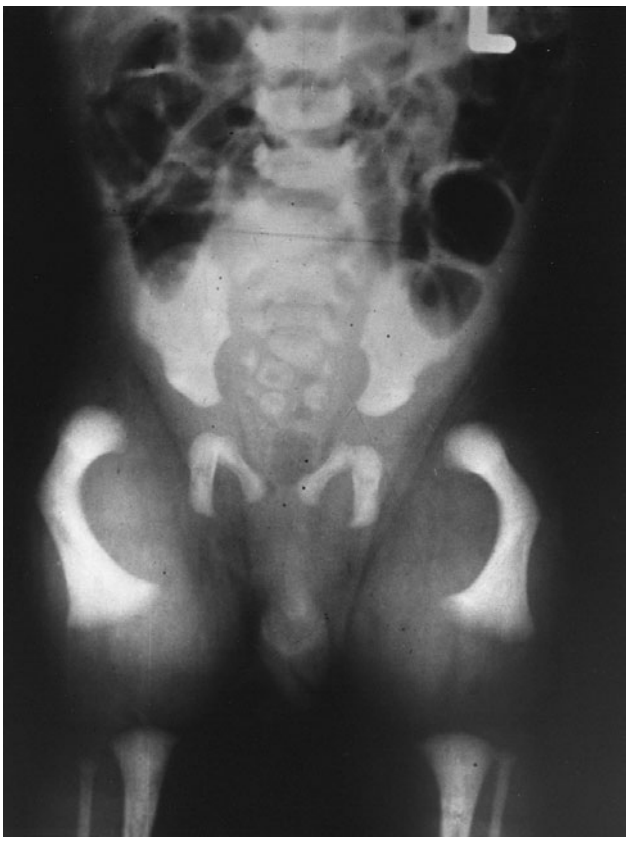
The patients have normal intelligence. The major findings are generalized shortness of both the limbs and trunk, normal head size, hypoplastic midface, long philtrum, cleft palate (15%), and short chin (Fig. 7–73). The chest is small and narrow, and most patients have restricted joint mobility. The hands and feet are normal, although clinodactyly has been described. Skin dimples are present over the bony prominences such as the greater trochanters.

Radiographically, all patients have very short femora with marked bowing and metaphyseal flaring (Fig. 7–74). Other frequent findings are short, flared ribs (100%), mild bowing of humeri, tibiae, and radii (75%), and platyspondyly (50%). Increased acetabular angles, Perthes-like changes (10,13), 11 pair of ribs (20%), and underossification of proximal tibial epiphyses are less common. The limb bowing and other radiographic features tend to improve with age. There is considerable variability in features (2).

One patient died because of pure red cell aplasia (17), one patient had severe combined immune deficiency (3), and another developed aplastic anemia and late-onset severe combined immune deficiency (RCM Hennekam, unpublished observation).

Prenatal diagnosis has been accomplished (1). Kyphomelic dysplasia can be readily distinguished from *campomelic dysplasia* by the extraskeletal manifestations, mental retardation, ambiguous genitalia, and severe tibial bowing and hypoplastic scapulae in the latter. The differentiation from *femoral hypoplasia-unusual facies syndrome* can be difficult (14), the hypoplasia of the femora being the most important difference. Several single case reports are available describing patients with related entities (6,8,11). *Antley-Bixler syndrome* and Stüve-Wiedemann

Fig. 7–74. *Kyphomelic dysplasia.* Radiograph showing severely bowed femora, unossification of proximal tibiae, and increased acetabular angles. [From D Viljoen and P Beighton, Dysmorphol Clin Genet 1(4):136, 1988.]



dysplasia should be excluded. A benign form of angulation of long bones associated with shortening of soft tissues was reported by Nakamura et al (12) in sibs.

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Lethal short-limbed dysplasias

There are a great number of rare types of lethal short-limbed dysplasias. They may be grouped into platyspondylic types, short-rib types, fragmented bones types, osteosclerotic types, and a miscellaneous group (Table 7–8). The conditions should be distinguished from achondrogenesis, hypophosphatasia, fibrochondrogenesis, atelosteogenesis, thanatophoric dysplasia, boomerang dysplasia, Caffey-Silverman dysplasia prenatal type, de la Chapelle dysplasia, Piepkorn dysplasia (73,91), and Schneckenbecken dysplasia. Prenatal diagnosis has been accomplished for most entities (14,25,26,28,37,70,88,98).

Table 7–8. Perinatally lethal short-limbed skeletal dysplasias

Entity	McKusick no.	Inheritance
With platyspondyly		
Torrance type	151210	Sporadic
San Diego type	270230	Sporadic
Calgary type	—	Sporadic
Luton type	151210	Sporadic
Yamagata type	—	Sporadic
Perth type	—	Sporadic
Shiraz type	250220	AR
Fibrochondrogenesis	228520	AR
With short ribs[a]		
Type I (Saldino-Noonan)	263530	AR
Type II (Majewski)	263520	AR
Type III (Verma-Naumoff)	263510	AR
Type IV (Beemer-Langer)	269860	AR
Thanatophoric dysplasia	187600	AD
With decreased bone density		
Hypophosphatasia, perinatal lethal type	241500	AR
Osteogenesis imperfecta type II	166210	AD
Achondrogenesis type I	200600	AR
Achondrogenesis type II	200610	AD
Epiphyseal stippling-osteoclast hyperplasia[b]	167220	AR
Piepkorn dysplasia	—	?
With increased bone density		
Blomstrand dysplasia	215045	AR
Caffey-Silverman prenatal type	114000	?AD
Raine dysplasia	259775	?AR
With fragmented bones		
Astley-Kendall dysplasia	—	AR
Dappled diaphyseal dysplasia	—	AR
Greenberg dysplasia	215140	AR
Miscellaneous		
Atelosteogenesis	108720	Sporadic
Boomerang dysplasia	112310	?
De la Chapelle dysplasia	256050	AR
Holmgren-Connor dysplasia	273680	AR

[a] Asphyxiating thoracic dysplasia (Jeune syndrome) and Ellis-Van Creveld syndrome are also characterized by short ribs, but are not tabulated here as they are not universally perinatally lethal.

[b] We object to naming a condition in humans after a character in videogames (Pacman dysplasia).

Lethal short-limbed dysplasia with platyspondyly. This is a heterogeneous group of lethal spondyloepimetaphyseal dysplasias, all characterized by expressed platyspondyly, varying involvement of epiphyses and metaphyses, and different histology. This naming is according to geographic location of the first authors, except for fibrochondrogenesis. The Shiraz type and fibrochondrogenesis are autosomal recessive; all other cases have been sporadic. The sporadic cases are probably autosomal dominant and lethal (69a).

Torrance type. Horton et al (45) described a single patient with a narrow thorax and protuberant abdomen—there were no additional clinical data—and Nishimura et al (68) and Van der Harten et al (92) described still other patients. The radiographic data were similar to those found in thanatophoric dysplasia, including short ribs and short tubular bones, but with diminished ossification of the cranial base, more extreme hypoplasia of vertebral bodies (disclike), wider sacrosciatic notches, and wider, more tubular-formed long bones showing metaphyseal enlargement and cupping. There was no proximal tibial hypoplasia or disproportionate widening of the fibula, as found in thanatophoric dysplasia.

Histologic analysis showed a relatively normal growth plate but with abnormal incorporation of degenerating chondrocytes in metaphyseal bone (92). The resting cartilage appeared hypercellular. Protein studies showed overmodification of type II collagen (35), but no mutations were found, so this finding may be a secondary effect.

San Diego type. The clinical features and radiographic changes of this variant were reported to be not distinguishable from those in Torrance type (45). The single reported case was identified because of

the histologic features: the growth plate was abnormal in poor column formation and there was a lack of ingrowth of chondrocytes in metaphyseal bone. The resting cartilage showed normal cellularity, although cells were larger than normal (92). This disorder is caused by mutations in *FGFR3* (13a).

Calgary type. A single case with another platyspondylic form of short-limbed dwarfism was described as having bilateral cleft lip and palate, normal trunk, small chest, rhizomelic shortening of limbs, and small hands and feet (74). There were no internal anomalies detected. Radiologically, there was osteopenia of tubular bones and pelvis, platyspondyly, short ribs, broad clavicles, hypoplastic scapulae, flared irregular metaphyses, and shortened, angulated diaphyses. Histologic changes were found both in growth plate, bone, and resting cartilage, suggesting involvement of both chondrocytes and osteoblasts.

Luton type. Winter and Thompson (97) described yet another type in a single case. The clinical features were hydramnios, low birth weight, macrocephaly, midface hypoplasia, slightly bifid nasal tip, intact palate, severe shortening of all limbs with extremely short, stubby, and tapering fingers, small chest, and protuberant abdomen. Visceral anomalies were confined to a dilated hypertrophied bladder; the brain was normal. Radiographic findings for the spine resembled those for the Torrance and San Diego types, but the long bones were less abnormal, showing shortening and splayed metaphyses. There was suggestion of spur formation especially of the femur and humerus. The pelvis was small and had flat acetabular roofs, round iliac bones, but no narrow sacrosciatic notches.

Histologically, the growth plate showed regular columns but with focal disorganization and ingrowth of degenerating chondrocytes in the newly formed bone. Some poorly organized fibrovascular tissue was seen intervening between resting cartilage and bone. The resting cartilage was hypercellular, with large ballooned chondrocytes, the ground substance showed patchy lobulation.

Yamagata type. Akaba et al (1a) described a case with frontal bossing, cloudy corneae, low nasal bridge, small thorax, and rhizomelic micromelia. The patient also had hypoplastic callosal body and larynx stenosis. Radiographic findings included extremely severe platyspondyly, short skull base, hypoplastic ilia, Madelung-like deformities, and delayed epiphyseal ossification.

Perth type. Goldblatt and Knowles (38) gave a detailed description of another sporadic case. Unusual clinical features were hydrocephaly, craniosynostosis of lambdoid and sagittal sutures, and unilateral cystic renal dysplasia. The radiographs resembled those of the other platyspondylic short-limbed dwarfisms, except for localized expansion at the angles. The resting cartilage was hypercellular and extensively vascularized. The columnization was poor, but chondrocytes were of good size.

Shiraz type. Sedaghatian (80) described two children from an Iranian family in which probably other cases had been born. Six other examples were reported (15,29,71,72). Autosomal recessive inheritance is likely. Clinical features are postnatal rhythm disturbances, hypotonia, and neonatal death. In one case, hyperphosphatemia was found. Facial features are not remarkable, except for posteriorly angulated or low-set ears. All limbs show rhizomelic shortness. In one case, clubfeet were present (71). Internal anomalies have been atrial septal defect (72), porencephaly (29), and partial lissencephaly (71). Radiologic changes include moderate platyspondyly, metaphyseal cupping, flaring, and irregularity of long and short tubular bones, disproportionately long fibula, and delayed ossification. The iliac crests are lace-like with sclerosis. Histologic studies show a long hypertrophic zone with dense hypertrophic cells and little intervening matrix (15,71,72). The hypertrophic cells often extend into the metaphysis. The chondroosseous morphology somewhat resembles that found in hypophosphatasia, but alkaline phosphatase levels have been normal.

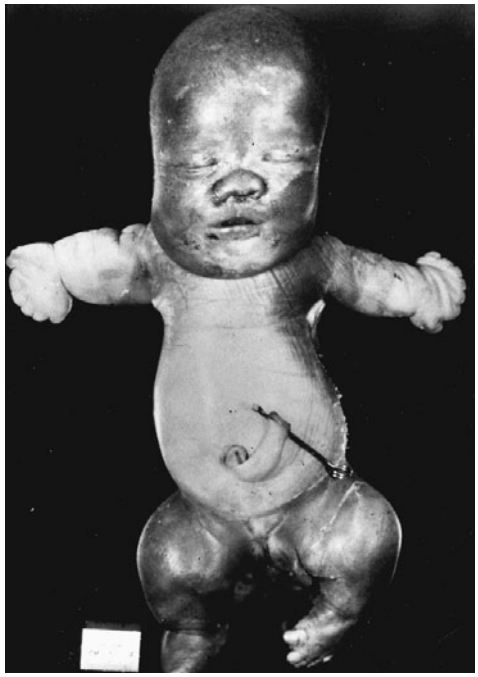


Fig. 7–75. *Short rib-polydactyly syndrome*, *type I* (*Saldino-Noonan*). Note micromelia, narrow chest, protuberant abdomen, and postaxial polydactyly. The forehead is prominent and the nose is wide with low nasal bridge; the nostrils are anteverted. (From M Richardson et al, J Pediatr 91:467, 1977.)

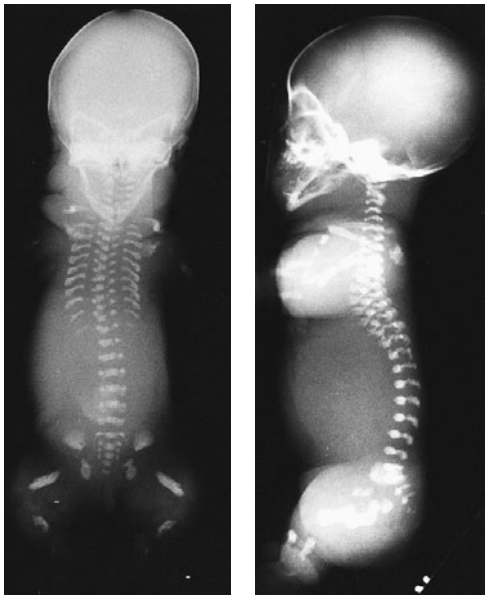
Short-rib syndromes. Although these syndromes have been separated into specific entities, there is evidence of some degree of a continuous phenotypic spectrum (11a).

Type I (Saldino-Noonan type). In 1972, Saldino and Noonan (79) first reported a short-rib syndrome clinically characterized by severe micromelia, narrow chest, protuberant abdomen, and postaxial polydactyly (Fig. 7–75). Radiographs showed very short ribs, small pelvic bones, square-shaped vertebral bodies, hypoplastic cervical spine, markedly shortened long tubular bones with pointed ends, notched tibiae, absent fibulae, and generalized underossification (Fig. 7–76). Reports of several additional patients have been published (9,27,39,77–79,83–87). It may represent a continuous spectrum (79a).

Prenatally, there is oligohydramnios or polyhydramnios, and hydrops. Cleft lip or palate has been reported (39,78), the tongue may be cleft, and the alveolar ridges are furrowed (79). The polydactyly (six or seven digits are frequently found) is postaxial, usually asymmetric, and more often on the hands. It is often accompanied by cutaneous syndactyly. Visceral anomalies include hypoplastic lungs and atresia of esophagus, duodenum, and anus. The intestines are short and malrotated. Various heart anomalies have been documented (transposition of great vessels, VSD, double-outlet left ventricle, endocardial cushion defect, persistence of left superior vena cava) (27). The kidneys may be absent, dysplastic, or cystic, and the ureters and bladder may be hypoplastic. The urethrovaginal opening is small, the uterus is absent or double. Several males with 46,XY karyotype had ambiguous genitalia (9,87). Other anomalies include agenesis of the gallbladder and fibrosis of the pancreas (9,77,78). Histological findings are available (83,84).

Inheritance is autosomal recessive, but all severely affected cases are clinically female, which is due at least in part to failure of secondary sexual differentiation (85). Affected sibs have been described (39,77,78), with marked concordance in radiological features.

Type II (Majewski type). In 1971, Majewski et al (60) described four newborns with a short rib–polydactyly syndrome and added 13 nearly identical cases from the nineteenth century literature. After delineation of the short rib syndrome type I by Saldino and Noonan (79), Spranger

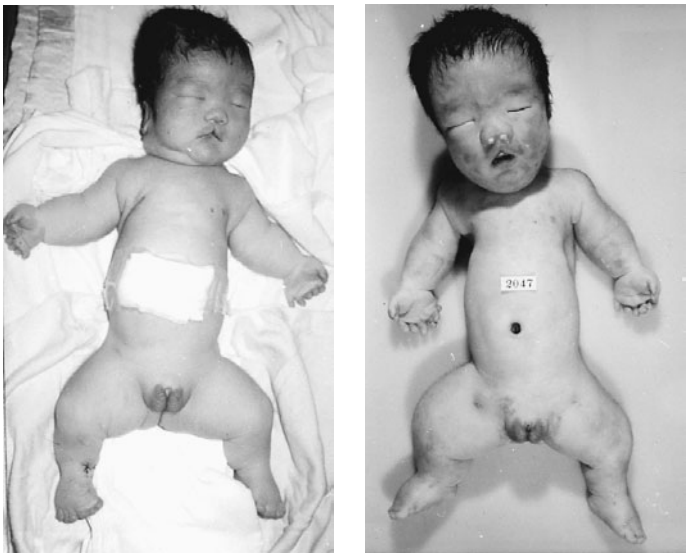


A B

Fig. 7–76. *Short rib-polydactyly syndrome, type I (Saldino-Noonan).* (A,B) The ribs are remarkably short, the ilia abnormally contoured, the femora peg shaped, the tibiae notched, and the vertebral bodies small and flattened. (Courtesy of AL Baudet, Houston, Texas.)

et al (87) concluded that only case 1 of Majewski et al had the short rib syndrome type II, and added one case of their own. The other three cases described by Majewski et al (60) had, in fact, type I. About 40 examples have been described (8,17,24,60,64,65,69,81,85,87,90). Several other possible cases from older literature have been summarized (60,87). The characteristics of type II are hydrops fetalis, short and narrow thorax, protuberant abdomen, short limbs, and pre- and postaxial polysyndactyly (Figs. 7–77 to 7–80). Inheritance is autosomal recessive (17,87). Urioste et al (90) described pericentric inversion of chromosome 4. The cause is unknown, although the resemblance with the severe form of Smith-Lemli-Opitz syndrome and hydrolethalus syndrome warrants studies of cholesterol metabolism. Prenatal diagnosis has been accomplished several times.

Fig. 7–77. *Short rib-polydactyly syndrome*, *type II* (*Majewski*). (A,B) Affected sibs. Note midline cleft of upper lip, short limbs, narrow chest, and polysyndactyly. (From T Motegi et al, Hum Genet 49:269, 1979.)



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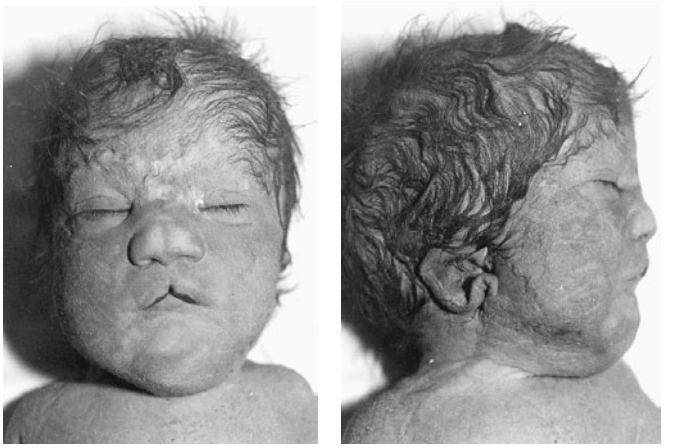
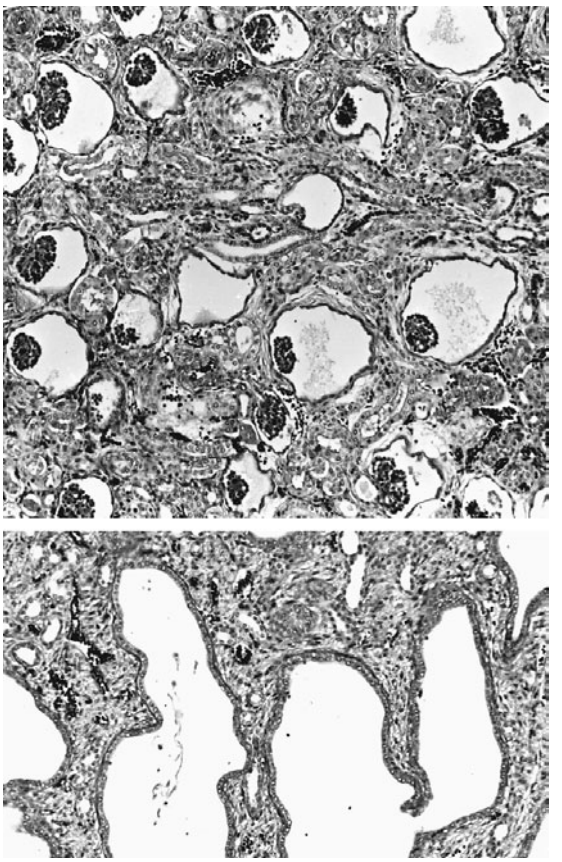


A B

Fig. 7–78. *Short rib-polydactyly syndrome*, *type II* (*Majewski*). (A,B) Median cleft lip and somewhat malformed pinnae. (Courtesy of JS Fitzsimmons, J Med Genet 19:141, 1982.)

Usually there is polyhydramnios. The infants are either stillborn or die shortly after birth. Some may have hydrocephaly (81), cebocephaly (69), deep-set eyes, notching of the mid-upper lip, cleft lip and palate (8,17,60,81,85,87), bifid or trifid tongue (8,60,64,90), ankyloglossia (60,69,85), notched gingiva (24), natal teeth (24,64), and somewhat malformed pinnae (69,81). The epiglottis, larynx, and lungs are hypoplastic. Several cases had intestinal malrotation, fibrocystic pancreas, enlarged

Fig. 7–79. *Short rib-polydactyly syndrome, type II* (*Majewski*). Cortex (top) and medulla (bottom) of kidney showing multiple glomerular cysts and focal cystic dilatation of distal tubules. (From T Motegi et al, Hum Genet 49:269, 1979.)



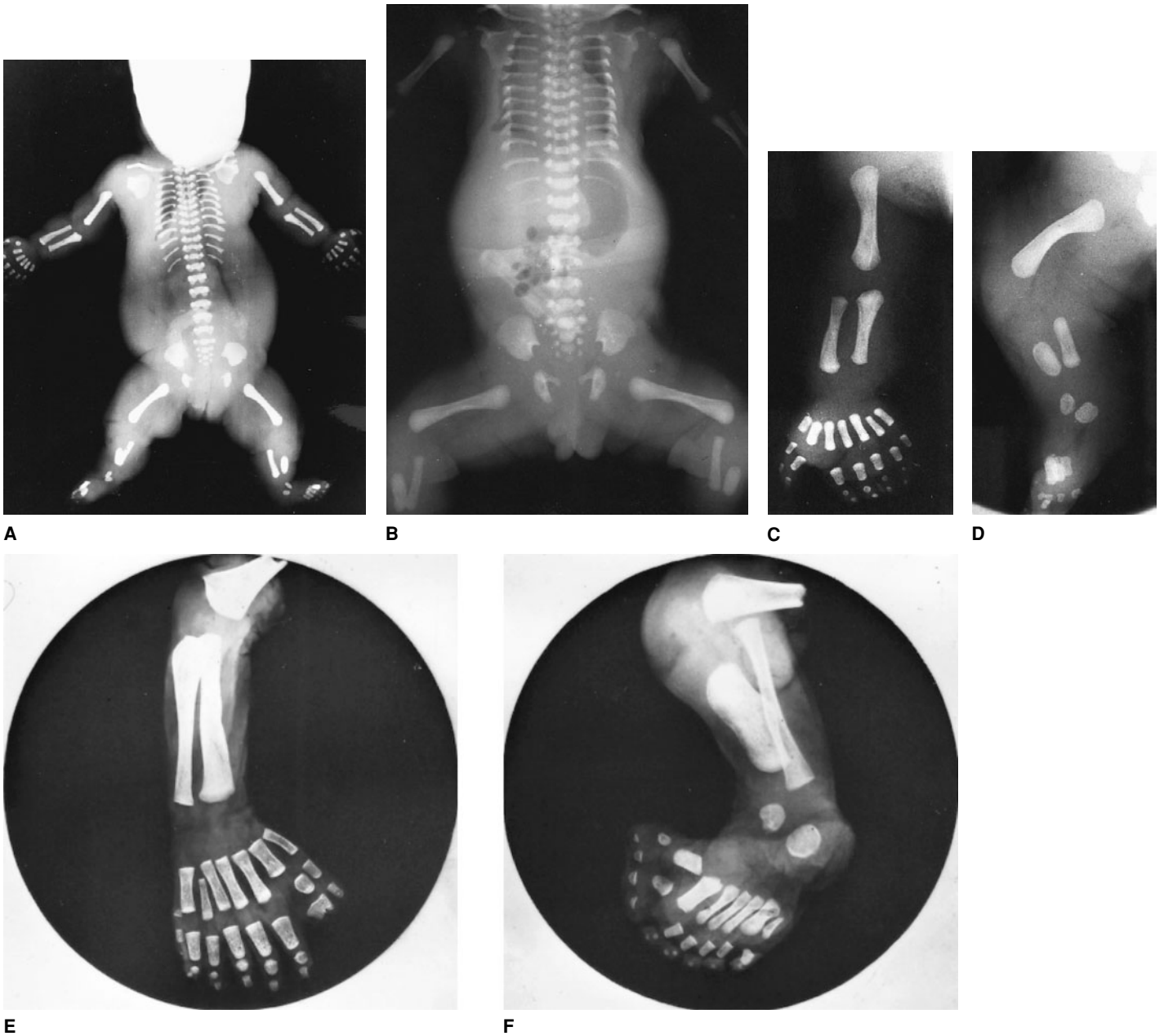


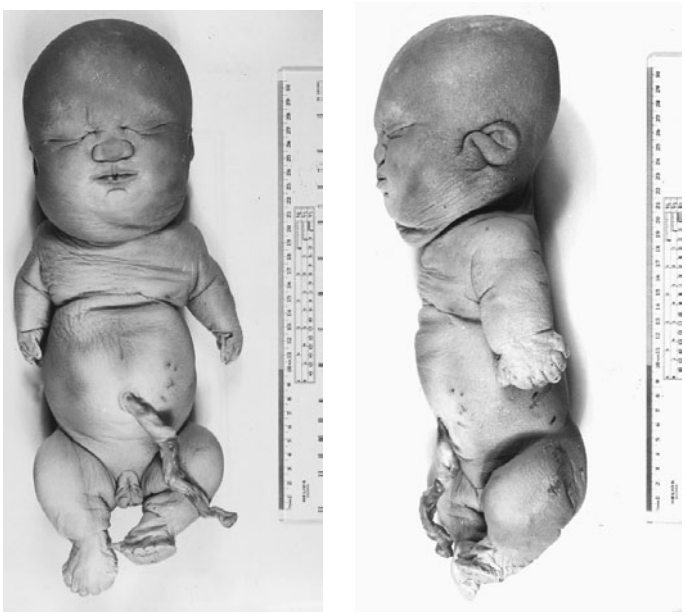
Fig. 7–80. *Short rib-polydactyly syndrome, type II* (*Majewski*). (A) Micromelia. (B) Short ribs, normal pelvis, and very abbreviated tibiae. (C) Shortened humerus, radius and ulna, and pre- and postaxial polydactyly. (D) Shortened femur and lower leg bones, particularly the tibia. (E,F) Compare with C and D. (B,C,D, courtesy of H Jorulf, Uppsala, Sweden. E,F from E Pitschi, Thesis, Zürich, 1904–1905.)

portal areas in the liver, and imperforate anus. Cardiac anomalies include persistent superior vena cava, truncus arteriosus, total anomalous pulmonary venous return, ASD, tetralogy of Fallot, and coarctation of aorta. Genitourinary anomalies include small or absent urogenital opening, hypospadias, micropenis, ambiguous genitalia, cryptorchidism, septate or hypoplastic uterus, and septate or rudimentary vagina. The kidneys are hypoplastic with multiple glomerular cysts and focal dilatation of distal tubules. Shortening of the limbs is mesomelic, especially the lower limbs. The degree of polysyndactyly is extremely variable, with up to nine digits per extremity.

Radiographs show very short horizontal ribs, preaxial and postaxial polydactyly, and short oval tibiae. The ilia appear to be essentially normal, and the vertebral bodies are square shaped and somewhat hypoplastic, especially in the thoracic and cervical spine. Ossification of the proximal epiphyses of the humeri and femora is premature, and sternal bone age may be advanced. The middle and distal phalanges are poorly ossified. In two unrelated cases, an occipital bone defect was found, as in hydrolethalus syndrome (81).

Type III (Verma-Naumoff type). Yet another lethal autosomal recessively inherited short rib syndrome was suggested by Verma et al (94) and Naumoff et al (67). Over 30 examples have been published (1b,7,9,11,26,42,52,58,67,84,85,94,98). Types I and III have many clinical and radiographic features in common and are differentiated by the configuration of the end of long bones and less severe changes in the ilia. Several authors have expressed doubts regarding the separation of the two types (9,40,84,85) and have suggested that they are allelic disorders, but other investigators (98) have rejected this fusion. Biochemical or molecular studies will have to settle this. Ho et al (43a) have further suggested that Jeune asphyxiating thoracic dystrophy is a variant.

The external clinical features in type III are indistinguishable from those in type I (Fig. 7–81). Polydactyly is an inconsistent feature and is



A B

Fig. 7–81. *Short rib-polydactyly syndrome, type III* (*Naumoff*). (A) Clinical phenotype strikingly similar to type I (Majewski). (B) Changes in ilia and long bones are less severe than in type I. (From R Bernstein et al, J Med Genet 22:46, 1985.)

often asymmetric. Visceral anomalies are often less extensive in type III; cardiac malformations are especially less common. Coarctation of the aorta, hypoplastic left or right heart, transposition of great vessels and cor biloculare have been noted. Ambiguous genitalia, including persistent cloaca, and less severe anomalies of the genitalia have been described.

Radiographic changes include very short ribs, short cranial base, mild platyspondyly with irregular outlines of vertebral bodies, hypoplasia of cervical spine, and horizontal trident-shaped acetabular margins with well-developed ischial and pubic bones. The metaphyses of long bones are widened, especially that of the tibia, and longitudinal spurring is found at the margin of the metaphyses of the distal humeri and proximal and distal radii and femora. Corticomedullary demarcation is marked. All hand bones are short and show changes similar to those in the long bones but the changes in the hand are less well marked. Histological changes have been reported to be similar to (9,40,83,85) or different from (99) the findings in type I.

Autosomal recessive inheritance is indicated by multiple instances of consanguinity, affected sibships, and segregation ratio (85).

Type IV (Beemer-Langer type). In 1983, Beemer, Langer, and coworkers (6) delineated another type of short rib syndrome. In retrospect, the cases described by Black et al (11) and Le Marec et al (54) are earlier examples. In total, 34 cases have been described (5,6,10,13,18,19,21,31, 32,41,43,46,54,56,59,89,93,96,100). Consanguinity in several instances and the occurrence of six pairs of affected sibs of both sexes fit autosomal recessive inheritance. In one case, a de novo paracentric inversion mosaicism involving 17q21 and 17q23 was found (18). Most affected infants are stillborn or die within hours after birth, but survival until 8 sweeks has been described (10).

Major clinical characteristics include hydrops and ascites, macrocephaly, prominent forehead, flat nasal bridge, median cleft upper lip and palate, narrow thorax, protuberant abdomen, omphalocele, short limbs, and sometimes preaxial polydactyly (Fig. 7–82). Cardiac anomalies have included preductal coarctation of the aorta, atrial and ventricular septal defect, and transposition of great vessels. There is often intestinal malrotation. The genitalia can be hypoplastic or ambiguous. Almost atretic ear canals (6), anophthalmia (21), additional oral frenula and hamartoma of the tongue and gingiva (10,31,43,54,56), and milia (56) are less frequent facial findings. Renal agenesis; hydronephrosis; atresia of ureteropelvic junction; renal cysts; fetal renal lobulations; intrahepatic bile duct cysts; ectopic pancreas; pancreatic cysts; polysplenia; lung hypoplasia, sometimes with segmentation defects; rudimentary epiglottis; and pyloric stenosis, in immature as well as premature stillborns, have been reported. Lurie (59) summarized brain malformations, which included hydrocephaly, Dandy-Walker malformation, agenesis of callosal body, hypothalamic hamartoblastoma, polymicrogyria, cerebellar hypoplasia, holoprosencephaly, aplastic optic and olfactory nerves, and occipital encephaloceles.

The radiologic signs include very short ribs, mild platyspondyly, highly placed clavicles, small scapulae, small iliac bones, and short and often bowed long bones with normal metaphyses. The tibiae are often longer than the fibulae and are not ovoid; this constitutes the major point of difference with type II (41,59). All small tubular bones are shortened (Fig. 7–82B,C).

The short rib syndromes must be differentiated from *orofacial digital syndromes*, *hydrolethalus syndrome*, *Smith-Lemli-Opitz syndrome*, *Jeune syndrome*, and *Ellis-van Creveld syndrome*. There are several reports of short rib syndromes that we cannot classify with certainty (14,34,47,90,98,101). In one report, a pericentric inversion including as a breakpoint chromosome 4p16, i.e., the locus for *FGFR3,* was detected (90).

Lethal short-limbed dysplasias with decreased bone density

Epiphyseal stippling–osteoclast hyperplasia. Shohat et al (82) described a single patient with a lethal skeletal dysplasia characterized by osteopenia, short long bones, distinct epiphyseal stippling, and increased number of osteoclasts in histological studies. Two siblings of different sex with the same signs were described (95), which suggests autosomal recessive inheritance. The cause has been suggested to be a deficiency of an osteoclast-inhibiting factor (95).

Both sibs were detected prenatally by sonography, and the pregnancy was terminated. The single patient died shortly after birth. One of the sibs was normocephalic, the other microcephalic. Hypotelorism, cloudy corneae, and short limbs with prominent genua vara were described. No major internal anomalies were present. Radiological changes included generalized osteopenia, with periosteal cloaking in one case. Stippling was found in the proximal femoral epiphysis, sacrum, and talus, in the calcaneus and cuboid bones, and, in one patient, also in the hands. There was rhizomelic and mesomelic shortening, with dense metaphyses and bowing of the femora. Platyspondyly and clefting of the vertebrae were present. Another case has been added (59a).

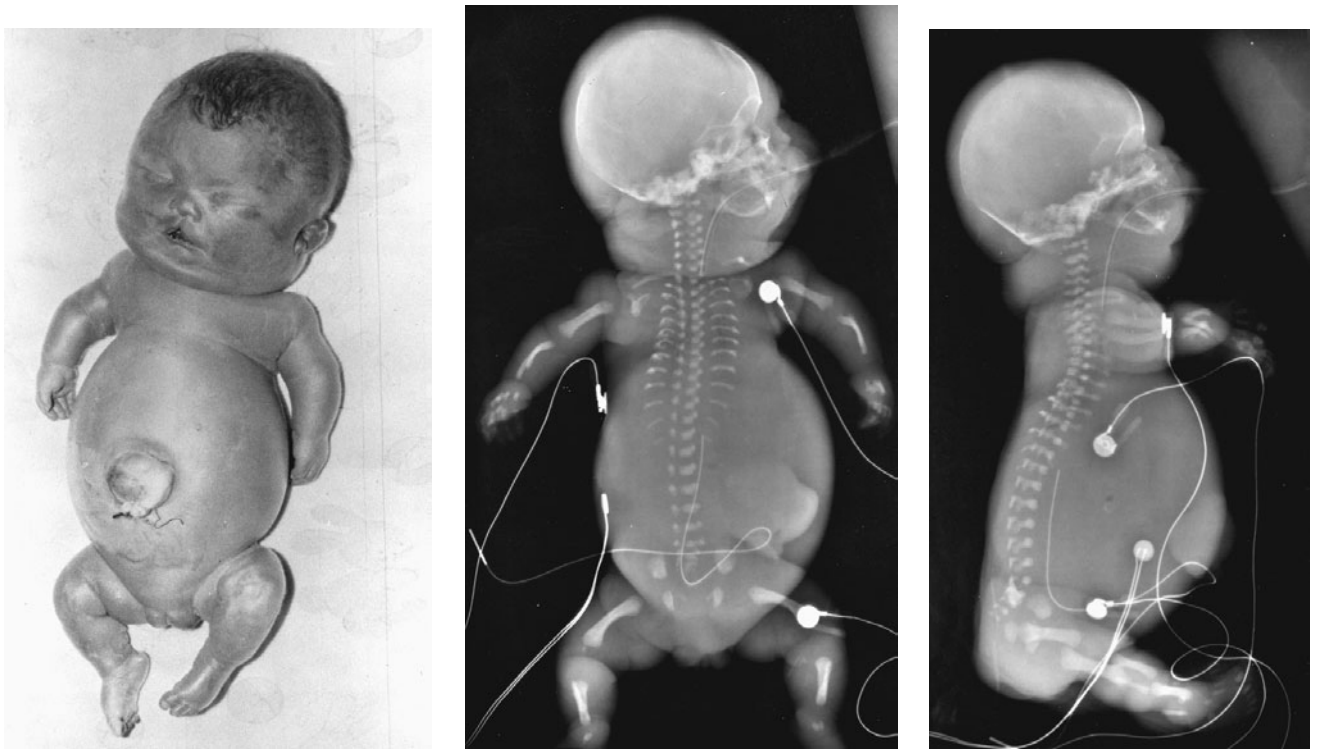
Morphological studies showed that the bone marrow was largely replaced by fibrous tissue, especially in the metaphyses, containing numerous normal-appearing osteoclasts and giant multinucleated osteoclast-like cells. The ultrastructural bone and cartilage morphology was normal.

The entity should be differentiated from *mucolipidosis type 2*, the various forms of *chondrodysplasia punctata*, and neonatal hyperparathyroidism.

Piepkorn dysplasia. Piepkorn et al (73) described a severely dysplastic infant with a marked lack of ossification of all bones except the clavicle. There was polyhydramnios, and the arms and legs were flipper-like. The palate was cleft. Persistence of left superior vena cava and urogenital abnormalities were also evident (Fig. 7–83). An old specimen was noted (70a).

Lethal short-limbed dysplasias with increased bone density

Blomstrand dysplasia. Blomstrand et al (12) described a lethal skeletal dysplasia that was especially characterized by increased bone density and advanced bone age. In total, 10 cases have been reported (12, 25,36,48,55,57,70,86,102), one of which was diagnosed in a 130-year-old museum specimen (70). In five of the six described families, the parents were consanguineous, and in four families, more than one child was affected, indicating autosomal recessive inheritance. The cause is



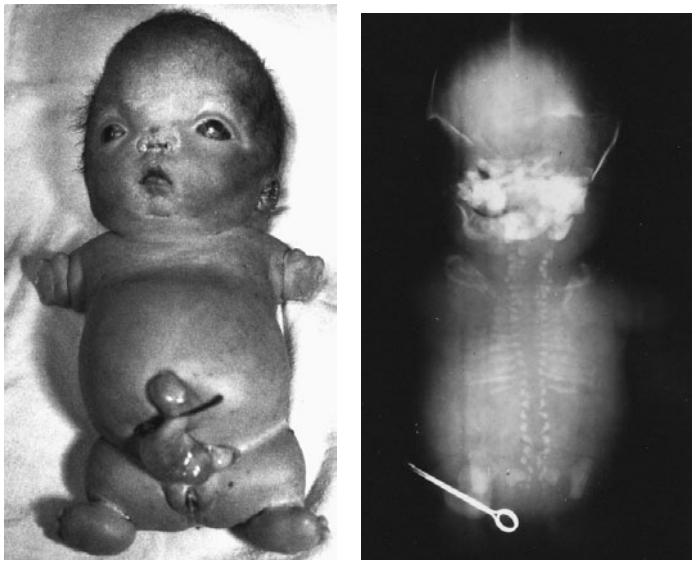
A B C

Fig. 7–82. *Lethal short-limbed dysplasia, type Beemer-Winter.* (A) Generalized edema, large head with flat face, broad nasal base, median cleft of upper lip, small edematous pinnae, short narrow thorax, and distended abdomen with omphalocele. (B,C) Short horizontal ribs, high clavicles, relatively normal ilia, and metaphyses of abbreviated long bones. There is no polydactyly of the hands or feet. (From FA Beemer et al, Am J Med Genet 14:115, 1983.)

a missense mutation in the gene coding for the receptor for PTH/PTH-related peptide (48,103). There appears to be heterogeneity (70b).

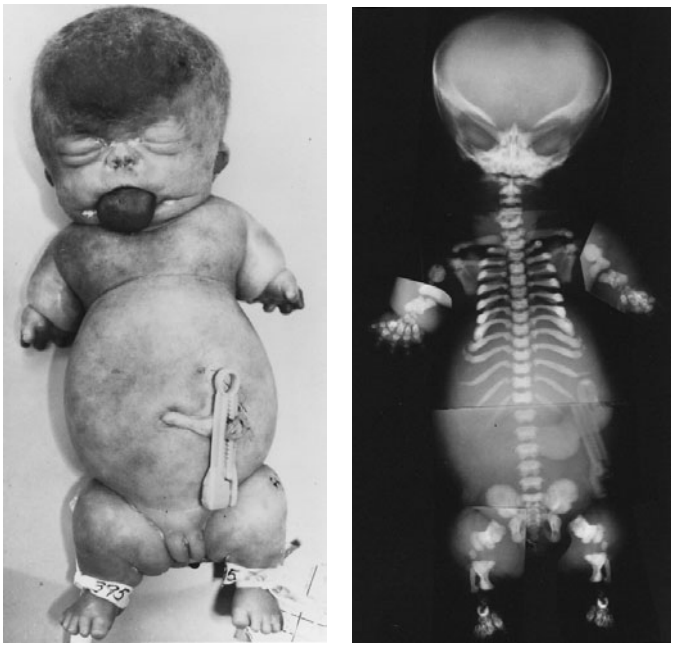
All affected infants were born immaturely or prematurely, and were stillborn or died shortly after birth. Clinical characteristics are polyhydramnios, and hydrops that may distort the face and give the impression of a low nasal bridge and very small nose, widely spaced protruding eyes, long philtrum, large tongue, and small chin (Fig. 7–84). The limbs are

Fig. 7–83. *Lethal short-limbed dysplasia, type Piepkorn.* (A,B) Note flipper-like arms and legs, and marked lack of ossification of all bones except clavicles. (From M Piepkorn et al, Teratology 16:345, 1977.)



A B

Fig. 7–84. *Lethal short-limbed dysplsia, type Blomstrand.* (A) Note low nasal bridge, macroglossia, short limbs, and narrow chest with large abdomen. (B) Long narrow thorax, widened anterior ribs, and severely abbreviated long bones with flared cupped metaphyses. Note extremely advanced bone age. (From S Blomstrand et al, Pediatr Radiol 15:141, 1985.)



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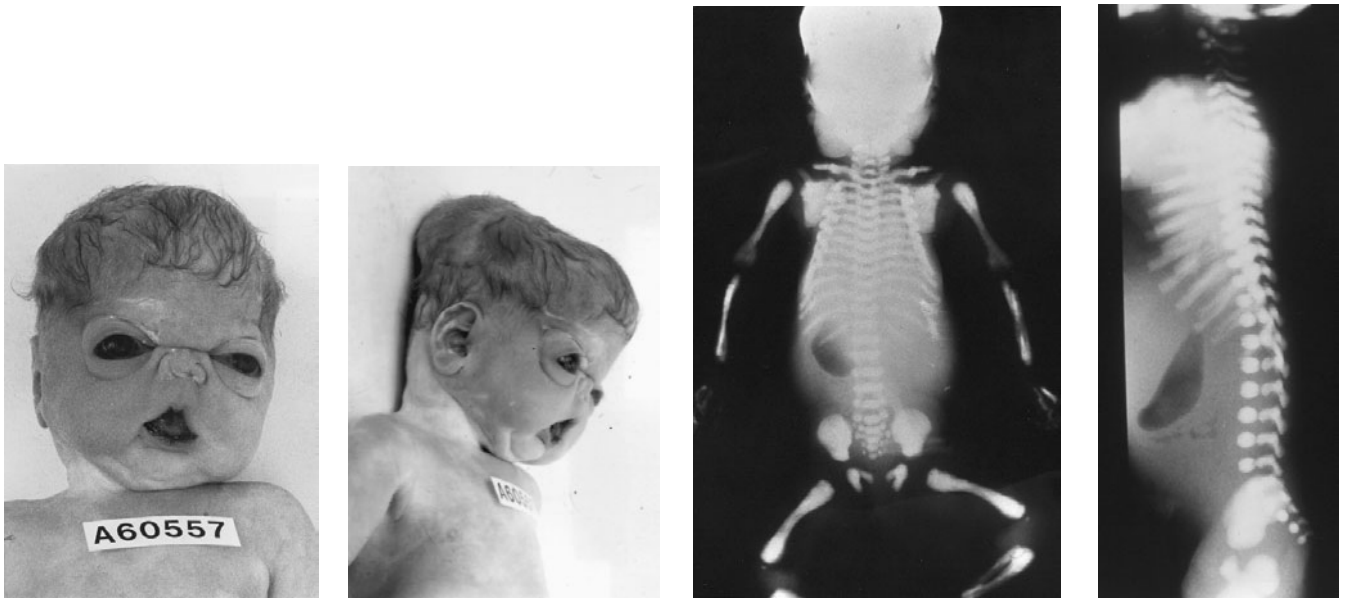


Fig. 7–85. *Lethal short-limbed dysplasia, type Raine.* (A,B) Large bulging fontanelles, marked exophthalmos, midface hypoplasia, triangular mouth, and micrognathia. (C,D) Generalized osteosclerosis and slightly hypoplastic vertebral bodies with short anterior-posterior diameter. (From AE Kan and K Kozlowski, Am J Med Genet 43:860, 1992.)

short and broad, with normal-sized hands and feet without polydactyly. Internal organs have been normal except for hypoplastic lungs, malrotation of bowel, and preductal aortic coarctation. Radiography has shown a small facial skeleton, short skull base, long, narrow thorax showing widening of the anterior rib ends, thick clavicles, and mild platyspondyly, with the sacral and coccygeal vertebrae already being ossified. In general, ossification is well advanced. The hyoid bones and thyroid cartilages are ossified, and in one patient, mineralized teeth were found in the hypoplastic mandible (57). The long bones are extremely short with marked metaphyseal flaring and cupping and fragmented irregular capital femoral epiphyses. The radii and ulnae may show acute bowing. Ossification of carpal, metacarpal, tarsal, and metatarsal bones is also advanced. Histologically, acceleration of enchondral ossification in the tubular bones, is apparent, as well as large epiphyseal ossification centers (57). In two families, hemosiderosis of the liver was found (25,55). The marrow space has been found to be reduced to a great extent, which probably explains this feature and the anemic hydrops. Ultrastructural studies have shown a high number of chondrocytes with pyknosis or karyorrhexis and altered rough endoplasmic reticulum, and unequal fibers in the bone matrix (57).

Raine syndrome. In 1989, Raine et al (75) described a newborn lethal disorder characterized by microcephaly, exophthalmos, hypoplastic nose, cleft palate, and diffuse osteosclerosis (Fig. 7–85). Several additional cases were reported thereafter (1–3,49,50,76). No sex predilection has been reported. Parents have been consanguineous (2,3,50,71a,80a) and affected sibs have been noted (76), indicating autosomal recessive inheritance. FitzPatrick et al (33) drew attention to a cholesterol metabolism disturbance, desmosterolosis, but follow-up studies in one patient (49) failed to show accumulation of desmosterol. There is some evidence that the gene maps to 7p (47a).

Nearly all patients have died shortly after birth from lung hypoplasia, but some have lived a few months (3,76). Striking facial characteristics are microcephaly, wide anterior and posterior fontanels and sagittal, lambdoidal, and metopic sutures (coronal sutures are ridged), midface hypoplasia with marked exophthalmos due to very shallow orbits, nasal hypoplasia with misshapen and anteverted nares, bowed upper lip, causing the mouth to be triangular, sunken midface, micrognathia, and low-set, dysplastic ears. The sunken nasal bridge allows the forehead to extend over the nose like a shelf. The soft palate and uvula may be cleft (2,3,75,80a); the gingiva are hyperplastic with gingival nodules. Atretic or stenotic choanae have been found (1–3,49,50). The neck is short, but otherwise no external anomalies have been described.

Radiologically, a generalized increased bone density is prominent, with extensive periosteal thickening of long bones and ribs. Corticomedullary demarcation is poor; the size of ribs and long bones is normal. The thorax is narrow. The ribs can show vertical lines suggestive of fractures (49,50), but no fractures are found histologically. The lateral ends of the clavicles and distal phalanges are hypoplastic. The cranial vault is retarded in ossification, but the bone that is present is markedly sclerotic. The vertebral bodies may be slightly hypoplastic.

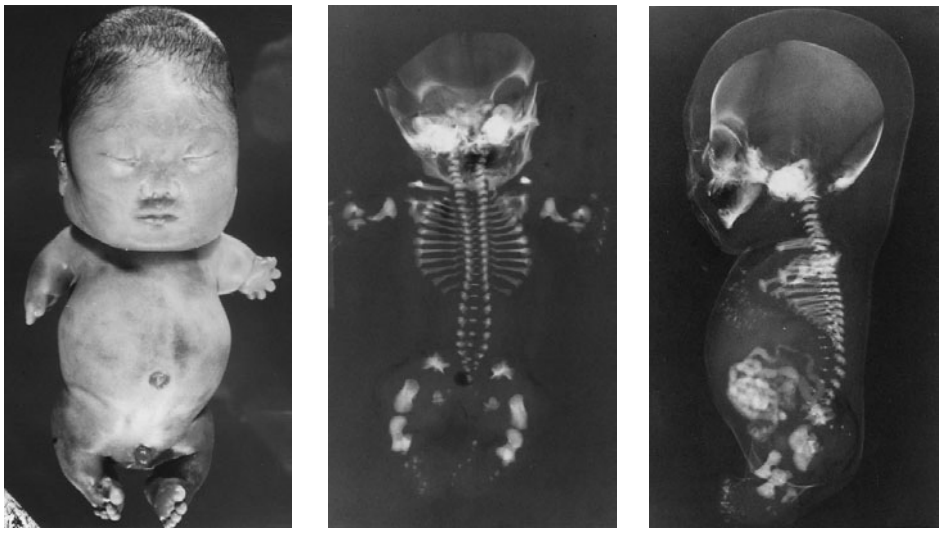
Necropsy has shown hypoplastic lungs, hyperplastic adrenals, but otherwise normal viscera. The brain may show calcifications, or small areas of gliosis with mineralization of the periventricular white matter basal ganglia and tentorium cerebelli (2,3). In one patient an ovary was calcified (49). Bone histology showed no abnormality of cartilage and growth plates, and normal enchondral ossification. There was a striking periosteal reaction with accumulated amorphous ground substance–like, Alcian blue–positive mucoid material arranged in globular masses among calcospherites of varying size and a large number of neutral lipid droplets in multinucleated giant cells (49), which likely were osteoclasts. Osteoblasts and fibroblasts were normal.

The differential diagnosis includes *achondrogenesis, Blomstrand dysplasia, Koide dysplasia* (9), and a dysplasia reported by Kozlowski et al (53).

Koide dysplasia. Koide dysplasia is a lethal short-limbed dwarfism characterized by midface hypoplasia, prominent nasal bones, severe platyspondyly, diminished ossification in the sacral region with some punctate calcifications, markedly trident pelvis, extreme hypoplasia of the iliac wings, and micromelic hypoplasia (51) (Fig. 7–86). The distal humeri are pointed. Kozlowski et al (53) described another lethal skeletal dysplasia with macrocephaly, midface hypoplasia, micromelia, protuberant abdomen, and edematous scalp and scrotum. Radiographs showed long, distally hooked clavicles, thin ribs, platyspondyly, and rhizomelia.

Lethal short-limbed dysplasia with fragmented bones

Astley-Kendall dysplasia. Astley-Kendall dysplasia was first described in 1980 (4) and is especially characterized by absent ossification of the cranial vault and multifocal ossification elsewhere. Elcioglu



A B C

Fig. 7–86. *Lethal short-limbed dysplasia, type Koide.* (A) Micromelia, large head, flat facies, large abdomen. (B,C) Radiographs showing short ribs, platyspondyly, crenated ilia, and less severely involved long bones. Note distally tapered humeri. (From T Koide, Pediatr Radiol 13:102, 1983.)

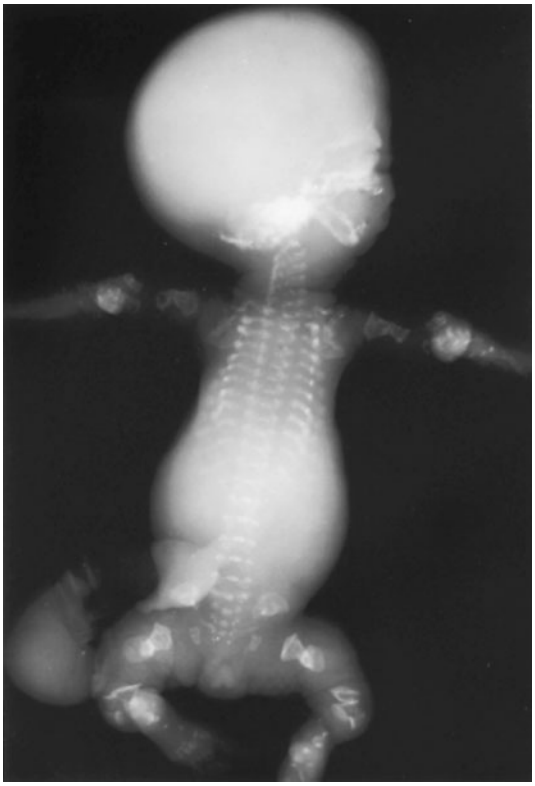
and Hall (30) and Colavita and Kozlowski (22) described other examples. Nairn and Chapman (66) reported three female sibs, but it has been suggested that these were examples of dappled diaphyseal dysplasia. Inheritance is presumed to be autosomal recessive.

The condition is lethal, either prenatally or shortly after birth. Except for a small thorax and short limbs, no other external or visceral anomalies have been reported. Radiologic changes (Fig. 7–87) include barely calcified calvaria with multiple wormian bones, well-developed base of the skull and facial bones, multiple areas of ectopic ossification centers in the spine but almost absent ossification elsewhere in the spine, and platyspondyly. The ribs are short and thin, with flaring ends and some transverse defects suggesting intrauterine fracturing. Multiple ossification centers are seen in the hands, feet, scapulae, and ischia. The ilia are crescentic in shape. In addition to being stippled, the long bones are short and sometimes bowed; the metaphyses are flared.

Histopathologic changes consist of dystrophic globular calcification within the epiphyses, vacuolated chondrocytes, widened lacunae, and disorganized growth plate (30).

Differential diagnosis includes *dappled diaphyseal dysplasia*, *Greenberg dysplasia*, *osteogenesis imperfecta type II*, different types of *chondrodysplasia punctata*, and *metatropic dysplasia*.

Fig. 7–87. *Lethal short-limbed dysplasia, type Astley-Kendall.* Note barely calcified calvaria, shortened extremities with transverse defects of humeri, femora, and tibiae with flared metaphyses, short ribs, space between ribs and vertebral bodies, platyspondyly, and crescent-shaped ilia. (From R Astley and AC Kendall, Ann Radiol 23:121, 1980.)

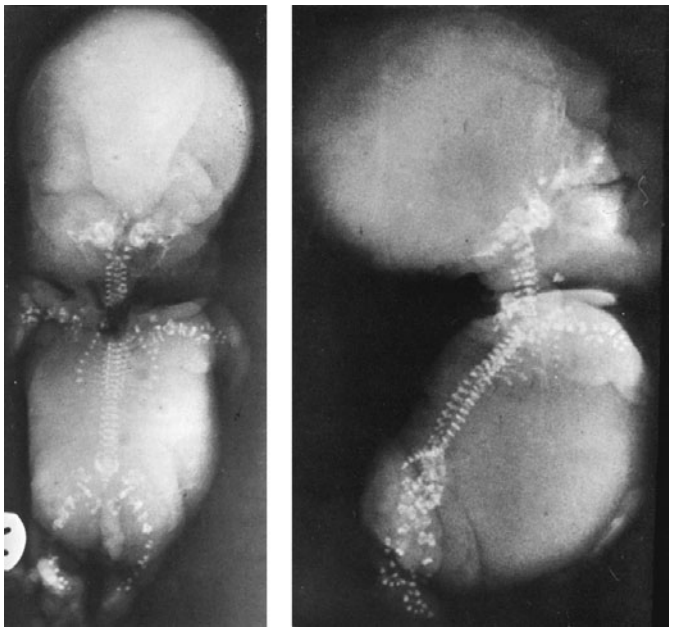


Dappled diaphyseal dysplasia. This condition was recognized by Carty et al (16). In retrospect, the three sibs described by Nairn and Chapman (66) may have had the same entity. Another case was only sparsely illustrated (86). Clinical characteristics are polyhydramnios, hydrops, and extremely short limbs. One patient had situs inversus. Radiographs have shown rudimentary calcification of the cranium and multifocal ossification of the long bones, which thus appear to be fragmented (Fig. 7–88). The epiphyses and diaphyses could not be distinguished. Multicentric ossification is also present in the scapulae, pelvis, and facial bones. Platyspondyly can be marked. The tubular bones of the hands and feet are unossified.

Microscopic examination shows no recognizable chondroosseous transformation or trabecular formation. Because three sibs were born to consanguineous parents, autosomal recessive inheritance is likely (66).

Greenberg dysplasia. In 1988, Greenberg et al (40) reported two sibs, the offspring of consanguineous parents, with a poorly ossified skull vault, mottled appearance of the long bones, and a lethal course. Spranger and Maroteaux (86) briefly reported another example, and Chitayat et al (20) and Gorlin have seen similar cases. It has been suggested that Greenberg dysplasia is a milder form of dappled diaphyseal dysplasia (86). Inheritance appears to be autosomal recessive (20). Kelley et al (49a) have demonstrated that the disorder is due to deficiency of sterol-delta 14-reductase.

Clinical features are polyhydramnios, hydrops fetalis, narrow thorax, rhizomelic shortened limbs, and broad hands with short fingers. The tissues may be fragile. Radiographically, the membranous bones of the skull are extremely poorly ossified, but the skull base is dense (Fig. 7–89). Midface hypoplasia is severe. The cervical vertebrae appear moth-eaten, otherwise there is platyspondyly with multiple ossification centers of the vertebral bodies and poor pedicular and laminar development. There can be calcifications near the larynx and trachea. The ribs exhibit unusual



A B

Fig. 7–88. *Lethal short-limbed dwarfism, type Carty* (*dappled diaphyseal dysplasia*). (A,B) Long bones and pelvis are replaced by multiple small ossified foci. The cranium is very poorly calcified. Note narrow rib cage and platyspondyly. Because of similar changes, the ribs appear fractured. (From H Carty et al, Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 150:228, 1989.)

ossification gaps with an anterior ossified, tail-like extension. The iliac wings are moth-eaten, the pubic bones and ilia are lace-like. Most long bones are mottled, being most pronounced at the ends of the bones. Clavicles are elongated.

Microscopically, chondroosseous changes are characterized by marked disorganization of tissue with interspersed masses of cartilage, bone, and mesenchymal tissues.

Lethal short-limbed dysplasia: miscellaneous type

Holmgren-Connor dysplasia. Holmgren et al (44), Connor et al (23), and Maroteaux et al (61) described an autosomal recessive severe micromelic dysplasia with slightly incurved limbs, hyperlaxity of extremities, disproportionately large skull, slightly flattened nasal bridge, and, in some cases, congenital heart defects. Most of the patients succumbed from respiratory distress within hours or days of birth or during the first weeks of life.

Radiographs show short long bones with incurved diaphyses, especially the femora, enlarged and slightly irregular metaphyses, striking well-developed and rounded lower femoral epiphysis, short, square iliac wings with a wide iliac angle, and short ribs with wide and somewhat irregular anterior ends (Fig. 7–90).

Histologically, the upper tibial growth cartilage has an irregular arrangement of cells, demasked fine fibers in the matrix, short primary trabeculae, and closure of some of the vascular lacunae by bony bridging.

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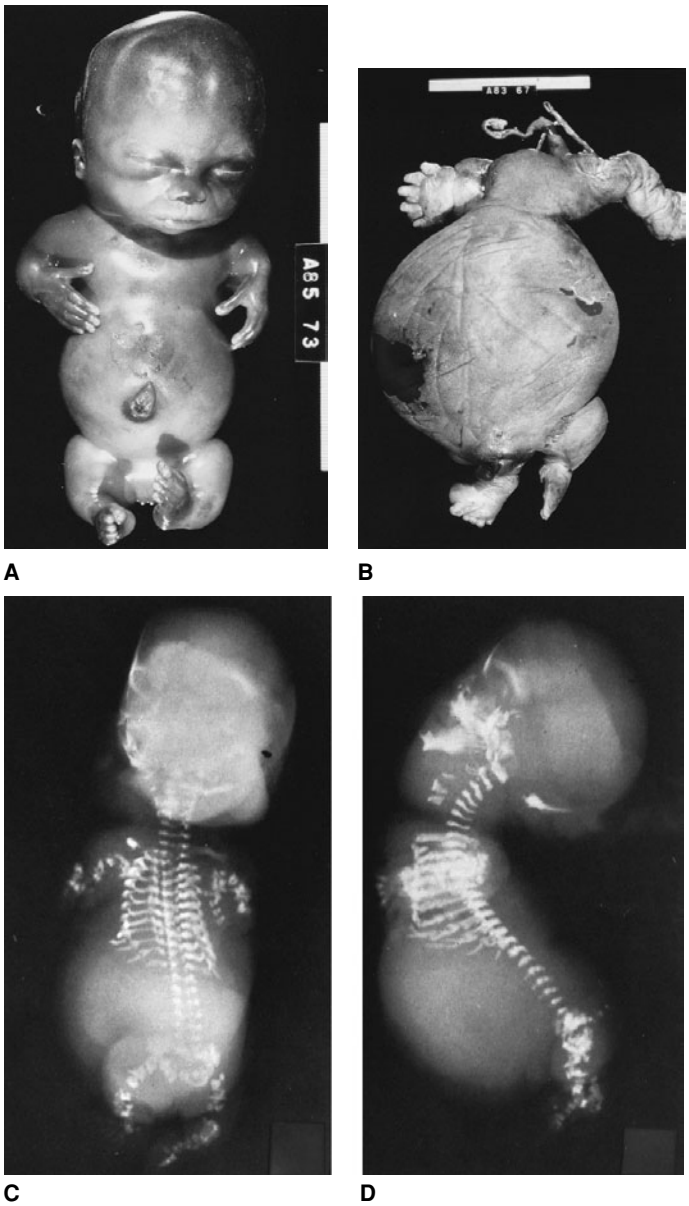

A B C D

Fig. 7–89. *Lethal short-limbed dysplasia, type Greenberg.* (A,B) Two sibs with severe dysplasia. Note hydrops fetalis in B. (C) Note deficient skull ossification and laryngeal and tracheal calcifications. (D) Moth-eaten long bones. (C,D from D Chitayat et al, Am J Med Genet 47:272, 1993.)

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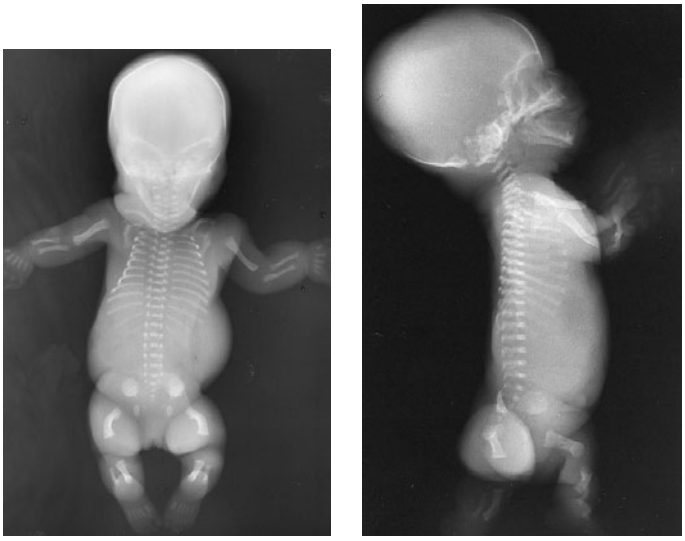

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Fig. 7–90. *Lethal short-limbed dysplasia, type Holmgren-Connor.* (A,B) Shortening of all bones with femoral and humeral bowing, short skull base, micrognathia, mild platyspondyly, and hypoplasia of iliac, pubic, and ischial bones. (From JM Connor et al, Am J Med Genet 22:23, 1985.)

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Megepiphyseal dysplasia

Gorlin et al (1) described a male with cleft palate, dislocated lenses, deafness, somatic and mental retardation, epicanthal folds, and snub nose. Striking were the enlarged joints (shoulders, elbows, hips, knees, ankles). Radiographic study showed marked shortening of long bones, with flared metaphyses and extremely large proximal and distal epiphyses. The carpal bones were large (Fig. 7–91).

Homocystinuria, found on biochemical study, would account for the dislocated lenses and the mental retardation, but the skeletal alterations were unique. The child was a product of father–daughter incest. The disorder, made homozygous by the incest, is possibly the same as bone dysplasia, midface hypoplasia, and deafness (OSMED). The patient described by McAlister et al (2) may have had the same disorder. The facies and skin, however, resemble those of gerodermia osteodysplasticum.

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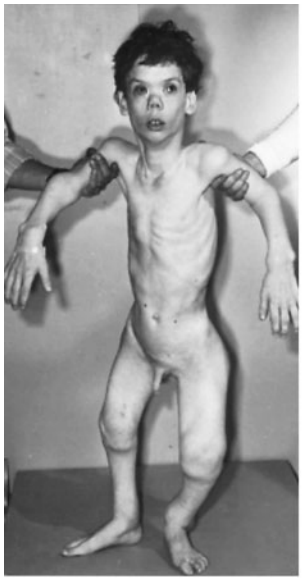
Metatropic dysplasia

Metatropic dysplasia was first described in 1966 by Maroteaux, Spranger, and Wiedemann (9). The name is derived from the Greek "metatropos,"



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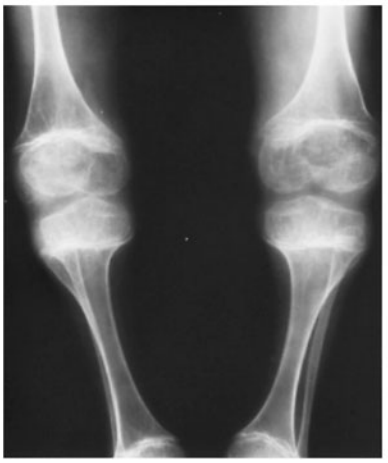

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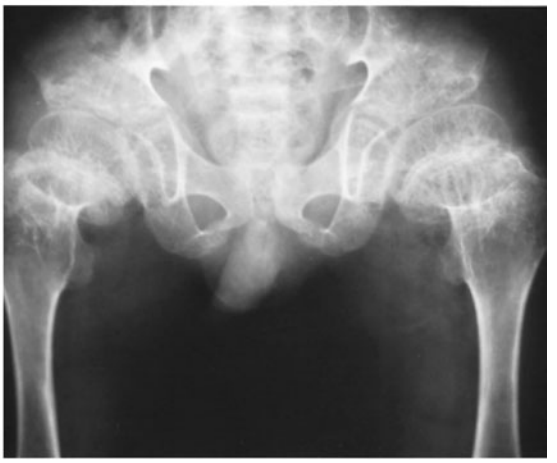

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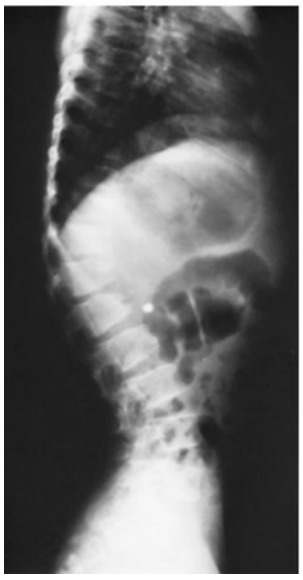

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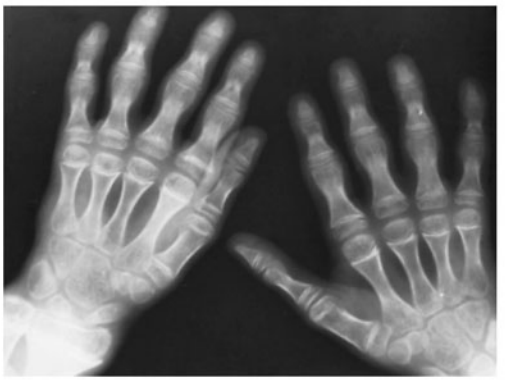


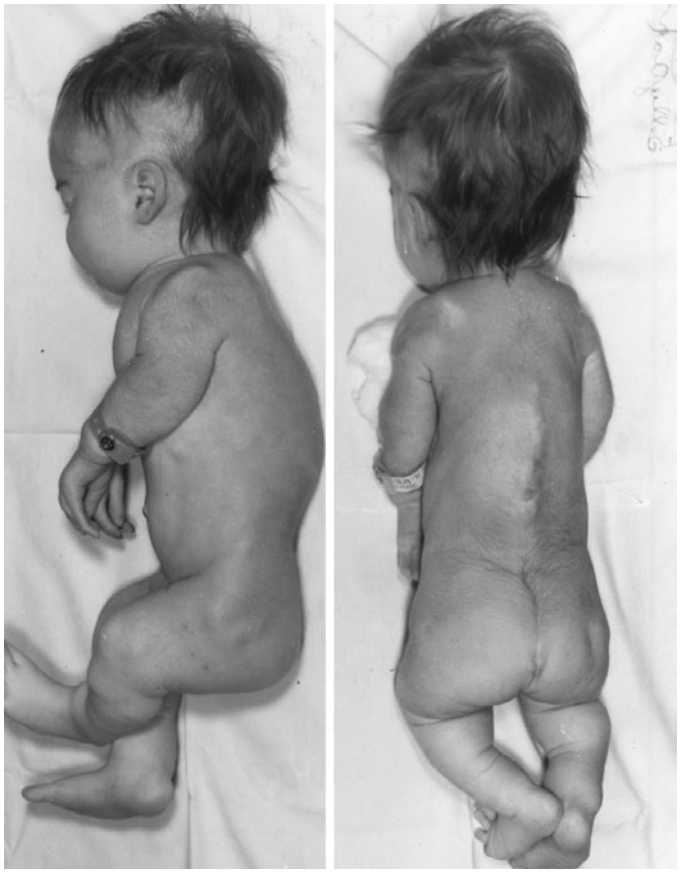
E

Fig. 7–91. *Megepiphyseal dysplasia.* (A) Bizarre facies marked by circumferential staphyloma and retrousse nose with anteverted nostrils. Note enlarged joints. (B) Huge epiphyses, with widened metaphyses of shortened long bones. (C) Markedly enlarged femoral heads, and trochanters. (D) Anterior wedging of several lumbar vertebrae. (E) Note flattened epiphyses of metacarpals, and large carpal bones.

meaning changing patterns. The main characteristics are long trunk and short limbs at birth, with subsequent development of short-trunk dwarfism because of progressive kyphoscoliosis (Figs. 7–92 and 7–93). About 50 cases have been described. An early patient may be that of Kaufmann in 1893 and Johannessen in 1898 (1). Another earlier case is that of de Groot (4) in 1951. There is some evidence for heterogeneity (1). There may be a perinatally lethal type I (12) and a nonlethal type II. Because of the occurrence of the lethal type in sibs of unaffected parents, autosomal recessive inheritance has been suggested. However, because the 14 known cases with the lethal type had 1 affected sib and at least 12 unaffected sibs, and no consanguinity has been reported, autosomal dominant inheritance is more probable, the occurrence in sibs being explained by germline mosaicism. Beck et al (1) further suggested that the nonlethal type is inherited as either autosomal recessive or dominant; as with the lethal type, autosomal dominant inheritance with (rarely) parental germline mosaicism seems more probable. Transmission of the disorder from an affected father to daughter has been described (1).

Skeleton. At birth, infants' length is normal or slightly above the mean (13) because of an unusually long trunk (Fig. 7–92). With time, the trunk becomes significantly shortened. At birth or within the first year of life, diminished joint mobility in most larger joints and hypermobility in the small joints can be found (1,9). The face has been described as being normal, with deep-set eyes and prominent nose, prognathism, or depressed nasal bridge (1–5,9,11,13). Several patients were macrocephalic, showing enlarged ventricles on CT scans (13). The chest may be narrow (2,13), thus respiratory problems may develop. Significant kyphoscoliosis develops (Fig. 7–93), which can be aggravated by hypopharyngeal air flow obstruction (2). No significant internal anomalies have been reported (10). Mental development is normal.

Radiologically, a major finding is the flattened and irregular vertebral bodies (Fig. 7–94). Already at birth, vertebral ossification is diminished, and defective ossification may remain clear until the end of puberty (13). The odontoid process can be hypoplastic; Shohat et al (13) found that this was associated with marked atlantoaxial subluxation. This can cause significant cord compression and even lead to dislocation (2,13), necessitating early surgical fusion. The thorax is narrow, and the ribs are short with distal splaying. The pelvis shows crescent-shaped iliac crests, and the lower portions of the ilia can be markedly hypoplastic, giving rise to wider horizontal iliac wings and shorter vertical wings. All long bones are shortened, and at birth the metaphyses are already grossly expanded



A B

Fig. 7–92. *Metatropic dysplasia.* (A,B) Note extremely long trunk, cat-back formation, and small tail-like appendage.

("mushrooming"). The femora may show a dumbbell shape. The tubular bones of hands and feet undergo epimetaphyseal changes.

Histologically, the major findings are absence of formation of normal spongiosa in metaphyses, islands of dysplastic chondrocytes in metaphyses and epiphyses, and disproportionate growth of long bones—i.e., arrest of endochondral growth and persistence of circumferential growth (3).

Other findings. Rarely, other symptoms have been reported, such as dilated ventricles that may need shunting (13), cleft palate (7,12), abnormal lungs, thyroid agenesis (10a), and sensorineural hearing loss (8).

Laboratory aids. Prenatal diagnosis of the severe lethal type has been accomplished at 20 weeks of gestation by ultrasound (8).

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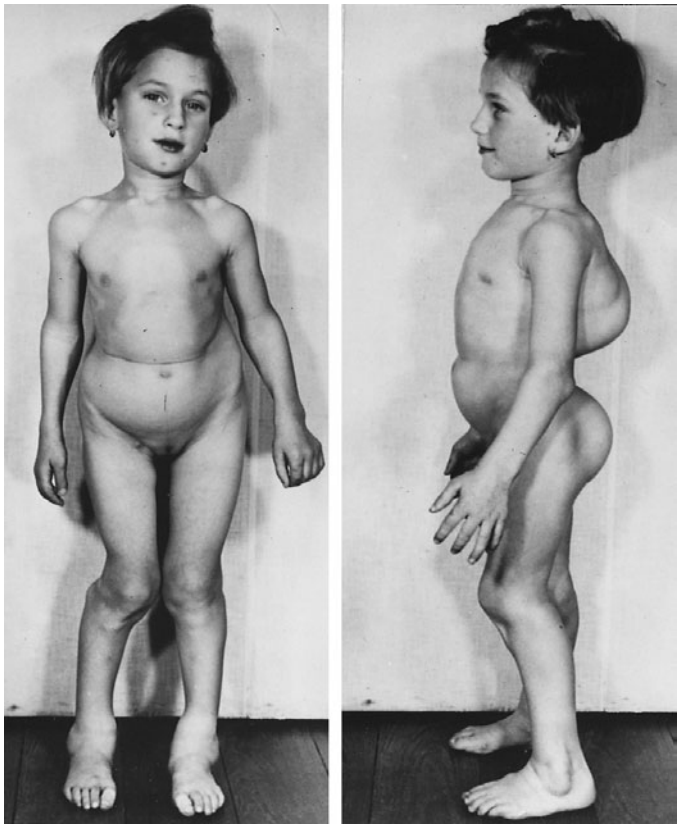
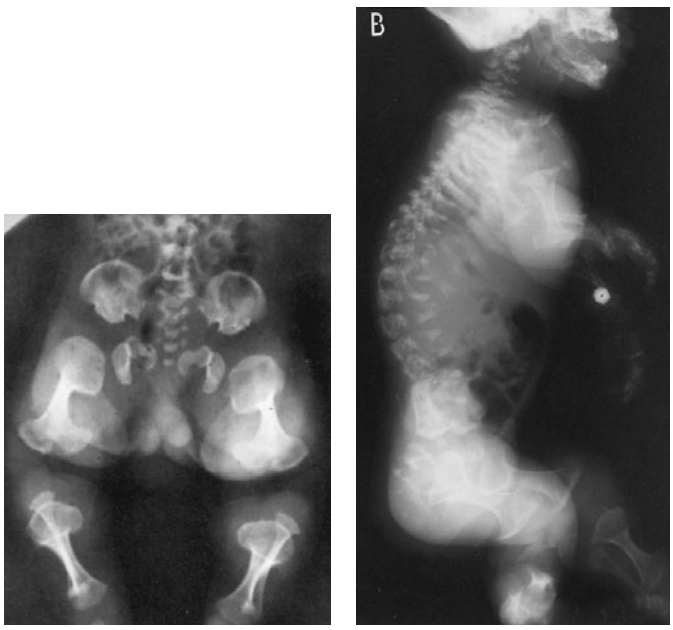


A B

Fig. 7–93. *Metatropic dysplasia.* (A,B) Note transformation of extremely long trunk into marked kyphoscoliosis. (From P Maroteaux et al, Arch Kinderheilkd 173:211, 1966.)

Fig. 7–94. *Metatropic dysplasia.* (A,B) Note wide mushroom-like metaphyses, shortening of long bones, dumbbell-shaped femora, and extremely marked platyspondyly.



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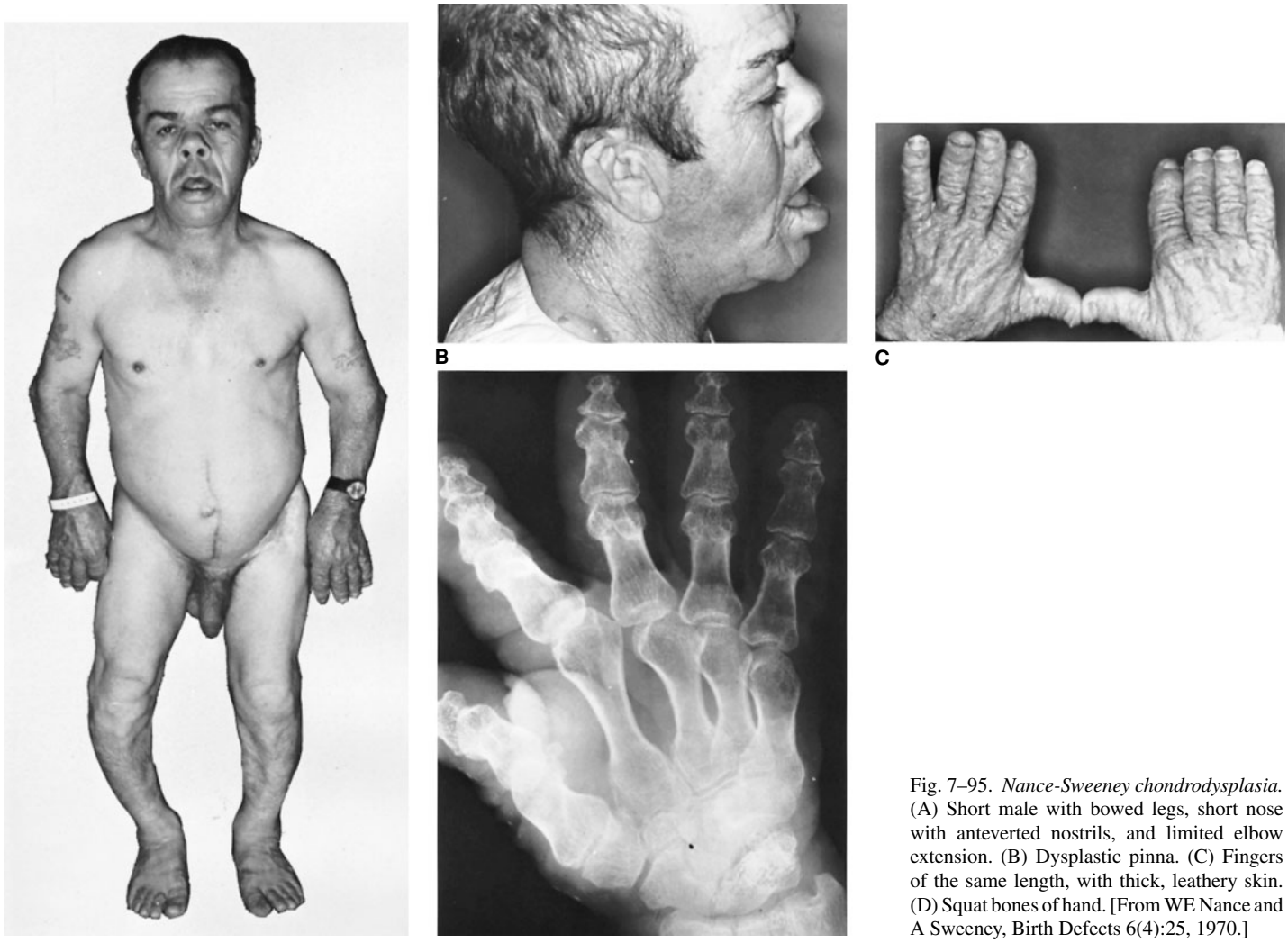

Fig. 7–95. *Nance-Sweeney chondrodysplasia.* (A) Short male with bowed legs, short nose with anteverted nostrils, and limited elbow extension. (B) Dysplastic pinna. (C) Fingers of the same length, with thick, leathery skin. (D) Squat bones of hand. [From WE Nance and A Sweeney, Birth Defects 6(4):25, 1970.]

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Nance-Sweeney chondrodysplasia

Nance and Sweeney (2) noted a chondrodysplasia characterized by short stature, cleft palate, and subcutaneous calcification (Fig. 7–95). Cousins were similarly affected and there was parental consanguinity, indicating autosomal recessive inheritance. Rosser et al (4) described another case, although comparison is hindered by the great difference in age between the two cases.

It has been suggested that the disorder is the same as bone dysplasia, midface hypoplasia, and deafness (homozygous OSMED) (1) although in the latter disorder subcutaneous calcifications are not present and epiphyses are large (4). The term "Nance-Sweeney chondrodysplasia" has also been discouraged by Spranger (5).

The facial characteristics included prominent forehead, flat nasal bridge, anteverted nares, cleft palate, and some micrognathia. The hearing loss was sensorineural.

The subcutaneous calcifications were in the abdominal wall and extremities (4) and in the external ears, ribs, hands, and epiphyseal centers of humerus, scapula, and femur (2). The skin was thick and leathery in the adult (2). Intelligence was normal. The adult height was 130 cm.

The radiographs at a young age showed small capital femoral epiphyses, shortening of all long bones with flared metaphyses and wide flattened epiphyses, and mild platyspondyly.

In the differential diagnosis, the condition reported by Oranje et al (3) should be considered. They reported a single patient with subcutaneous calcifications and metaphyseal dysplasia, but without midface hypoplasia, cleft palate, or hearing loss.

References (Nance-Sweeney chondrodysplasia)

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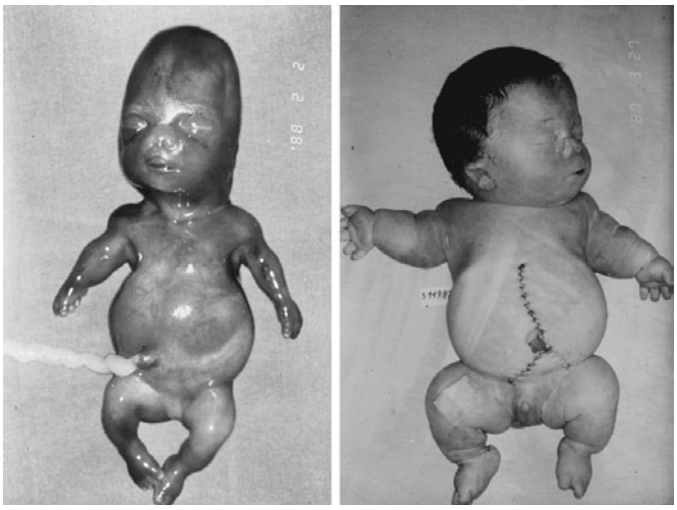

A B

Fig. 7–96. *Opsismodysplasia.* (A) High forehead with frontal bossing, hypertelorism, small nose with flat nasal bridge, anteverted nostrils, and long philtrum. Short hands and feet and bell-shaped thorax are also evident. (B) Flat wide nasal bridge, abnormal pinnae, short hands with all fingers the same length, narrow thorax, and distended abdomen. (From K Tyler et al, Am J Med Genet 83:47, 1999.)

Opsismodysplasia

In 1984, Maroteaux et al (3), employed the term "opsismodysplasia" ("opsismos" in Greek means late or delayed) to describe a rhizomicromelic dwarfism originally reported by Zonana et al (8) in 1977. In total, 11 patients have been reported in detail (1,3,4,6–8) and others have been briefly mentioned (2,3,5). The occurrence in sibs of different sex (3,6) and parental consanguinity (1,4,6) point to autosomal recessive inheritance. Several patients died in infancy or childhood because of respiratory complications due to narrow thoracic cage and hypotonia. A boy in adolescence is known (4). Mental development is normal. Santos and Saraiva (4) provide an excellent review.

The disorder is recognizable at birth and characterized by short stature, hypotonia, and short hands with digits of equal length. The thumbs and halluces tend to be wide. The head is large, the forehead is high and bossed with large anterior and posterior fontanels. The nose is small with anteverted nostrils and the philtrum is long (Fig. 7–96). The thorax is short and narrow, the abdomen protuberant. Herniae (3,8), hydrocephaly (8), and genital hypoplasia (4) have been reported.

Radiographic changes include severe bone retardation (delayed appearance of distal femoral and proximal tibial epiphyses), shortness of long bones with short, thick diaphyses, and irregular cup-shaped metaphyses, those of the metacarpals and metatarsals being especially concave (Fig. 7–97). The pelvis somewhat resembles that of asphyxiating thoracic dysplasia, showing square iliac bones, lateral and medial spurs, and horizontal acetabular roofs. The vertebral bodies are thin and lamellar. Ossification of the base of the skull and cervical vertebral bodies can also be severely delayed. Histologically, the cartilage shows a wide and irregular hypertrophic zone with thick connective tissue septa, balloon-shaped cells having abnormal lacunae, and irregular calcification and vascular invasion (3). Immunohistochemical studies have shown type I collagen (in lieu of type II) in the hypertrophic zone in the growth cartilage.

References (Opsismodysplasia)

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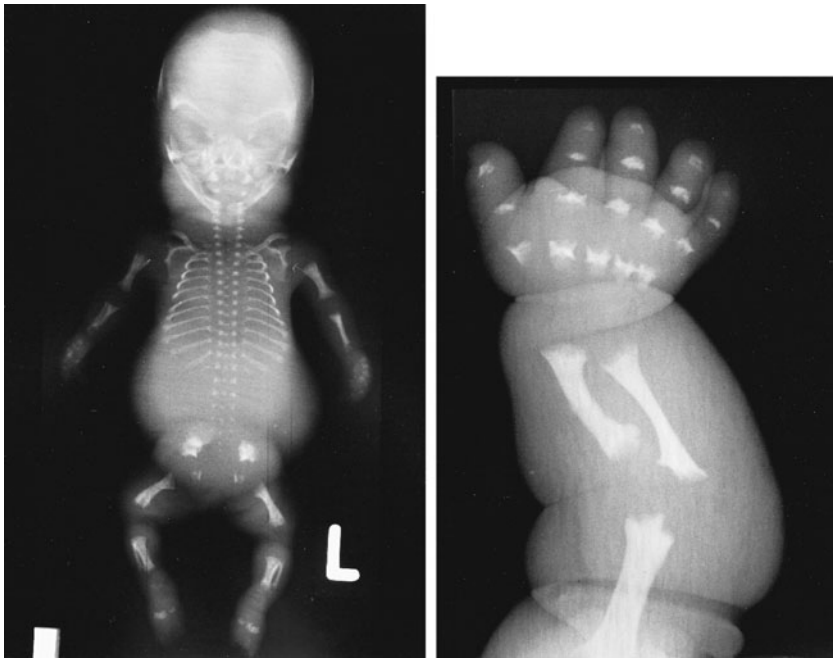
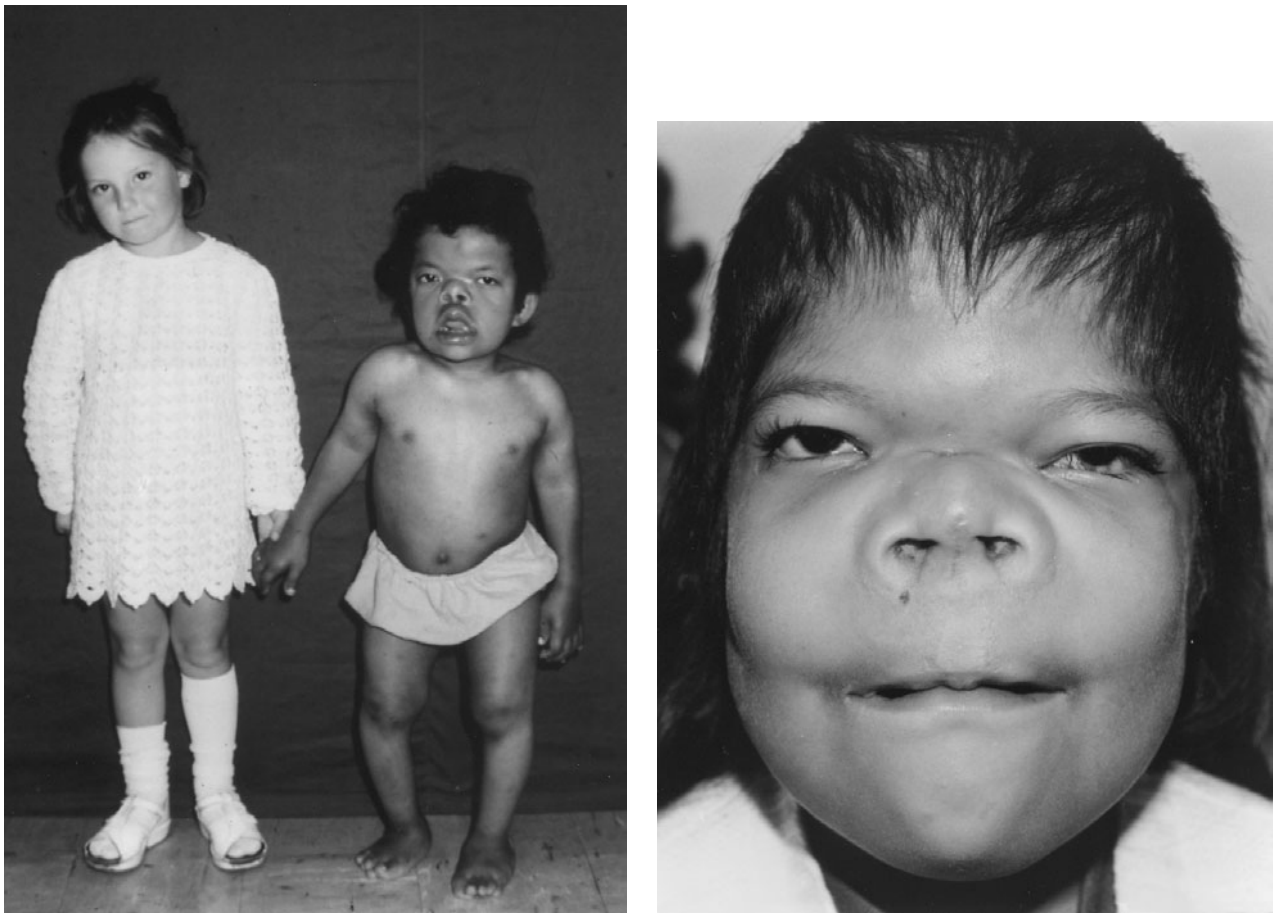


A B

Fig. 7–97. *Opsismodysplasia.* (A) Delay in bone maturation with square iliac bone, horizontal acetabular roof, flat hypoplastic vertebral bodies, short ribs, short long bones, widened metaphyses, and bent femora. (B) Shortness of long bones and irregular cup-shaped metaphyses. There is also shortness of metacarpal and phalangeal bones. (From K Tyler et al, Am J Med Genet 83:47, 1999.)



A B

Fig. 7–98. *Osteoglophonic dysplasia.* (A,B) Ocular hypertelorism, anteverted nostrils, coarse facies, and short stature. (From P Beighton, J Med Genet 26:572, 1989.)

Osteoglophonic dysplasia

The term "osteoglophonic dysplasia," derived from the Greek and meaning hollowed-out bone, was introduced by Spranger (see 1); however, strictly translated, "osteoglyphic" would be a better term (4). The disorder is a distinctive skeletal dysplasia characterized by disproportionate short stature, craniosynostosis, unerupted teeth, multiple lucent metaphyseal defects, and anterior beaking of vertebral bodies (Figs. 7–98 to 7–100). Osteoglophonic dysplasia was first described by Fairbank (3) in 1958 as a case report of *acrocephaly with abnormalities of the extremities,* and several other examples have been reported since that time (1,1a,2,4–10). Because the disorder affects patients of both sexes and vertical transmission, including a father–son transmission (6,7), has occurred, autosomal dominant inheritance is suggested. The cause is unknown, although the finding of mutations in the fibroblast growth factor receptors in other entities showing craniosynostosis and skeletal dysplasia warrants similar studies in osteoglophonic dysplasia (9).

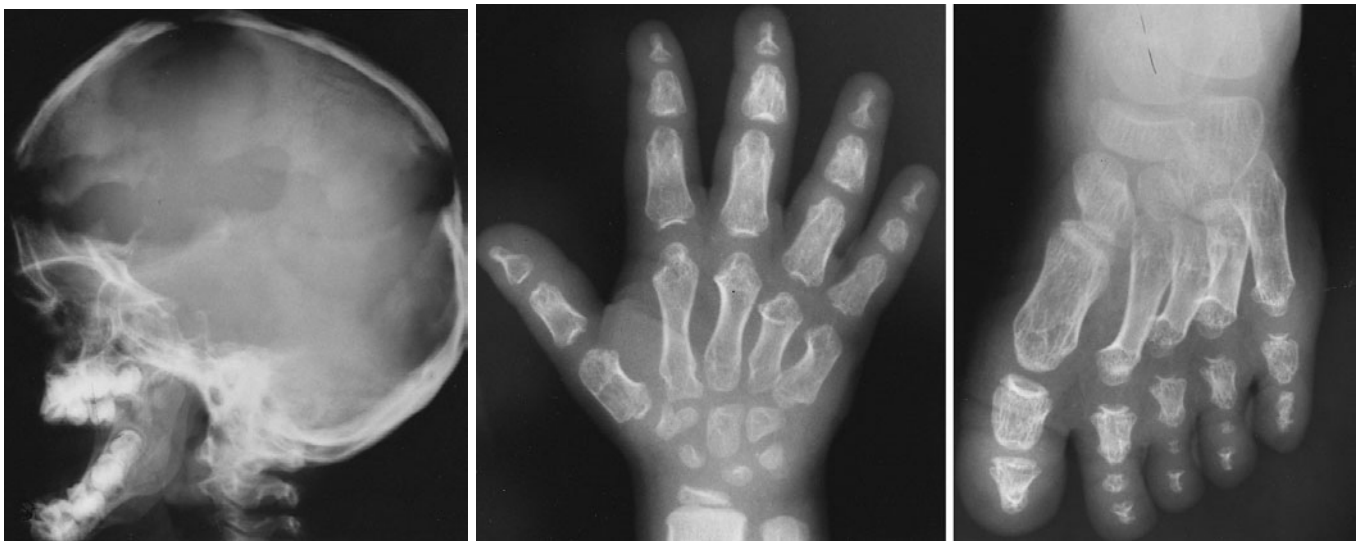
Intelligence is normal, although several patients were first thought to be retarded. Two patients died in infancy (8,10) from respiratory problems. Another patient died of pneumonia at age 27 years (MM Cohen Jr, unpublished observation). Both Beighton (1a) and Sklower Brooks (9) provide good reviews.

Craniofacial findings. Craniosynostosis has occurred in all cases to date, and multiple sutures are usually involved. Head shape may be brachycephalic, oxycephalic, or cloverleaf (6). Hydrocephaly occurred in one instance (6). Facial features include frontal bossing, shallow orbits with maxillary hypoplasia, proptosis, hypertelorism, low nasal bridge, anteverted nares, and mandibular prognathism. Radiographically, there are multiple unerupted teeth.

Musculoskeletal findings. Shortening of the extremities may be noted at birth but becomes increasingly apparent in childhood. Adult height has been between 97 and 146 cm. The long bones are undermodeled with generalized osteoporosis, cortical thickening, and loss of normal trabecular patterning. Lucent, fibrous, dysplasia-like changes are present throughout the metaphyses and are most prominent in the distal femurs and proximal tibias. The tubular bones of the extremities are short and broad; markedly dysplastic changes are observed in the epiphyseal ossification centers. Maltese cross changes have been reported in the phalanges (10). Pseudarthroses, fractures, and nonossifying fibromata have been noted (1a,9). In the spine, platyspondyly with anterior projection of the vertebral bodies is a prominent feature. In affected adults, resolved lucent defects result in grossly distorted, somewhat widened, and somewhat cystic-appearing metaphyses in many long bones. Other features include symmetrical flattening and lateral migration of the femoral heads, dysplastic and dislocated humeral heads, type B brachydactyly, hypoplastic or absent middle phalanges in the feet, and thoracolumbar scoliosis. Otherwise, the spinal curve is usually normal.

Other findings. Instances of cryptorchidism and inguinal hernia have been noted (6,9). A patient with classic findings of osteoglophonic dysplasia studied by MM Cohen, Jr had, in addition, documented renal phosphate wasting and osteomalacia. Serum calcium, serum phosphorus, and alkaline phosphatase concentrations have been within normal limits in all cases except for the one instance with renal phosphate wasting, noted above.

Differential diagnosis. The disorder should be differentiated from *hypophosphatasia.*



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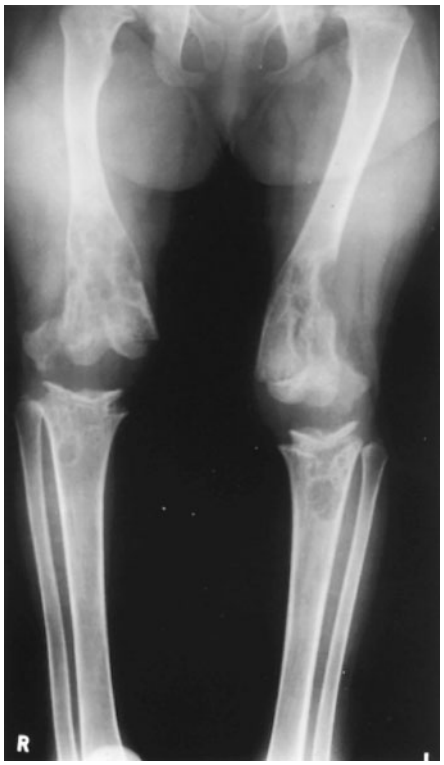

D

Fig. 7–99. *Osteoglophonic dysplasia.* (A) Oxycephalic skull, unerupted teeth, hypoplastic maxilla, and relative mandibular prognathism. There are calvarial defects secondary to surgery for craniosynostosis. (B,C) Brachycephaly of hands and feet. (D) Lower femoral and upper tibial metaphyses are expanded and contain multiple defects the patellae are dislocated. (A–C from TE Keats et al, AJR Am J Roentgenol 124:46, 1980. D from P Beighton et al, Pediatr Radiol 10:46, 1980.)

References (Osteoglophonic dysplasia)

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Schneckenbecken dysplasia

Graf et al (5), in 1972, and Laxova et al (7), in 1973, reported a lethal neonatal disorder described as thanatophoric dysplasia. A similar condition was described in 1986 by Knowles et al (6) and by Borochowitz et al (1). Inheritance is autosomal recessive. Affected sibs and parental consanguinity have been documented (1,5–7).

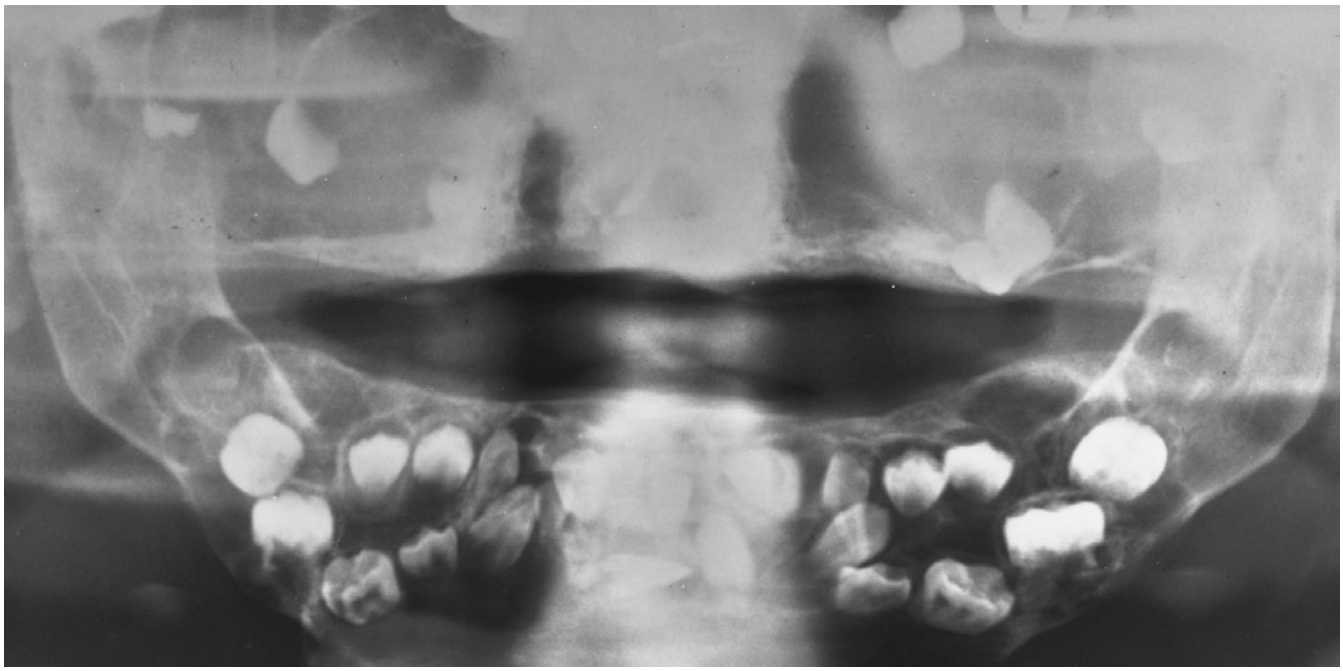

Fig. 7–100. *Osteoglophonic dysplasia.* Unerupted teeth.

The infants were edematous, and hydramnios was an almost constant feature. The head was large, the neck was short, and the face exhibited midfacial flattening (1–10). Two children had cleft palate (1,8).

The long bones were short with thick, dumbbell-like metaphyses. The clavicles had a handlebar form and the scapulae were hypoplastic. The vertebral bodies were flat and the ribs were short and splayed. The ischia were short, vertical, and precociously ossified. There was a snail-like appearance to the ilia, hence the term "Schneckenbecken" from the German. The pubic bones were hypoplastic (Figs. 7–101 and 7–102). The ankle bones were precociously ossified with three ossification centers. Brachydactyly was evident. Microscopically, the cartilage exhibited increased cellular density and hypervascularity, with each chondrocyte containing a large round central nucleus (6). Horseshoe kidneys, hydroureters, and hydronephrosis were found (5).

The disorder should be differentiated from *thanatophoric dysplasia, achondrogenesis,* and *fibrochondrogenesis.*

References (Schneckenbecken dysplasia)

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2. Camera G et al: 'Snail-like pelvis' chondrodysplasia: A further case report. Am J Med Genet 40:513–514, 1991.

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4. Giedion A et al: Case report 693. Schneckenbecken dysplasia. Skeletal Radiol 20:534–538, 1991.

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8. Nikkels PGJ et al: Schneckenbecken dysplasia—radiology and histology. 4th International Skeleletal Dysplasia Meeting, Baden-Baden, Germany, 30 July-1 August, 1999.

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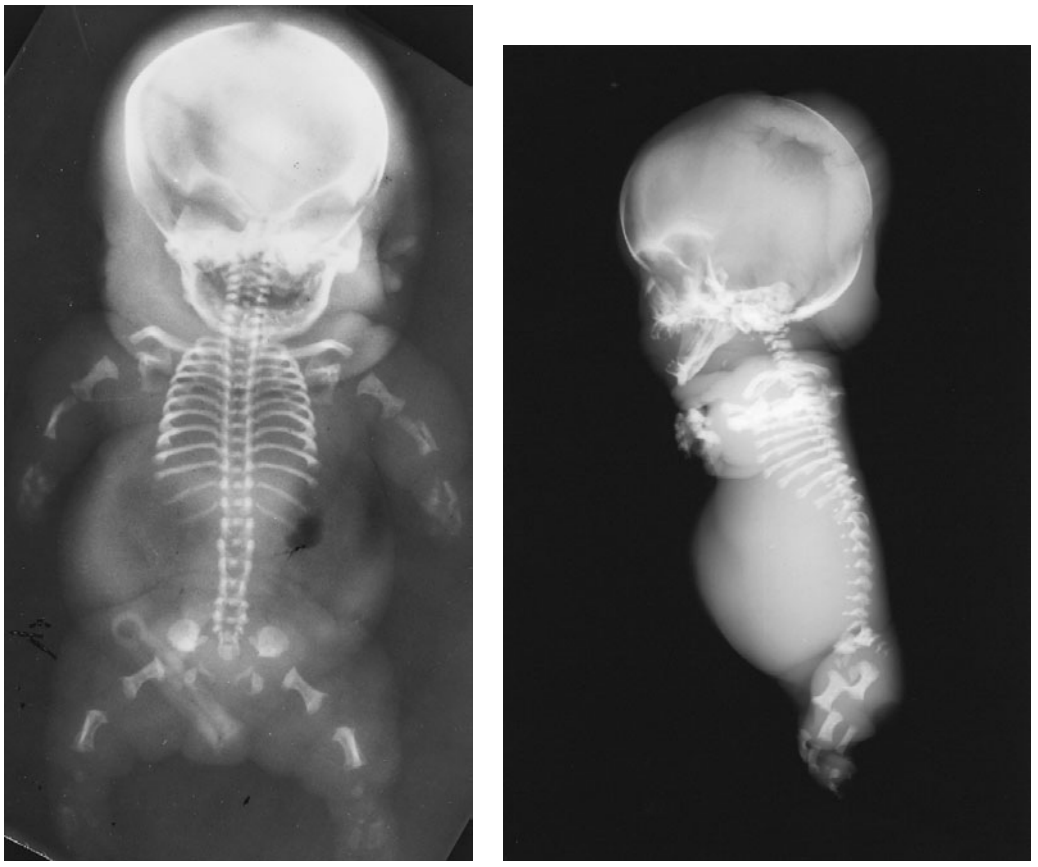
Spondylo(meta)(epiphyseal) dysplasias

The spondylo(meta)(epiphyseal) dysplasias comprise a huge group of skeletal dysplasias sharing anomalies of the vertebral column, metaphyses, and epiphyses of the long bones in a variable combination. Some are detectable at birth, in others the full (often radiologic) picture emerges only in childhood or later in life. There are entities in which the signs are confined to the skeleton and others with extraskeletal signs. A summary of the most important entities is provided in Table 7–9. Two entities (spondyloepiphyseal dysplasia congenita and spondyloepimetaphyseal dysplasia with joint laxity) are described in further detail; for the other entities, the reader is referred to the original references (Table 7–9).

Spondyloepiphyseal dysplasia congenita. Spondyloepiphyseal dysplasia (SED) congenita, first described by Spranger and Wiedemann in 1966 (92), is characterized by short stature, myopia, cleft palate, and radiographic anomalies of the vertebrae, epiphyses, and (to a lesser extent) the metaphyses. Prevalence is approximately 1/100,000 (96,105). The disorder has autosomal dominant inheritance (46,89,92), with unexpected recurrence being explained by germline mosaicism (42). It can be grouped together with Kniest dysplasia; achondrogenesis type II; hypochondrogenesis; Stickler syndrome; spondyloepimetaphyseal dysplasia (SEMD), Strudwick type (100); SED tarda (7,25,81); and SED with brachydactyly (84) as type II collagenopathies (8,74,75,93). This grouping is discussed in more detail in the section describing Kniest dysplasia (above). Mutations in the *COL2A1* gene have been found (23,60), with deletions, duplications, amino acid substitutions, and exon-skipping mutations occurring (99).

Clinical findings. Short stature leads to final height attainment of 84–128 cm (47,105). There is disproportionate shortness of neck and trunk, and coxa vara. The head appears to sit upon the trunk and is often held in retroflexion (Fig. 7–103), requiring stabilization of the cervical spine in some patients (60). The extremities are proportionately shortened but the hands and feet are normal. The chest is small and bell shaped and the abdomen protuberant. Stiffness, limitations at the hips, and waddling gait are evident. Most patients exhibit pectus carinatum, moderate thoracic kyphoscoliosis, and, in particular, lumbar lordosis. Talipes varus occurs in about 10%–15% of cases. Nonprogressive myopia of five diopters



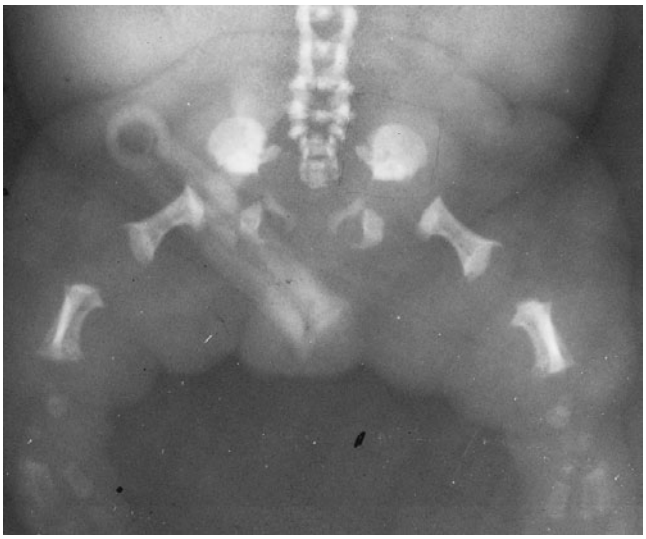
A B

Fig. 7–101. *Schneckenbecken dysplasia.* (A) Short long bones with enlarged metaphyses, handle bar-shaped clavicles, hypoplastic scapulae, flattened vertebral bodies, short splayed ribs, and abnormal ilia. (B) Extreme platyspondyly. Note lordosis of lumbosacral region and short ribs. (B courtesy of PGJ Nikkels, Utrecht, The Netherlands.)

or greater has been documented in about half of the children. In those with high myopia, vitreoretinal degeneration is encountered. Retinal detachment is rare (40,105), despite earlier reports (89,92).

Moderately severe (30–60 dB) sensorineural hearing loss, especially marked in the high tones, occurs in about 30% of patients (72). Cleft palate is noted in about 15%–20% (10,46,56,65,72,89,97,105). Mental deficiency has been rarely documented (10,72).

Fig. 7–102. *Schneckenbecken dysplasia.* Enlarged radiograph showing snail-like ilia (Schneckenbecken). (From Z Borochowitz et al, Am J Med Genet 25:47, 1986.)



Radiographic findings. In the affected infant, vertebral bodies appear ovoid on lateral view (Fig. 7–104). The odontoid is usually hypoplastic and may dislocate. As the child matures, there is platyspondyly with posterior wedging of vertebral bodies. Mild to moderate metaphyseal alterations are noted in the long bones of infants. Ossification of the sternum, pubic bones (Fig. 7–105), distal femoral and proximal tibial epiphyses, talus (Fig. 7–106), and calcaneus is retarded. The iliac bones are hypoplastic. The upper femoral epiphyses are small and deformed, late to develop, and in the coxa vara position (Fig. 7–107) (55,68,90,92). Humeral pseudoarthrosis has been reported in a mother and child (35a).

Differential diagnosis. Spondyloepiphyseal dysplasia congenita should be differentiated from *Kniest dysplasia*, *Stickler syndrome*, *Morquio syndrome*, and many of the other disorders mentioned in Table 7–9. Epiphyseal dysplasia can be secondary to congenital hypothyroidism (28). Cervical kyphosis is seen in numerous disorders, both lethal and nonlethal. The lethal forms include *atelosteogenesis II*, *campomelic dysplasia*, and a Larsen-like syndrome; the nonlethal ones include *diastrophic dysplasia*, *Larsen syndrome*, oto-facio-cervical syndrome of Fara, *Rolland-Desbuquois syndrome*, *Burton syndrome*, Berk-Tabatznik syndrome, and dominant cervical kyphosis (84a).

References [Spondylo(meta)(epiphyseal) dysplasias]

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Table 7–9. Osteochondrodysplasias characterized by a combination of spondylic and/or metaphyseal and/or epiphyseal dysplasia

Entity	McKusick no.	Pattern of inheritance	Chromosomal localization	Spondylic dysplasia	Metaphyseal dysplasia	Epiphyseal dysplasia	Other major nonskeletal features
SED congenita	183900	AD	12q13.1	++	+	++	Myopia, cleft palate
SED tarda, X-linked (14,45,69)	313400	XL	Xp22.1	++	−	+	—
SED tarda (7,25,81)	184100	AD	12q13.1	+	−	+	—
SED tarda, Toledo type (brachyolmia) (38,87)	271630	AR	—	+	−	+	—
SED, Mseleni type (1,103)	—	AR?	—	++	−	++	—
Kniest dysplasia	156550	AD	12q13.1	+	+	+	Myopia, cleft palate, hearing loss
Stickler syndrome, type I	108300	AD	12q13.1	+	−	+	Myopia, cleft palate
Stickler syndrome, type II	184840	AD	1p21	+	−	+	Cleft palate, hearing loss
SED, Maroteaux type (26)	184095	AD	—	+	−	+	—
SED with craniosynostosis	602611	AR	—	+	−	+	Mental retardation, cleft palate, cataract, craniosynostosis
SED with mental retardation (52)	271620	AR	—	+	−	+	Mental retardation
SED tarda with mental retardation (48)	600093	AR	—	+	−	+	Mental retardation, microcephaly, dysmorphic face
SED with atlanto-occipital instability (83)	600561	AD	—	+	−	+	Cervical instability
SED with punctate corneal dystrophy (19)	183850	AD?/XL?	—	+	−	+	Disorganized dermal collagen fibrils
SED with brachydactyly (84)	120140	AD	12q13.1	+	−	+	Short hands and feet
SEMD, Irapa type (9,44)	271650	AR	—	+	+	+	Arthrosis
SED, Namaqualand type (13)	120140	AD	12q13.1	+	−	+	Normal height, iliac exostoses
Progressive pseudorheumatoid dysplasia (30,31)	208230	AR	6q16	++	−	+	Rheumatoid arthritis
Dyggve-Melchior-Clausen syndrome	223800	AR	—	++	(+)	+	Mental retardation
Wolcott-Rallison syndrome (3,94,96)	226980	AR	15q11?	+	−	+	Infantile diabetes mellitus
Immuno-osseous dysplasia, Schimke type (64)	242900	AR	—	+	−	+	Lymphopenia, nephrotic syndrome
SEMD, Strudwick type (6,24,25,53,91,100)	184250	AD	12q13.1	++	+	+	—
SEMD, type II (79)	602111	AD	—	+	++	+	—
SEMD, X-linked (21)	300106	XL	—	++	+	+	—
SEMD with joint laxity	271640	AR	—	+	+	+	Joint dislocations
SEMD with short limbs and abnormal calcification (4,16,58)	271665	AR	—	+	+	+	Mental retardation, calcifications
SEMD with brachydactyly and scoliosis (2,32)	603262	AR	10q23	+	+	+	Normal intelligence, domed skull
SEMD, Shohat type (33,88)	—	AR	—	+	++	+	Dysmorphic face
SEMD with hypotrichosis (62,104)	183849	AD	—	+	+	+	Congenital hypotrichosis, positive sweat test
SEMD, micromelic type[a] (34,54,71,102)	601096	AR?	—	+	+	++	Callosal body agenesis
SEMD with abnormal dentition (82)	601668	AR	—	+	+	+	Oligodontia, pointed incisors, thin fingers
Sponastrime dysplasia (59)	271510	AR	—	++	+	−	Hypoplastic midface
Opsismodysplasia	258480	AR	—	+	++	−	Hypotonia, dysmorphic facies
SMD with dentinogenesis imperfecta (15)	184260	AD?	12q13.1?	+	+	+	Dentinogenesis imperfecta
SMD, X-linked (37)	313420	XL	—	+	+	−	—
SMD, Kozlowski type (39a,57,77)	184252	AD	—	+	+	−	—
SMD, Sutcliffe type (57)	185255	AD	—	+	++	+	—
SMD, Schmidt type (includes Algerian type) (86)	184253	AD	—	+	++	−	Myopia
SMD, Japanese type (42a)	—	AD	—	+	+	−	
SMD, Sedaghatian type (80)	250220	AR	—	+	+	+	Cardiac arrhythmia, renal cortical necrosis
SMD, type A4 (27)	—	AR?	—	+	++	−	—
SMD with osteolysis (78)	603389	?	—	+	+	−	Osteolysis, distal phalanges, painful joints
Spondylocostalmetaphyseal dysplasia (36)	—	?	—	+	+	−	Craniosysnostosis, hydrocephaly, renal cysts
ASPED (35)	105835	AD	—	−	−	++	Hypermobile fingers, hypodontia
MED, Fairbank type[b] (17,18,24)	132400	AD	19p12	(+)	−	+	—
MED, Ribbing type[b](11,24)	600204	AD	19p12	−	−	+	—
MED, type II (24,73,101)	600969	AD	1p32.3	−	−	+	—
MED with myopia and conductive hearing loss (12)	132450	AD	—	+	−	++	Cataract, myopia, hearing loss
MED with schisis and rhizomelia (63)	601560	?	—	(+)	−	+	Cleft palate, micrognathia, rhizomelia
MED with radial ray hypoplasia (29)	—	?	—	−	−	+	Radial ray hypoplasia
MED with macrocephaly and dysmorphic face (5)	—	AR	—	−	−	+	Frontal lobe atrophy, lymphedema
Pseudoachondroplasia (17,28,43,47,50,70)	177170	AD	19p12	+	+	+	—
Hip dysplasia, Beukes type (22)	142669	AD	—	−	−	+	—
CODAS (20)	600373	?	—	+	−	+	Cataract, hearing loss, dental anomalies

[a] Heterogeneity within the reported cases is possible.
[b] Are allelic disorders (also called MED, type I).
CODAS, cerebro-ocular-dental-auricular-skeletal syndrome; MED, metaepiphyseal dysplasia; SED, spondyloepiphyseal dysplasia; SEMD, spondyloepimetaphyseal dysplasia.

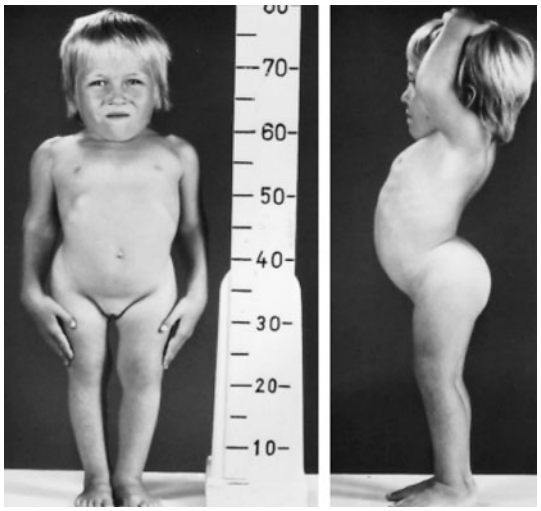

Fig. 7–103. *Spondyloepiphyseal dysplasia congenita.* Markedly reduced stature, shortened neck and trunk, severe myopia, and retinal detachment. Note marked lumbar lordosis. (Courtesy of J Spranger, Kiel, Germany.)

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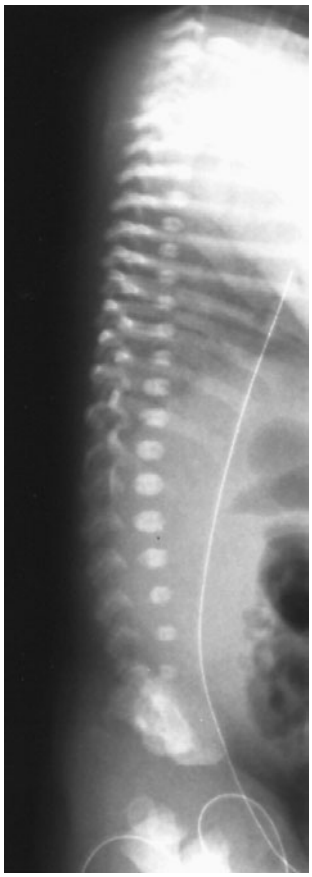
Fig. 7–104. *Spondyloepiphyseal dysplasia congenita.* Ovoid vertebral bodies.



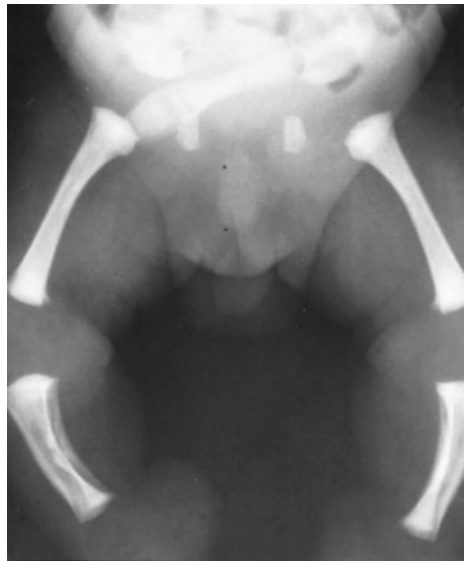


Fig. 7–105. *Spondyloepiphyseal dysplasia congenita.* Note retardation in ossification of pubic bones. [From W Holthusen, Ann Radiol (Paris) 15:253, 1972.]

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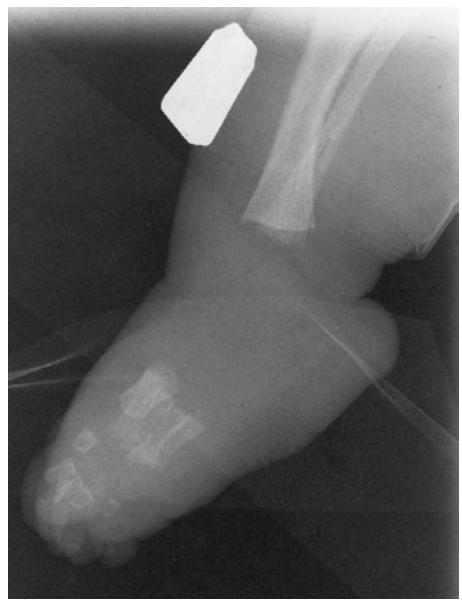
Fig. 7–106. *Spondyloepiphyseal dysplasia congenita.* Failure of calcification of talus and calcaneus.



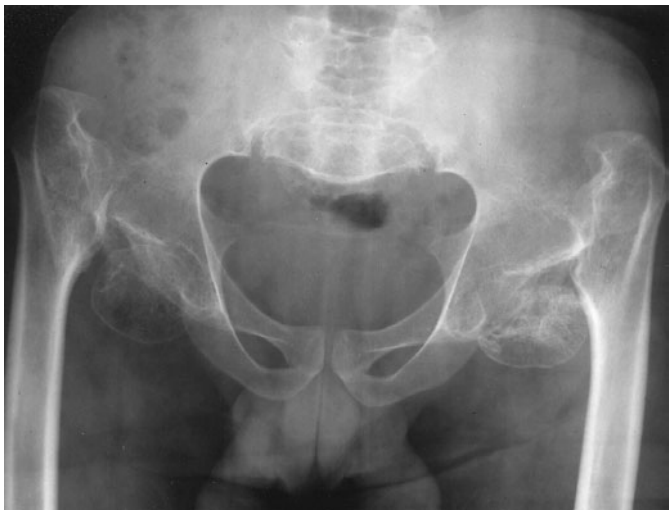


Fig. 7–107. *Spondyloepiphyseal dysplasia congenita.* Dislocated hips with femoral heads in the acetabula.

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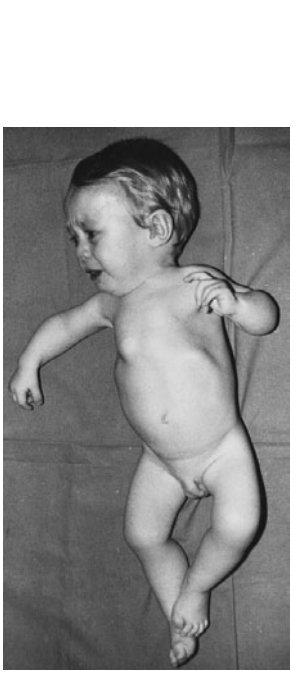
Spondyloepimetaphyseal dysplasia with joint laxity. Beighton and Kozlowski (1) first defined this entity in Afrikaners in 1980. Subsequently, about 25 patients with the disorder have been reported (1–4,6, 8,9,11,12,14–18; RCM Hennekam, unpublished observations). An early example is that of Maloney (12). Farag et al (9) noted an affected sibship with consanguinity. Torrington and Beighton (17) were able to trace the origin of the disorder in eight South African families to two females. Inheritance is autosomal recessive (3). Linkage studies have excluded *COL1A1*, *COL1A2*, *COL2A1*, *COL10A1*, fibrillin and elastin (4). It has been suggested that the defect lies in the processing of collagen or other components of connective tissue (4).

The syndrome, evident at birth, is manifested by dwarfism, articular hypermobility, spinal malalignment, thoracic asymmetry, bilateral dislocation of radial heads, and talipes equinovarus (Fig. 7–108). The hips are dislocated in about 30% of patients and there is genua valga in 80%. The terminal phalanges, particularly of the thumbs, are spatulate. A more or less specific profile of the metacarpophalangeal pattern is available (1). Spine malalignment is progressive (11). Paraplegia or early death from cardiorespiratory failure is common. Congenital heart anomalies (VSD, ASD) have been found in 30% of patients.

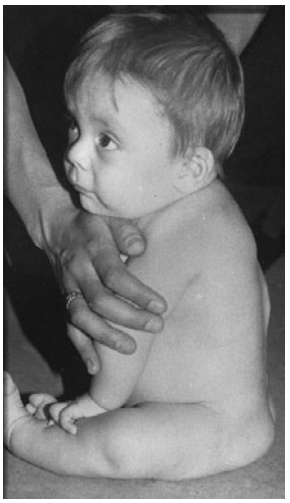
The face tends to be oval and flat with protuberant eyes, blue sclerae, and long philtrum. Cleft palate is present in 30%. The skin is somewhat hyperelastic with a doughy consistency. Rare symptoms have included mental retardation, myopia, lens dislocation, Hirschsprung disease, and megaureter (4).

The tissues are not fragile and healing is unimpaired, which allows surgical procedures without specific precautions. The spinal malalignment is very refractory to treatment. Despite bracing and internal fixation, children often develop spinal cord compression, paraplegia, and cardiorespiratory embarrassment. Beighton et al (4) reported that 10 affected children died within the first two decades; 2 adults were still alive.

The differential diagnosis includes *diastrophic dysplasia,* especially in the neonatal period, *Larsen syndrome, Ehlers-Danlos syndrome, articular type,* and the many other forms of spondyloepimetaphyseal dysplasia (Table 7–9). Goldblatt et al (10) reported a still different autosomal recessive entity that had, in addition to skeletal symptoms, dentinogenesis imperfecta. Growth was below the third centile. Mild brachydactyly, genua vara, and genua recurvata were evident. Radiographic changes included short long bones, broad cupped metaphyses, and "banana peel" configuration of distal radius. Iliac wings were flared, the sciatic notch was small, acetabular roof horizontal, and vertebral bodies were biconvex. A type II



A



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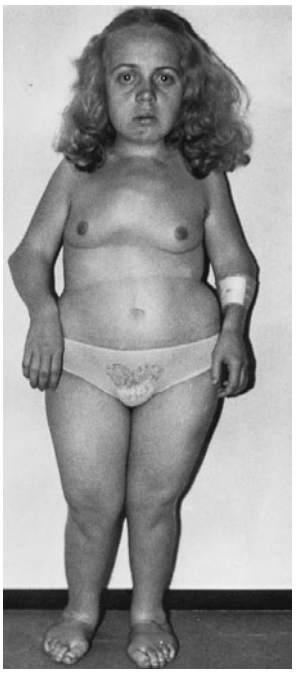

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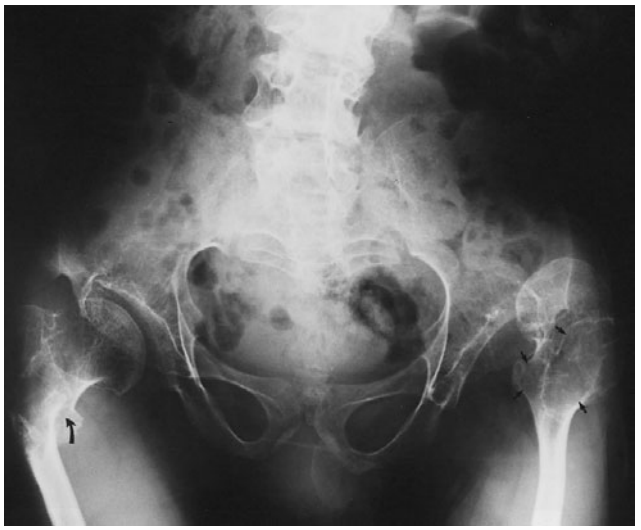

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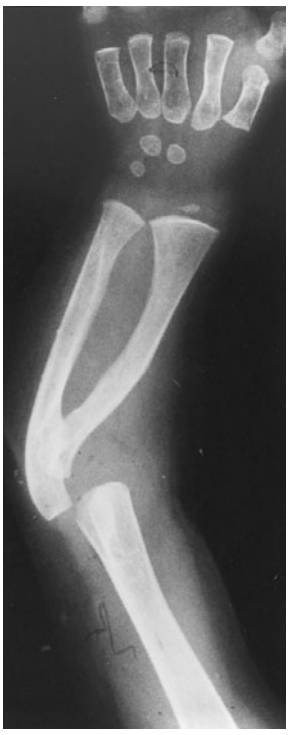

E

Fig. 7–108. *Spondyloepimetaphyseal dysplasia with joint laxity.* (A) Short limbs, thoracic asymmetry, and elbow deformity. (B) Oval face, protuberant eyes, and malaligned spine. (C) Age 20. Note short stature, thoracic asymmetry, genua valga, oval face, prominent eyes, and long upper lip. (D) Dislocated left hip; osteoporotic ends of narrow femoral shafts show highly abnormal trabecular pattern with cyst formation. Note decreased interpediculate distances. (E) Proximal shortening of radius and ulna with subluxation of elbow joint. (A, B from P Beighton et al, S Afr Med J 64:772, 1983. C from P Beighton et al, Clin Genet 26:308, 1984. D,E from P Beighton and K Kozlowski, Skeletal Radiol 5:205, 1980.)

collagen defect was found (5). Phaoke et al (13) reported a neonate with multiple joint dislocations, short stature, metaphyseal dysplasia, deficient calcification of the neurocranium, natal tooth, and lymphedema. Castriota-Scanderbeg et al (7) described a newborn with mild short-limb dwarfism without metaphyseal changes, but with joint dislocations, and severe immunodeficiency.

References (Spondyloepimetaphyseal dysplasia with joint laxity)

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Thanatophoric dysplasia

Thanatophoric dysplasia, first described by Maroteaux et al (66,67), is almost always incompatible with life. The word "thanatophoros," from the Greek, means death-bringing. The condition is characterized by marked shortening of the extremities with numerous skin folds, relatively normal trunk length, narrow thorax, and either disproportionately large head with frontal bossing, protruding eyes, and low nasal bridge or, less commonly, cloverleaf skull. Many articles on the subject have appeared dealing with a variety of different topics, including frequency (12,17,19), affected sibs (30,76), monozygotic twins (20,43,64,86,89), sibs misdiagnosed as having thanatophoric dysplasia (36,39,87), differential diagnosis (1,18,24,32,35,58,69,81,88), separate types of thanatophoric dysplasia (59,73), radiologic features (59), histopathology of long bones (75,81,82,102), cloverleaf skull heterogeneity (20,52,69,78,83), cloverleaf skull histopathology (7,53), neuropathology (21,41,101), and prenatal diagnosis (11,12,22,27).

Although usually lethal at birth, long-term (150–170 days) survival has been reported (3,59,70,94). More than 150 cases have been described to date. An early case with cloverleaf skull is that of Vrolik (98) in 1849.

Epidemiology. Connor et al (19) found a birth prevalence of 1/42,221 and suggested a mutation rate of $11.8 \pm 4.1 \times 10^{-6}$ mutations per gene per generation. Stoll et al (95) and Cobben et al (17) reported a birth prevalence of 1/25,000. Orioli et al (74) found a birth prevalence of all lethal skeletal dysplasias of 1/10,000. Hall (38) noted a propensity of births during the summer and early fall.

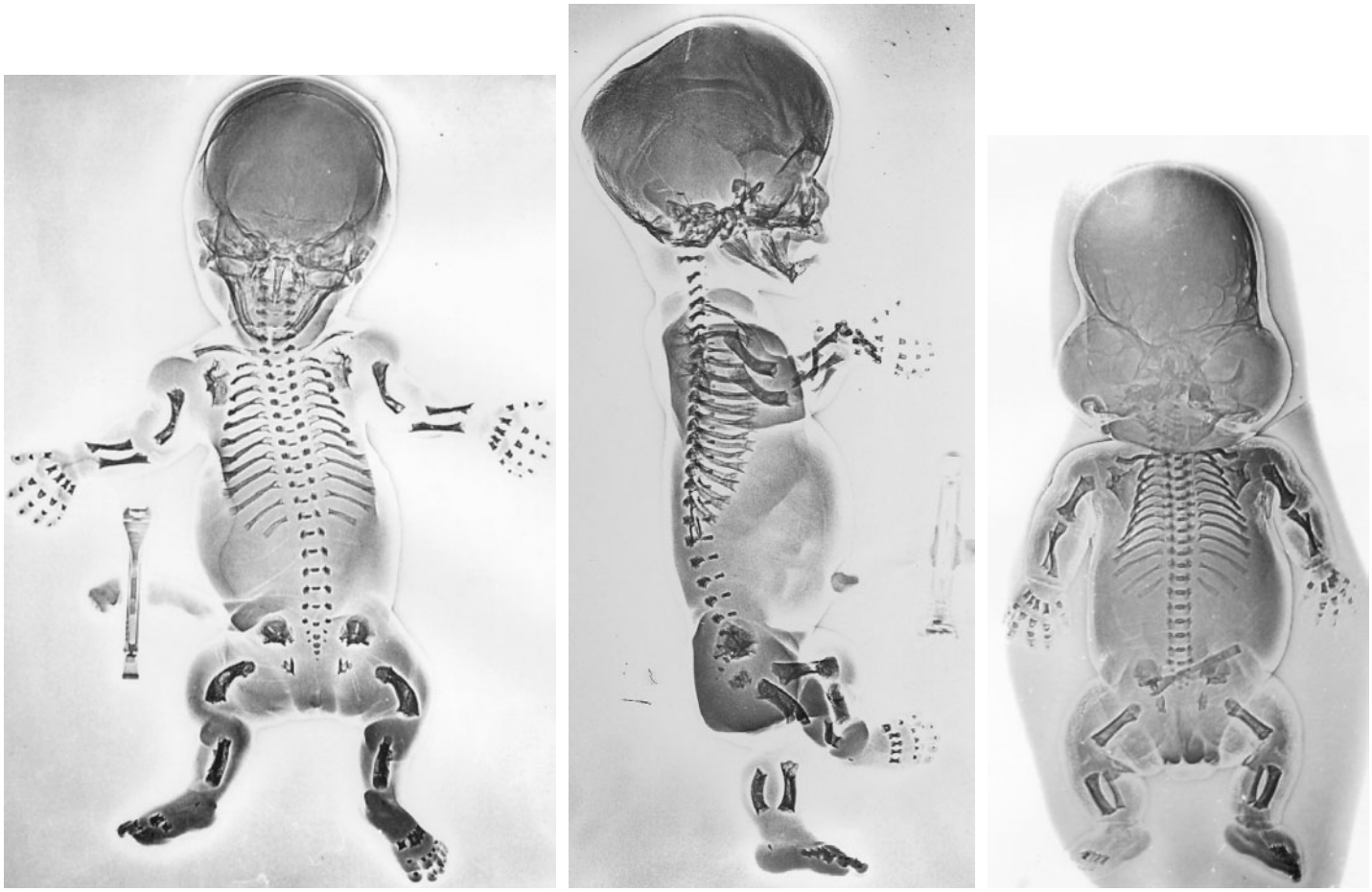
Histology and pathogenesis. Endochondral ossification is severely disturbed in thanatophoric dysplasia. This is manifested by abnormal columnization, maturation, and hypertrophy of chondrocytes in the growth plates (82,102). Cultured fibroblasts from patients with achondroplasia can be distinguished from normal fibroblasts on the basis of total intracellular mucopolysaccharide content and the relative proportion of dermatan sulfate (23). Ornoy et al (75) studied light microscopic and transmission and scanning electron microscopic findings in 13 cases and found that in growth plates, areas with less abnormal cartilage and bone alternated with areas of severely abnormal cartilage and bone. They suggested that the pathogenesis of the skeletal abnormalities is based on focal replacement of the growth plate and periosteum by persisting abnormal, mesenchymal-like tissue from which the abnormal bone originates. Their findings were confirmed by Brenner et al (9).

Nosology and genetics. Langer et al (59) distinguished two types of thanatophoric dysplasia (Figs. 7–109 to 7–113). In type 1, the long tubular bones, particularly the femora, are curved and the vertebral bodies are very flat (Fig. 7–109A,B). In type 2, the femora are straight, the vertebral bodies are not as flat as in type 1, and cloverleaf skull is virtually always present (Figs. 7–109C and 7–113). Type 2 is less common than type 1 (2,5,7,46,47,54,55). In contrast, type 1 occurs without cloverleaf skull in the vast majority of cases, and, when occasionally present, it is mild. Although Langer et al (59) noted some overlap in the diagnostic criteria of type 1 and type 2, they suggested that, on the basis of the evidence available to date, thanatophoric dysplasia represents two closely related but separate entities rather than variable expression of a single entity. However, Horton et al (43) reported monozygotic twins with type 1, discordant for (mild) cloverleaf skull.

The cause for both types of thanatophoric dysplasia was found to be mutations at different sites in *FGFR3* (6,13,72,84,85,96). Because mutations were found in many patients but not in all, genetic heterogeneity is suggested. Additional indication for heterogeneity was found by in vitro studies of clonal growth of chondrocytes, in which different responses of chondrocytes were found (9). The background of the FGFRs is described in the section on achondroplasia (above). *FGFR3* expression in cartilage and bone has been shown to be activated (25,71). Most patients with type 1 have Arg248Cys substitution, and all patients with type 2 had Lys650Glu substitution (96,100). Other mutations have been reported (6,85,96,100). All mutations have been de novo. Wilcox et al (100) studied 91 cases and found a *FGFR3* mutation in all of them. Cloverleaf skull can be present in cases with different mutations. Histologic findings were not conclusive for dividing patients into different groups, suggesting the influence of other genetic, environmental, or stochastic factors. Both types represent lethal autosomal dominant mutations. This is further supported by the finding of advanced paternal age (68) and its occurrence in identical twins (103). The affected sibs with type 2 thanatophoric dysplasia reported by Partington et al (76) could be explained on the basis of gonadal mosaicism. The overall recurrence risk is very low (43,89). Although several claims have been made about affected sibs with presumed thanatophoric dysplasia, subsequent radiographic and histologic studies have demonstrated that these infants had other types of lethal short-limbed dwarfism (43,81,82,92).

Natural history. Thanatophoric infants are either stillborn or survive for a few days and, on occasion, for several months, usually succumbing to respiratory distress that can be explained in most instances by the narrow thorax, muscular hypotonia, and alterations in bronchial cartilages. Survival beyond 1 year has rarely been observed (3,56a,59,64,70,94). Langer et al (59) noted a patient who survived to 19 years of age. Baker et al (3) reported a patient 9 years of age who had the Arg248Cys substitution commonly found in type 1. He and others (56a,64) developed acanthosis nigricans, which also occurs in Crouzon syndrome when caused by a *FGFR3* mutation. He was very severely mentally retarded. For further discussion, see the section on *unique skeletal dysplasia, developmental delay, and acanthosis nigricans, (SADDAN)* (below). In approximately 70% of cases, there is a history of hydramnios. At least one-third of thanatophoric infants are premature and born by breech presentation (81).

Craniofacial features. In type 1 thanatophoric dysplasia, the head is disproportionately large, with head circumference being as large as



A B C

Fig. 7–109. (A,B) *Thanatophoric dysplasia* (*curved bone type*). Xeroradiograph showing midfacial hypoplasia, micrognathia, narrow thorax, very short ribs, hypoplastic flattened vertebral bodies, abbreviated long bones, curved humeri and femora, short metapodial bones, and phalanges. (C) *Thanatophoric dysplasia with cloverleaf skull*. Note cloverleaf skull, abnormal clavicles and ribs, hypoplastic vertebrae, small pelvic bones, abbreviated long bones, and small bones of extremities. In contrast to classic thanatophoric dysplasia, the femora and humeri are straight with irregular metaphyseal plates. (From R Elejalde, Am J Med Genet 22:669, 1985.)

40 cm. Characteristic features usually include frontal bossing, protruding eyes, and low nasal bridge (Fig. 7–110). Cloverleaf skull anomaly is found in type 2 (Fig. 7–113). Histologic study of the cranial base demonstrates disarrayed chondrocytes (7). In detailed anatomic and histologic study, Kokich et al (53) showed that the synchondroses, usually present at birth, between the presphenoid, basioccipital, exoccipital, and supraoccipital components of the skeletal floor were absent; the cranial base was completely united as one bone. This results in dramatic foreshortening of the cranial base. In some cloverleaf skulls, the sagittal and lambdoidal sutures are synostosed (7,76). In others, coronal, sagittal, and lambdoidal sutures are involved (53). In cases of type 1 thanatophoric dysplasia without premature synostosis involving the cranial vault (18,59), the trilobular skull configuration is usually absent or minimally manifested. This severe cloverleaf skull anomaly is probably not dependent on the dysplastic changes in the cranial base per se, but results from the restricting influence of the particular pattern of prematurely synostosed cranial sutures on the normal expansion of the brain.

Neuropathology. Neuropathologic study of several cases has demonstrated abnormally deep sulci in the temporal lobe, dysgenesis of the parahippocampal area, agenesis of Ammon's horn, and periventricular heterotopia limited to the temporal lobe with polymicrogyria in the adjacent area. These findings were present in thanatophoric dysplasia both with and without cloverleaf skull (21,41,52,101)

Hydrocephaly is a common finding in thanatophoric dysplasia with cloverleaf skull. Diverticulum formation in areas of focal temporal dysplasia has been reported in one instance (41), as was spinal cord injury due to neural arch stenosis (29).

Other abnormalities. Low-frequency findings in thanatophoric dysplasia may include cleft lip/palate (37), congenital heart defects (47), soft tissue syndactyly of fingers and toes (10), and adenomyosis of the pyloric muscular layer (93). Acanthosis nigricans may develop in those patients who live longer (3).

Prenatal diagnosis. Prenatal diagnosis on the basis of ultrasonic and radiographic findings has been reported in several instances (8,11, 12,22,27,28). Since almost all examples of thanatophoric dysplasia are sporadic, it has not been possible to single out couples at risk. Thus, early prenatal diagnosis, which is theoretically possible, has not been the rule.

Differential diagnosis. Differential diagnosis of thanatophoric dysplasia includes *heterozygous achondroplasia*, *homozygous achondroplasia*, different types of *achondrogenesis*, severe *hypophosphatasia*, and different short limb syndromes (81,92). The cloverleaf skull malformation is known to be both etiologically and pathogenetically heterogeneous.

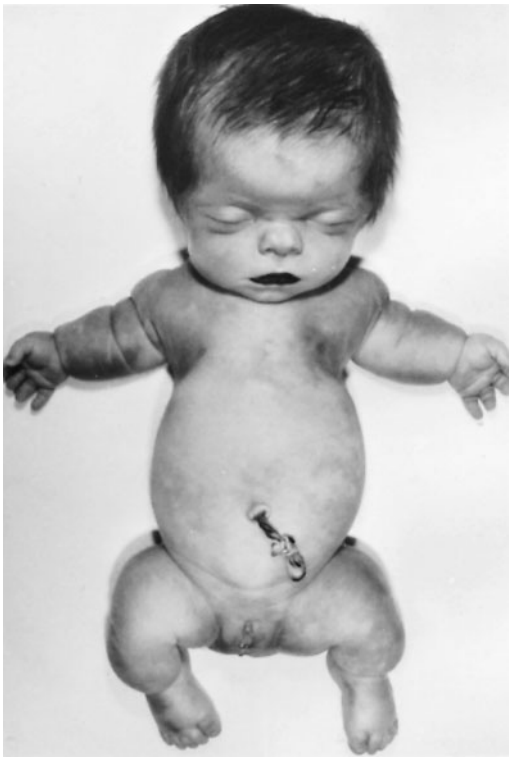
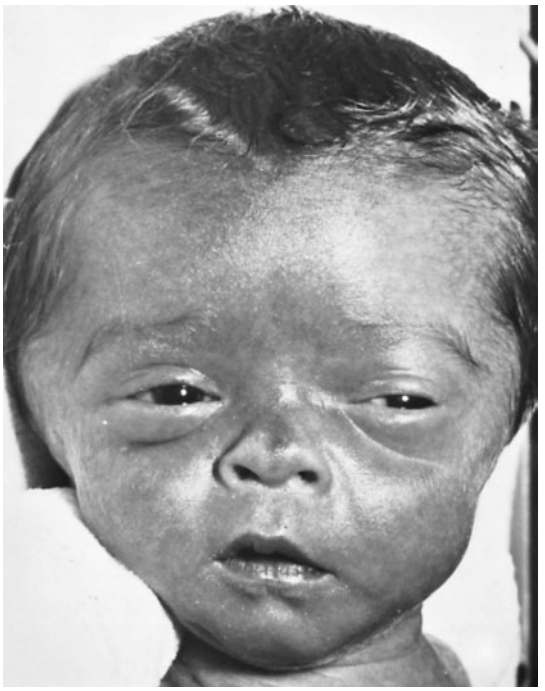


Fig. 7–110. *Thanatophoric dysplasia* (*curved bone type*). Short neck, short bowed extremities with shortened digits, constricted upper part of chest, and large abdomen.

Fig. 7–111. *Thanatophoric dysplasia* (*curved bone type*). Enlarged head circumference with frontal bossing, hypertelorism, and proptosis. (From A Giedion, Helv Paediatr Acta 23:175, 1968.)



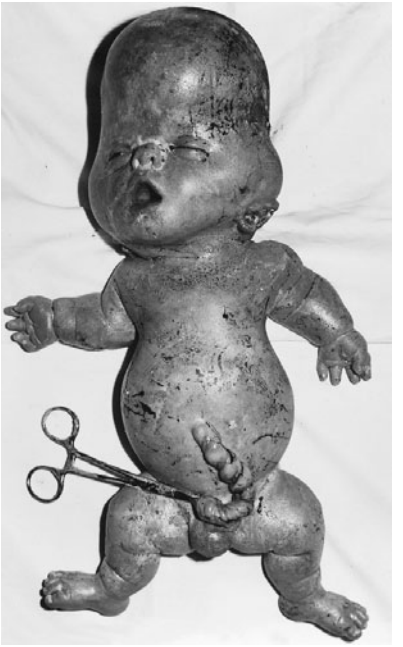
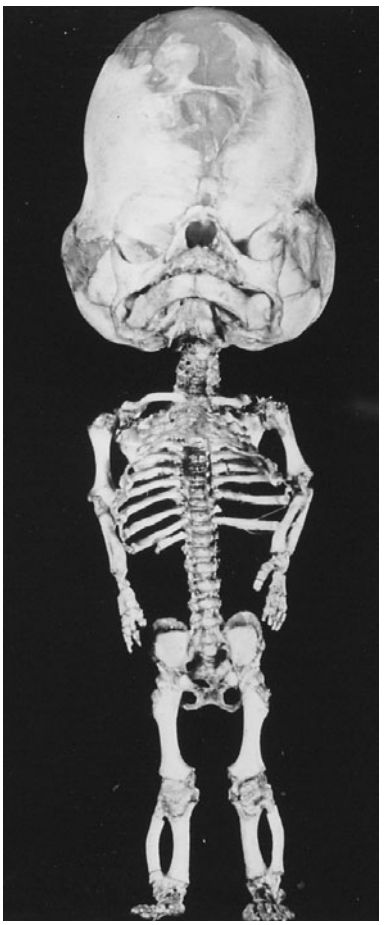


Fig. 7–112. *Thanatophoric dysplasia* (*straight bone type*). Trilobular skull, depressed ears parallel to shoulders, short neck, small thoracic cage, protuberant abdomen, micromelia, and relatively normal trunk length. (From MW Partington et al, Arch Dis Child 46:656, 1971.)

Fig. 7–113. *Thanatophoric dysplasia* (*straight bone type*). Skeleton of infant with cloverleaf skull. Skull is large in comparison with rest of skeleton. Note normal clavicles, narrow thoracic cage, short extremities, straight femora, and relatively normal length of spine. (Courtesy of Pathology Museum of St. Bartholomew's Hospital, London.)



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Unique skeletal dysplasia, developmental delay, and acanthosis nigricans (SADDAN)

In 1999, Tavormina et al (4) and Bellus et al (2) described a syndrome they called "SADDAN," standing for *S*evere *A*chondroplasia, *D*evelopmental *D*elay, and *A*canthosis *N*igricans. The severity of the phenotype can perhaps be thought of as less severe than thanatophoric dysplasia but more marked than achondroplasia. The term "SADDAN" will become established because the precedent has been set (2,4). However, we are concerned that the term "severe achondroplasia" may be misleading because one might think that the disorder is really achondroplasia but of a more severe degree than usual.

The mutation involves the same FGFR3 amino acid residue (650) affected in thanatophoric dysplasia type 2, but instead of the usual thanatophoric dysplasia type 2 mutation (Lys650Glu), a methionine is substituted (Lys650Met) for a lysine. Furthermore, the nucleotide change (1949A→T) is adjacent to the one for thanatophoric dysplasia, type 2 (1948A→G). The Lys650Met mutation has constitutive receptor kinase activity that is three times greater than that observed for Lys650Glu (4).

Those individuals with the mutation usually survive into adulthood, although a V-P shunt may be necessary (2).

The phenotype closely resembles that of achondroplasia.

Skin. Acanthosis nigricans develops during infancy and first involves the neck, axilla, groin, and dorsum of the hand and progresses with time to involve the back, chest, and palms (Fig. 7–114A–C). The epidermal layer is somewhat thicker than that found in other disorders with acanthosis nigricans. Insulin resistance is not the cause of acanthosis nigricans in SADDAN (2,4).

Skeletal system. The skull is large with frontal bossing and midface hypoplasia. The sinuses are prominently pneumatized and the calvaria is asymmetrically thickened. There has been no evidence of craniosynostosis (Fig. 7–114D). G Bellus suggested that cementomas are present in the jaws (August, 2000).

The spine exhibits platyspondyly and narrowing of the interpediculate distances caudally. In adults, the vertebral bodies are high and square with severe anterior scalloping, extreme kyphosis, and exaggerated lumbar lordosis. The ribs are shorter and the chest circumference smaller than in achondroplasia (2).

In newborns, the pelvis is thanatophoric dysplasia–like with extremely short iliac bones and very narrow sacrosciatic notches. With growth, the pelvis becomes more achondroplasia-like with flattening of the acetabular roof (2).

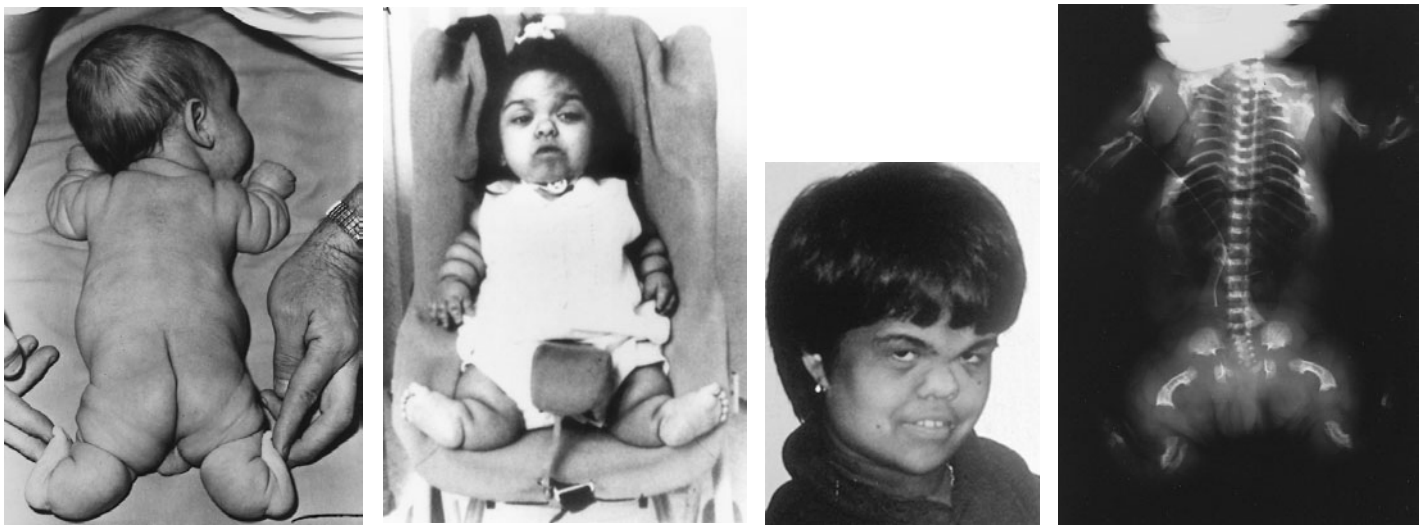
Long bone changes are dramatic in newborns and are thanatophoric dysplasia–like. Femoral bowing is severe and bowing of the tibia and fibula may be observed. The humerus tends to be larger than that found in thanatophoric dysplasia type 1. The radius is short with dislocation of the head, and there is compensatory bowing of the ulna. During infancy, short metacarpals and broad phalanges are neither thanatophoric dysplasia–like nor achondroplasia-like (2).

The histopathologic changes found at the costochondral junction are similar to those found in thanatophoric dysplasia, type 1.

Central nervous system. Generalized seizures during infancy, various degrees of hydrocephalus, and cervical spine stenosis have been reported (2). These features can also be found in rare instances of thanatophoric dysplasia survivors (1,3). Other findings in SADDAN include a very thin splenium of the corpus callosum and a paucity of white matter with prominence of the ventricles and sulci. These abnormalities are not found in achondroplasia.

In the surviving patients with SADDAN, developmental delay has been noted (2).

Acanthosis nigricans may also be seen in *crouzonodermoskeletal syndrome, Beare-Stevenson cutis gyrata syndrome*, and in rare cases of thanatophoric dysplasia, type 1 with extended survival (1).



A B C D

Fig. 7–114. *Unique skeletal dysplasia, developmental delay, and acanthosis nigricans (SADDAN).* (A) Six-month-old showing unusual curvature of lower legs, large head, and excessive skin folds. (B) Note redundant skin folds, bent lower limbs, and acanthosis nigricans. (C) Facies similar to that in achondroplasia. Note acanthosis nigricans. (D) Neonatal radiograph showing severe bowing of femora and reverse bowing of tibiae. Femora and pelvis are very similar to that of thanatophoric dysplasia, type 1, but platyspondyly is not as severe. (A,B,D from GA Bellus et al, Am J Med Genet 85:53, 1999. C courtesy of G Bellus, Denver, Colorado.)

References [Unique skeletal dysplasia, developmental delay, and acanthosis nigricans (SADDAN)]

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Spondyloepiphyseal dysplasia, craniosynostosis, cataracts, cleft palate, and mental retardation

Nishimura et al (1) reported four Japanese sibs with spondyloepiphyseal dysplasia, craniosynostosis, cataracts, mental retardation, and cleft palate (Figs. 7–115 and 116). Inheritance appears to be autosomal recessive. The cataracts, possibly congenital, became evident during early childhood.

Radiologic changes included coronal synostosis, mild epiphyseal dysplasia, particularly of the distal tibiae, strikingly delayed patellar ossification, mild metaphyseal splaying, hypoplastic ilia with iliac flare, and platyspondyly with ovoid or posteriorly humped vertebral bodies.

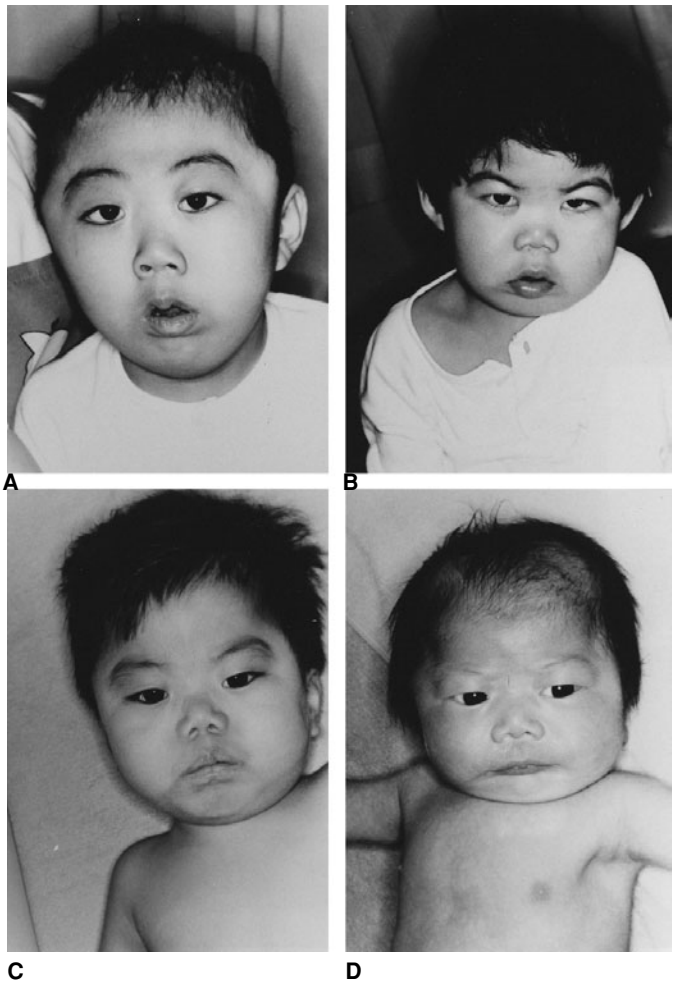
Reference (Spondyloepiphyseal dysplasia, craniosynostosis, cataracts, cleft palate, and mental retardation)

1. Nishimura G et al: Previously undescribed spondyloepiphyseal dysplasia associated with craniosynostosis, cataracts, cleft palate, and mental retardation: Report of four sibs. Am J Med Genet 77:1–7, 1998.

Cerebro-ocular-dental-auricular-skeletal (CODAS) syndrome

The CODAS syndrome is a rare multiple congenital anomalies syndrome comprising unusual facies, unusual skeletal changes, and unusual teeth (1–3). Two patients were of Mennonite ancestry. Inheritance may be autosomal recessive.

Fig. 7–115. *Spondyloepiphyseal dysplasia, craniosynostosis, cataracts, cleft palate, and mental retardation.* (A–D) Facies of four sibs showing flattened facies, depressed nasal bridge, and small nose with anteverted nares. (From G Nishimura et al, Am J Med Genet 77:1, 1998.)



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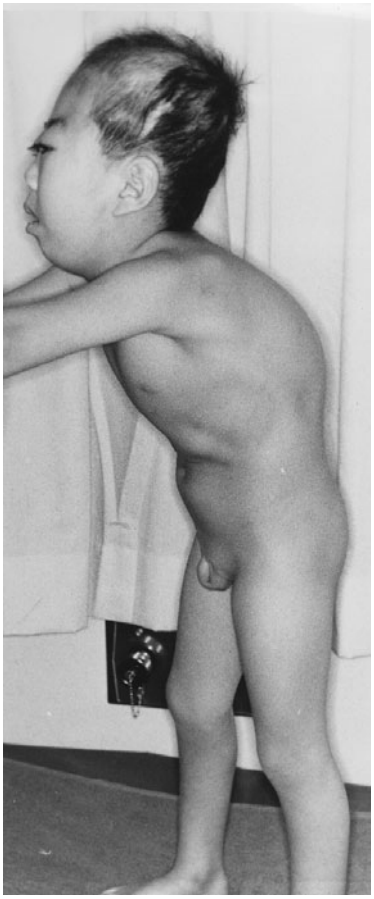


Fig. 7–116. *Spondyloepiphyseal dysplasia, craniosynostosis, cataracts, cleft palate, and mental retardation.* Patient 1, shown in Figure 7–115A, with kyphosis, sloping forehead, and brachycephaly. (Courtesy of G Nishimura, Tochigi, Japan.)

The facies is characterized by grooved nose, bilateral ptosis, congenital cataracts, facial hypotonia, anteverted nares, epicanthic folds, and overfolded and crumpled pinnae (Fig. 7–117).

Skeletal changes included short humeri, genua valga, pes planus, delayed bone age, coronal clefts of lumbar vertebrae, epiphyseal dysplasia, marked joint laxity with dislocation, proximally placed thumbs, and squared ilia. Stature is short.

The teeth, both deciduous and permanent, exhibited enamel projections from the cusp tips.

References (Cerebro-ocular-dental-auricular-skeletal (CODAS) syndrome)

1. Cabral de Almeida JC et al: CODAS syndrome: A new distinct MCA/MR syndrome with radiologic changes of spondyloepiphyseal dysplasia: Another case report. Am J Med Genet 55:19–20, 1995.

2. Innes AM et al: CODAS (cerebral, ocular, dental, auricular, skeletal anomalies) syndrome: Recognizable multiple congenital anomalies syndrome is likely inherited as an autosomal recessive trait—first report of an affected male. David W. Smith Workshop on Malformations and Morphogenesis, Schlangenbad, Germany, Aug. 3–9, 1999.

3. Shebib SM et al: Newly recognized syndrome of cerebral, ocular, dental, auricular, skeletal anomalies: CODAS syndrome—a case report. Am J Med Genet 40:88–93, 1991.

Multicentric osteolysis,Torg-like

Several disorders of multicentric osteolysis have recessive inheritance. The syndromes of Torg, Winchester, Thieffrey-Kohler, and François principally involve the carpal, tarsal, and interphalangeal joints. Progressive bone loss and crippling arthritic deformities mimic severe juvenile rheumatoid arthritis. Al-Mayouf et al (2) and Al Aqeel et al (1) collectively described 12 patients from seven unrelated Saudi Arabian families. Inheritance is clearly autosomal recessive.

All patients had distal arthropathy. Ten patients presented with deformed hands and about half of these exhibited pain in the hands. Involvement of the extremities began in the first few months of life.

Radiographically, osteopenia and undertubulation of bones affected the distal more than the proximal areas and the upper limbs more severely than the lower limbs. Osteolysis was also seen in carpal and tarsal bones. Common findings were sclerotic cranial sutures, brachycephaly, and broad medial clavicles. Stature was short.

Large, painful, fibrocollagenous palmar and plantar pads were evident as well as mild hirsutism of the body.

Facial changes including high forehead and proptosis are seen as well as narrow nasal bridge, bulbous nose, and micrognathia. Normal intelligence and normal renal function separated this form of multicentric osteolysis from several others.

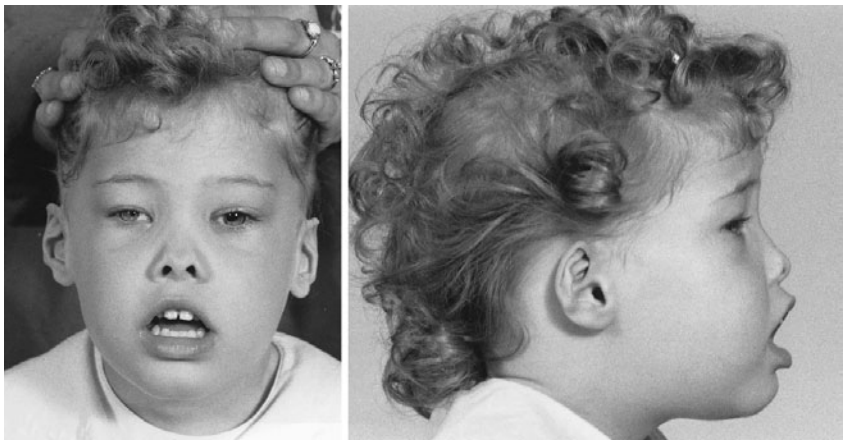
There is marked similarity to the patient described by Torg et al (8). A facies similar to that seen in this syndrome was reported by Szoke et al (7) and others (4–6). The same facial changes were reported in the autosomal dominant form noted by Carnevale et al (3).

References (Multicentric osteolysis, Torg-like)

1. Al-Aqeel A et al: Inherited multicentric osteolysis with arthritis: Variant resembling Torg syndrome in a Saudi family. Am J Med Genet 93:11–18, 2000.

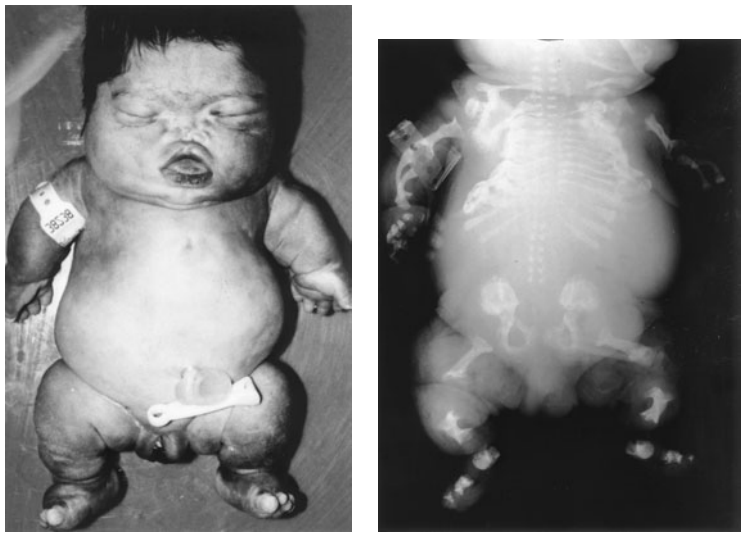
2. Al-Mayouf SM et al: Two forms of idiopathic osteolysis: Nodulosis [arthropathy and osteolysis (NAO syndrome)]. Am J Med Genet 93:5–10, 2000.

3. Carnevale A et al: Idiopathic multicentric osteolysis with facial anomalies and neuropathy. Am J Med Genet 26:877–886, 1987.



A B

Fig. 7–117. *Cerebro-ocular-dento-auricular-skeletal (CODAS) syndrome.* (A,B) Four-year-old patient with facial hypotonia, flat nasal bridge, and low-set dysmorphic pinnae. The child had genua valga, pes valgus, short stature, and teeth with unusual cusp extensions. (From SM Shebib et al, Am J Med Genet 40:88, 1991.)



A B

Fig. 7–118. "*Baby rattle*" *pelvis dysplasia.* (A) Severely shortened limbs, protuberant belly, markedly flattened midfacies. (B) Long bones are shortened, vertebral bodies unossified. Note bifid distal humeri. Most striking is "baby rattle" pelvis dysplasia. (Courtesy of V Cormier-Daire et al, November, 2000.)

4. Franceschino P et al: Osteolisi carpotarsale idiopatica: Descrizione di un nuovo caso clinico revisione della literature. Rev Ital Pediatr 16:728–730, 1990.

5. Rizzo R et al: Idiopathic multicentric osteolysis: Family report and review of the literature. Clin Dysmorphol 2:251–256, 1993.

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7. Szoke G et al: Idiopathic carpotarsal osteolysis with Bartter's syndrome. A case report and review of the literature. Clin Orthop 310:120–129, 1995.

8. Torg JS et al: Hereditary multicentric osteolysis with recessive transmission: A new syndrome. J Pediatr 75:243–252, 1969.

"Baby rattle" pelvis dysplasia

Cormier-Daire et al (1) described a lethal skeletal dysplasia having distinct radiologic and chondro-osseous morphologic features. Clinically, the limbs were severely shortened. The fontanelles were very large, the midface hypoplastic, and the belly protuberant (Fig. 7–118A).

The humeri of the limbs had bifid distal ends and the vertebral bodies were unossified. The most striking feature from which the name is derived is the "baby rattle" pelvic configuration with tall and broad ilia (Fig. 7–118B).

Microscopic examination of long bones showed absent enchondral ossification, regions of mesenchymal within resting cartilage, and abnormal mesenchymal ossification.

Achondrogenesis, pyknoachondrogenesis, *atelosteogenesis II,* and *Greenberg dysplasia* must be excluded.

Reference ("Baby rattle" pelvis dysplasia)

1. Cormier-Daire V et al: "Baby-rattle" pelvis dysplasia. Am J Med Genet 100:37–42, 2001.

Chapter 8
Syndromes Affecting Bone: Craniotubular Bone Disorders

General considerations

There has been much confusion attendant to genetic disorders of bone characterized by modeling errors of tubular and cranial bones. Gorlin et al (3) divided craniotubular dysplasias into Pyle disease, craniometaphyseal dysplasia, craniodiaphyseal dysplasia, frontometaphyseal dysplasia, Schwarz-Lélek syndrome, dysosteosclerosis, and oculodentoosseous dysplasia. The craniotubular hyperostoses consist of Van Buchem disease, sclerosteosis, congenital hyperphosphatasia, autosomal dominant osteosclerosis, and Camurati-Engelmann disease. Later, Gorlin (2) thought that Lélek's report represented an example of craniometaphyseal dysplasia or possibly an entity unto its own, and considered the report of Schwarz to be an example of craniometadiaphyseal dysplasia. Furthermore, Pyle disease was no longer considered a craniotubular bone disorder as the skull is so mildly involved. More extensive discussions may be found in Beighton and Cremin (1) and Whyte (4).

References (General considerations)

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2. Gorlin RJ: Craniotubular bone disorders. Pediatr Radiol 24:392–406, 1994.
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4. Whyte MP: Skeletal disorders characterized by osteosclerosis or hyperostosis. In: Metabolic Bone Disease and Clinically Related Disorders, 3rd ed, LV Avioli, SM Krane (eds), Academic Press, San Diego, 1998.

Craniometaphyseal dysplasia

This disorder, often erroneously reported as Pyle disease, is characterized by unusual facies and club-shaped metaphyseal flaring of long bones. Autosomal dominant (1–6,8,10–12,14–29) and, less frequently, autosomal recessive (31–36,38–45) inheritance patterns have been observed. Extreme variability in the dominant form does not allow for differentiation from the recessive form, whereas the latter appears to be somewhat less variable. Although recessive cases generally appear to be more severe than dominant examples, in a sporadic case it is not possible to clinically distinguish between the two forms (19,37). We cannot classify the cases of Girdwood et al (33) and Sinow et al (43) into either the dominant or recessive type. The case of Schaefer et al (23) surely must represent the autosomal dominant form of craniometaphyseal dysplasia. The cases of Kienböck (15) appear to represent various disorders. About 80 cases have been reported, with most being of the autosomal dominant type (vide infra). Recent reviews are those of Beighton (1) and Richards (21). There appears to be altered bone turnover (7,9,11,30), and stature and intellect are normal. A gene for the dominant form has been mapped to chromosome 5p15.2–p14.1 (20). The recessive form has been mapped to 6q21–q22 (34a).

Usually within the first year of life, rarely at birth, the root of the nose begins to broaden and an elevated wing of bone gradually extends bilaterally over the nasal bridge to the zygomas. With age, this pattern may regress. Increasing bony sclerosis narrows the nasal lumen, leading to obstruction, with resultant mouth breathing (2,22) (Figs. 8–1A–C and 8–2).

Bony overgrowth and sclerosis of the skull base result in variable compression of cranial nerves VII and VIII. Peripheral facial nerve paralysis, headache, or vertigo occur in about 30% of patients (2,5,16). Hypertelorism is a constant feature, and nystagmus is common. Rarely, there is visual loss because of optic atrophy (12,16); this suggests bony encroachment on the optic foramina. The alveolar ridges may be thickened and the teeth malaligned. Occasionally there is delayed eruption of permanent teeth.

Bony alterations in the temporal bone and pyramid produce mixed hearing loss that becomes evident in childhood in about one-half the cases. Chronic otitis media is common. Encroachment is slowly progressive until there is moderate to severe (30–90 dB) hearing loss by the fourth decade (2,5,13,16).

Hyperostosis and sclerosis involve the frontal and occipital portions of the calvaria, skull base, and, less often, mandible. There is increased bone deposit on the walls of the paranasal sinuses and underpneumatization of mastoid cells. Most marked is frontonasal hyperostosis (Fig. 8–1D). The ribs are wide and dense. Long bones have a club-shaped metaphyseal flare that is far milder than that seen in Pyle disease and may be minimal during the first years of life. Cortical hyperostosis of diaphyses is noted in the young, but it disappears with age. Short tubular bones exhibit the same changes as those noted in long bones (Fig. 8–1E,F).

While one cannot differentiate between dominant or recessive inheritance in the isolated patient, separation from those with Pyle disease and craniodiaphyseal dysplasia is usually clinically easy. Reardon et al (41), however, have pointed out the difficulty of diagnosis in some cases.

References (Craniometaphyseal dysplasia, autosomal dominant form)

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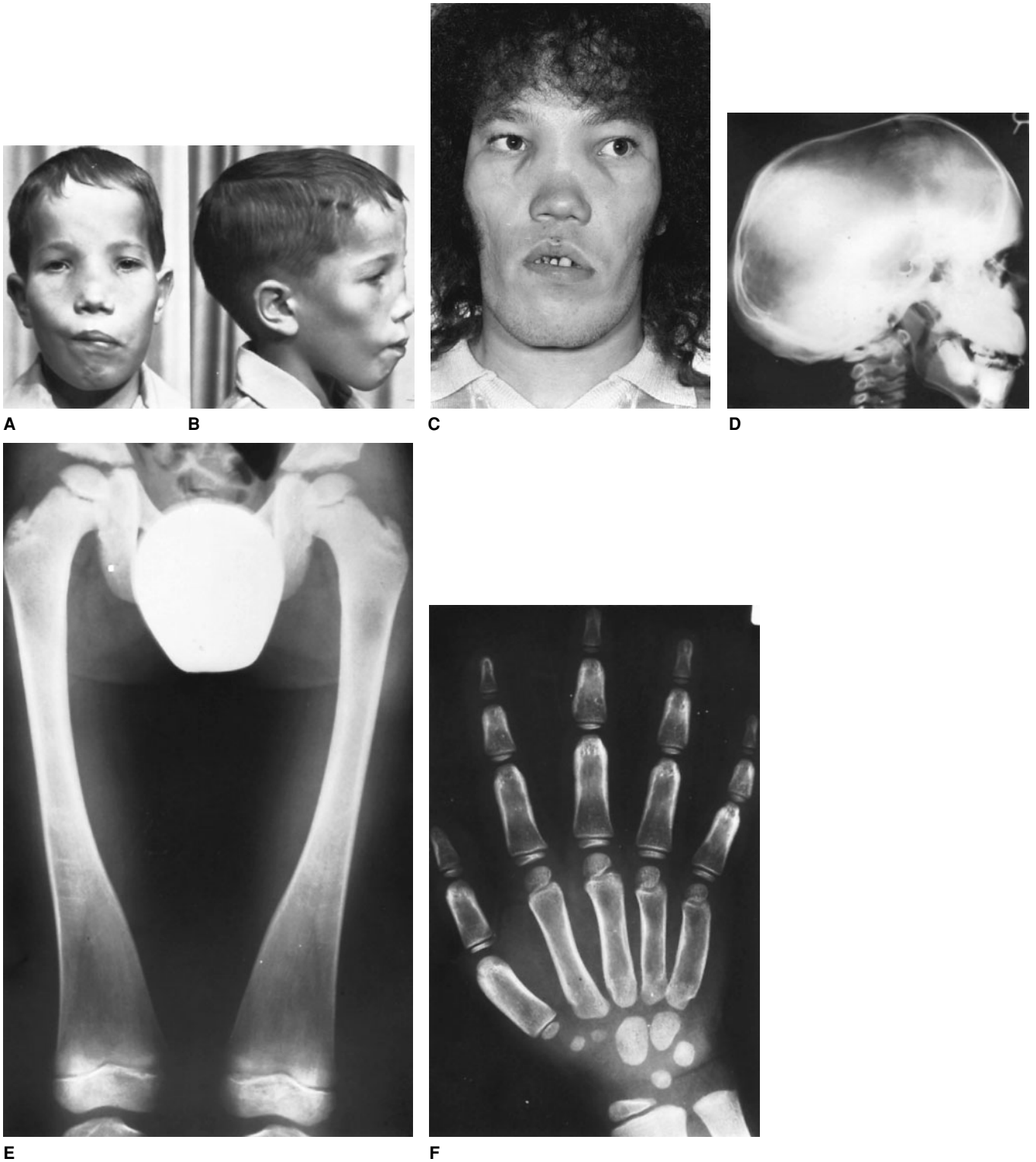

Fig. 8–1. *Craniometaphyseal dysplasia, dominant form*. (A,B) Eleven-year-old boy with progressive hearing loss. Note widened nasal bridge, left facial palsy. His mother and sister were similarly affected. (C) Same patient as an adult. Note hypertelorism, broad nasal bridge, enlarged paranasal area, and left facial paralysis. (D) Skull of 6-year-old male showing fronto-occipital hyperostosis, sclerosis of skull base and facial bones, underpneumatization of sinuses and mastoids, and dolichocephaly with postcoronal depression of parietal bones. (E) Femora of a 6-year-old male showing club-shaped metaphyseal flare, minimal diaphyseal sclerosis. (F) Hands of same child exhibiting undermodeling of short tubular bones, with distal cortical sclerosis of phalanges.

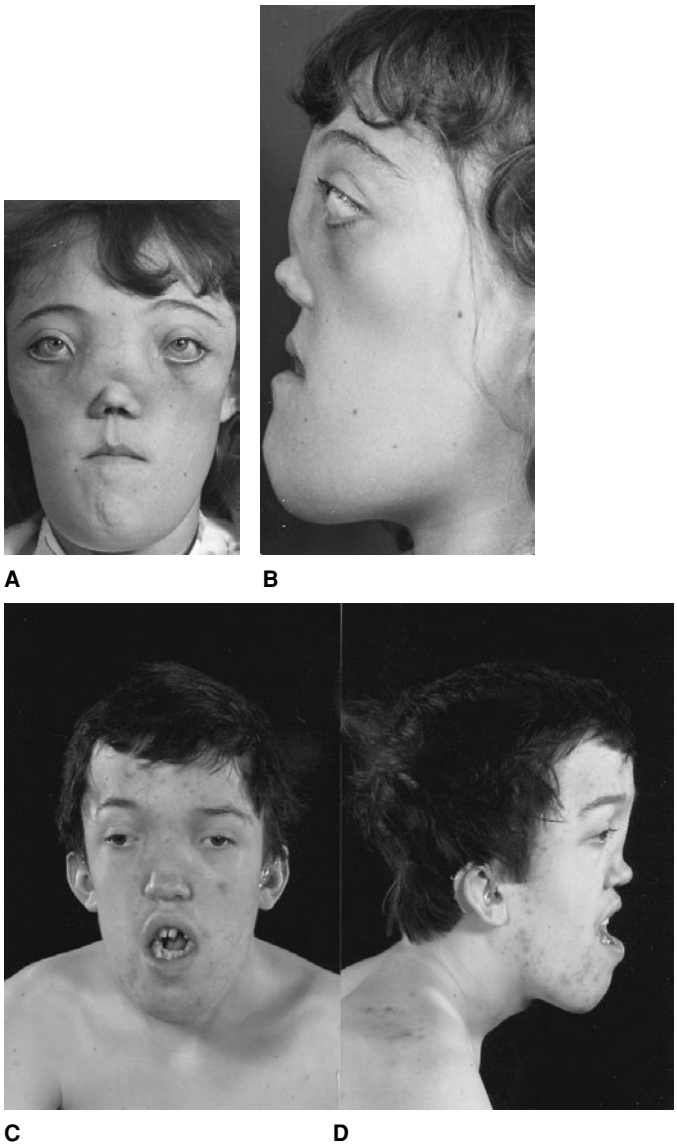

Fig. 8–2. *Craniometaphyseal dysplasia, recessive form*. (A,B) Head appears rather large with extremely broad and flat nasal body. Paranasal masses and mandibular prognathism are due to bony involvement. (C,D) Note similar changes. (C,D from N Elçioglu and CM Hall, Am J Med Genet 76:245, 1998.)

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References (Craniometaphyseal dysplasia, autosomal recessive form)

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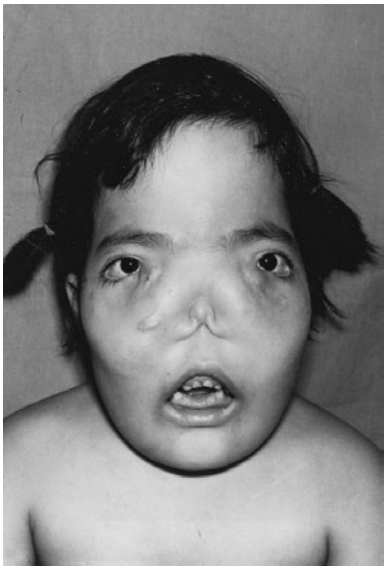
Craniodiaphyseal dysplasia

Joseph et al (10) first used the term "craniodiaphyseal dysplasia" to designate a severe bone disorder characterized by massive generalized hyperostosis and sclerosis, involving in particular the skull and facial bones (Fig. 8–3A–D). They noted the similarities with the case reported previously by Halliday (8). In total, 15 patients have been described (1,3,5,8–18,20,22). The patient described by Gemmell (6) may have had a mild form of the disease and the patient described by Schaefer et al (19) and again by Thurnau et al (21) most probably had autosomal dominant craniometaphyseal dysplasia. All cases are sporadic, except for the sib pair described by de Souza (4) whose diagnosis may be more compatible with Van Buchem disease (3). Parental consanguinity was described once (8). Inheritance may be autosomal dominant, with all cases representing spontaneous mutations. Brueton and Winter (3) provide an excellent review. The movie *Mask* was about a patient with craniodiaphyseal dysplasia.



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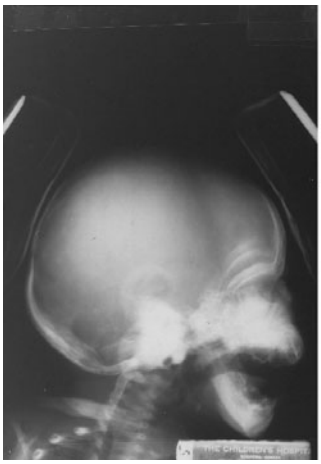

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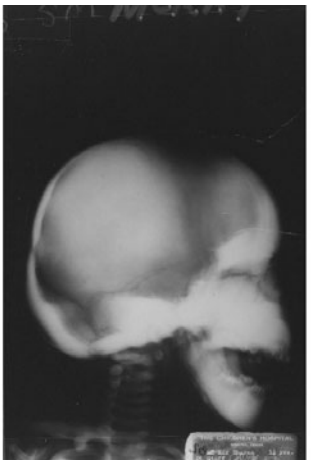

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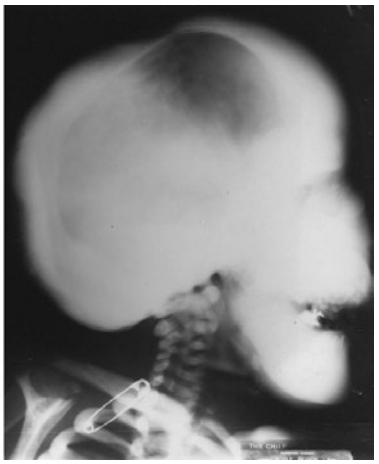

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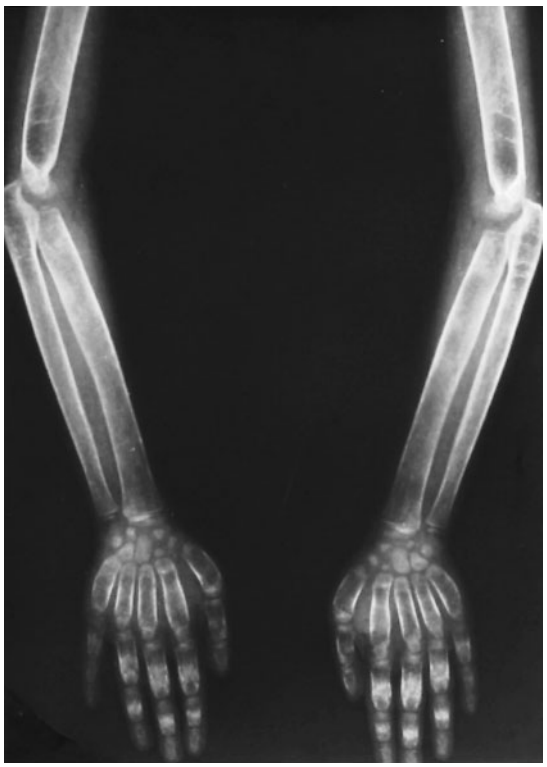

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Fig. 8–3. *Craniodiaphyseal dysplasia*. (A) Five-year-old showing marked enlargement of cranium, facial bones, and mandible. Note severe ocular hypertelorism and dental malocclusion. (B–D) Lateral radiographs at 3 1/2 months, 18 months, and 5 years showing progression of hyperostosis. Note absence of paranasal sinuses and mastoids. (E) Osteoporosis, "policeman's nightstick" appearance, lack of normal modeling. (A–D from RI Macpherson, J Can Assoc Radiol 25:22, 1974. E from E Stransky et al, Ann Paediatr 199:393, 1962.)

Already in infancy some facial abnormalities are evident, but within a few years, facial and cranial thickening, distortion, and enlargement become more expressed (3). Nasal obstruction and recurrent upper respiratory infections appear within the first few years or even first few months of life, often before the characteristic facial appearance is clear. Marked bony thickening, hypertelorism, paranasal bossing, nasal flattening, and severe dental malocclusion and maleruption of teeth generally follow. Bilateral choanal stenosis can be demonstrated within the first few years. All patients develop lacrimal duct obstruction resulting from bony overgrowth, and most have diminished visual acuity or blindness and progressive hearing impairment as a result of compression of cranial nerves. Seizures may occur (8,20).

Developmental milestones are delayed (6,8,20), but this delay is probably at least in part due to diminished sensory perceptions. Many patients complain of early morning headaches (13). Lack of sexual maturity has been reported (20), and growth is retarded (6,10,14,20). Right ventricular cardiac failure occurs (16,20), and early death is common (8,11,16,20). Histologically, facial bone fragments show dense hyalinized fibrous tissue within the periosteum, containing focal cell clusters of fibrocytes and lymphocytes (15). Bony trabeculae are very thick and have very thick uncalcified osteoid seams (1,15).

Radiographically, the whole skull, including the neurocranium and the facial bones as well as mandible, are severely sclerotic and hyperostotic. The paranasal sinuses and mastoids do not develop. There is moderate thickening and marked sclerosis of the ribs and clavicles. The long tubular bones do not exhibit metaphyseal flare, but rather have a variable cylindrical shape ("policeman's nightstick shape") and show diaphyseal endostosis (Fig. 8–3E). The short tubular bones of the hands

and feet, particularly the first metapodial, also exhibit cylinderization. Spinal sclerosis is more marked in the vertebral arches than in the vertebral bodies (3). Tucker et al (22) have described the radiographic changes that occur over time.

Several investigators have found elevated levels of serum alkaline phosphatase but normal levels of calcium and phosphorus (1,9–11,14, 16–18,20,22). No reliable prenatal diagnosis is available.

The differential diagnosis includes *Van Buchem disease, Camurati-Engelmann disease*, and *craniometaphyseal dysplasia*.

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Craniometadiaphyseal dysplasia, wormian bone type

Craniometadiaphyseal dysplasia was first described by Schwarz (5) as a distinct syndrome comprising mild sclerosis of the skull base, marked frontal bossing, and abnormal modeling of the tubular bones (Fig. 8–4). Affected sibs reported by Williams et al (6) were also reported in more detail by Langer et al (2). The patient described by Lélek (3) was first thought to have the same entity, but probably had craniometaphyseal dysplasia (1). Therefore, the eponym "Schwarz-Lélek syndrome" (1) is no longer used and has been replaced by the term "craniometadiaphyseal dysplasia." Another case was reported by Santolaya et al (4). The occurrence of affected sibs and parental consanguinity points to autosomal recessive inheritance (2,4,6).

Clinically, the skull circumference is large, often above the 98th centile. The closure of the anterior fontanel is delayed. The forehead is prominent, the eyes are relatively large with downward-slanting palpebral fissures, the malar bones are hypoplastic, and the jaw protrudes (Fig. 8–4A). The palate is high, and two patients have had natal teeth (2,6). Increased caries (5) and dental hypoplasia (2,4,6) have been described.

The lower limbs may be bowed, and all patients had coxa valga (Fig. 8–4B). One patient (5) had short stature. All patients had sustained multiple fractures that caused severe scoliosis, chest deformity, and a distorted pelvis in one adolescent patient (5).

Radiographically, the changes in the humerus, hands, clavicles, and ribs resemble those found in Pyle disease—i.e., absence of normal diaphyseal constriction, poor metaphyseal flaring, and widened short tubular bones (4). The cortex is thin, the bones, osteoporotic. In infancy, there is delayed ossification of the cranial vault, causing a large anterior fontanel and thinning of the calvaria with wormian bones. Hyperostosis and mild sclerosis of the skull base as well as of the maxilla and mandible are present. The paranasal sinuses are obliterated. Occipital horns were noted in three patients (2,5,6). In some patients a moderately increased alkaline phosphatase level was found (4,5).

References (Craniometadiaphyseal dysplasia, wormian bone type)

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Osteopetrosis

Osteopetrosis is a group of disorders characterized by failure of resorption of the primary spongiosa by osteoclasts, resulting in increased osseous density in which cortical and cancellous bone cannot be distinguished radiographically. Histologically, there is an increased number of osteoclasts (14,29,50,63).

Osteopetrosis has been traditionally divided into two groups: congenital or malignant autosomal recessive type and adult or benign autosomal dominant form. However, there is considerable further genetic heterogeneity: (*a*) severe autosomal recessive osteopetrosis (Albers-Schönberg disease, precocious type); (*b*) mild autosomal recessive osteopetrosis (intermediate type); (*c*) autosomal recessive osteopetrosis with renal tubular acidosis (carbonic anhydrase II deficiency), and (*d*) benign autosomal dominant osteopetrosis (delayed type). Still other forms likely exist. All forms appear to be due to defects in osteoclastic resorption (71a).

Severe autosomal recessive osteopetrosis (Albers-Schönberg disease). This disorder is characterized by increased density of nearly all bones and the following complications that occur from failure of resorption of the primary spongiosa and its resultant persistence: anemia, hepatosplenomegaly, blindness, deafness, facial paralysis, and osteomyelitis (28,48). Over 500 cases have been reported. The exact incidence is unknown, but it has been estimated to be 1:200,000 (39), with a higher incidence occurring in Costa Rica (48) and Saudi Arabia (28). Bollerslev and Anderson (8) estimated that 5.5 in 100,000 persons in Denmark have the disorder. Autosomal recessive inheritance with frequent occurrence in sibs and consanguinity has been demonstrated (19,48). The recessive disorder was mapped at chromosome 11q13 (34). Mutations in the TCIRG1 osteoblast-specific unit of the vacuolar protein pump have been

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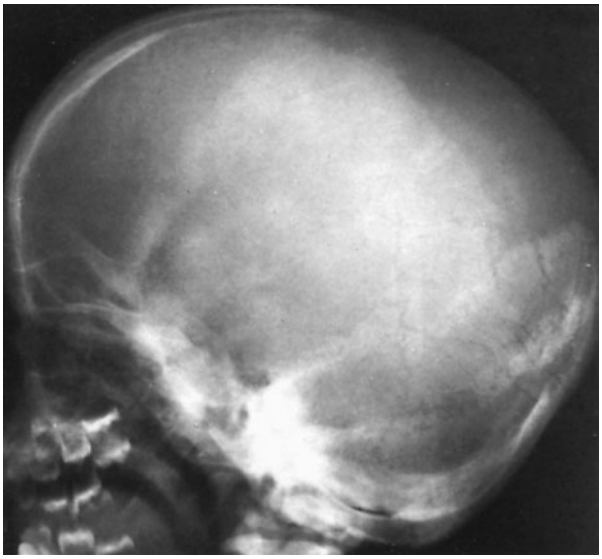

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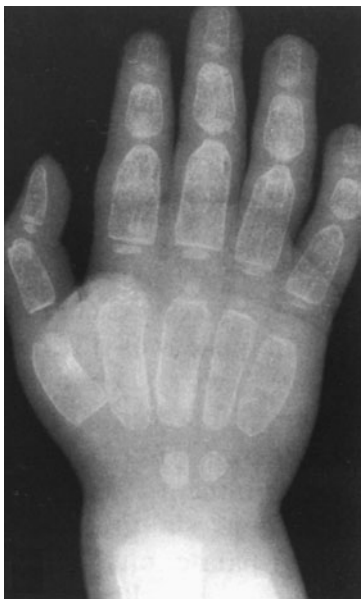

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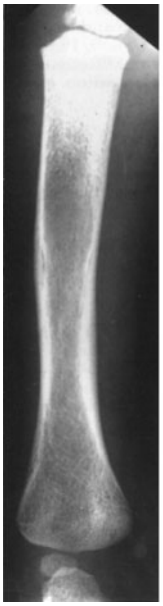

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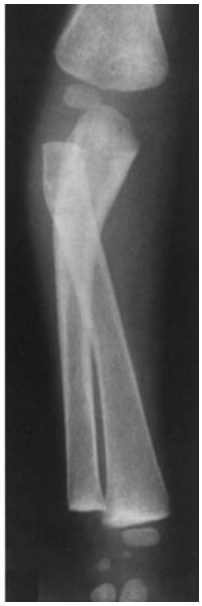

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Fig. 8–4. *Craniometadiaphyseal dysplasia, wormian bone type*. (A) Brothers at age 5 and 3 years, respectively. Note large head and parietal bulging. Older sib shows a prominent forehead, depressed nasal bones, prominent eyes with slight downward slant of palpebral fissures, and malar hypoplasia. (B) Two-year-old with unossified area in the superior anterior, and posterior parietal areas. Multiple wormian bones are present in occipital, temporal, and posterior parietal bones. (C) Bones are wide and lack normal diaphyseal constriction. (D,E) Long tubular bones of upper limbs. Wide diaphysis not showing the usual constriction. Lack of the normal metaphyseal flaring and thin cortices. (A,D,E from JM Santolaya et al, Am J Med Genet 77:241, 1998. B,C from LO Langer et al, Skeletal Radiol 20:37, 1991.)

found (25a,42a). The pathogenesis remains unknown. A deficiency in the macrophage-colony stimulating factor (M-CSF) type 1 has been suspected, but has since been found to be unlikely (28,34,56). Pathogenic mechanisms have been extensively discussed by Reeves et al (60), Whyte (77), and Lajeunesse et al (44).

Without treatment, life span is greatly reduced and rarely exceeds a few years (28). After allogeneic bone marrow transplantation, the chances for survival are much better, although a considerable number of patients still die in early childhood (27). Other treatment strategies have been tried (42).

Clinical findings. All tubular bones may be involved, but growth is usually normal. The skull is thickened and dense, mainly at its base, but the calvaria, mastoid bones, and paranasal sinuses are poorly aerated, and the facial bones appear denser than normal (58) (Fig. 8–5A,B). Especially revealing are the MRI studies (16a).

Defective vision and nystagmus are extremely common and are the first symptom (at a median age of 2 months) in half of the patients (15,28). Optic atrophy eventuating from pressure of bone on optic veins is a relatively common complication (1,36). In some cases a primary retinal degeneration exists, indicating possible heterogeneity (49,62). Facial paralysis results from the pressure of dense bone on the foramen of the seventh cranial nerve (6,45). Mental retardation occurs in about 20% of patients (45). Between 25% and 50% of patients have moderate mixed sensorineural and conductive hearing loss, beginning in infancy (5,39,53). The audiograms have been compared to those found in otosclerosis (25). In about half the cases there is a history of otitis media (79a). Temporal bone changes include a small middle ear cavity lined by hypertrophic mucosa, small fallopian canal, and abnormal, sclerotic bone covering the otic capsule (33). The ossicles lack medullary cavities. Intracerebral calcifications at birth have been described (57).

Musculoskeletal findings. The bones are extremely uniformly dense but not distorted in form. The epiphyses, metaphyses, and diaphyses are similarly affected. The cortical and cancellous bones are indistinguishable radiographically (Fig. 8–5C). Alternate radiolucent bands can be seen in the metaphyses and diaphyses of long bones (26). Fractures are common. Because of upward slanting of the greater sphenoid wings, a "space alien" appearance may be noted in the frontal view (23). Older children may show a "hair-on-end" phenomenon in the calvaria. Prenatal X-ray diagnosis has been accomplished (54).

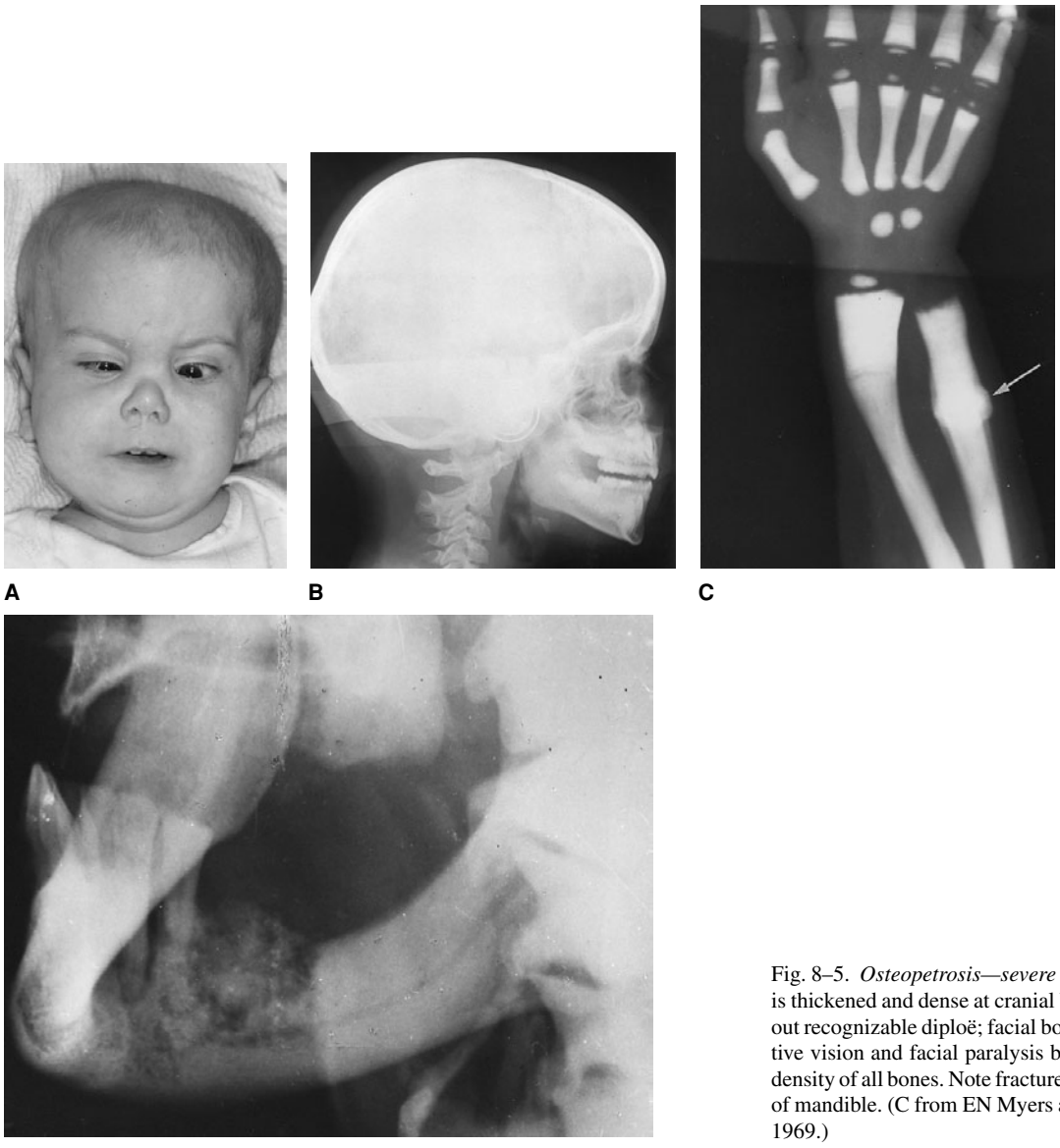


Fig. 8–5. *Osteopetrosis—severe autosomal recessive form.* (A,B) Skull is thickened and dense at cranial base; calvaria is involved as well without recognizable diploë; facial bones appear denser than normal. Defective vision and facial paralysis become evident. (C) Marked increased density of all bones. Note fractures of radius and ulna. (D) Osteomyelitis of mandible. (C from EN Myers and S Stool, Arch Otolaryngol 89:460, 1969.)

Hematopoietic findings. Although the liver and spleen are normal at birth, in over 50% of cases they enlarge in childhood because of extramedullary hematopoiesis. Hemolytic anemia and thrombocytopenia are found in 65% of cases (38), and generalized lymphadenopathy has been noted in about 20%.

Oral manifestations. Osteomyelitis of the jaws, presumably the result of deficient blood supply, seems to be a significant complication of dental extraction (20,80). It may lead to extraoral fistulas. Primary molars and all permanent teeth are greatly distorted and remain totally or partially embedded in basal bone (7). Ankylosis of cementum to bone has been described (82). The teeth appear to be secondarily affected by failure of bone resorption and/or osteomyelitis (Fig. 8–5D). Many authors have remarked on the high incidence of dental caries.

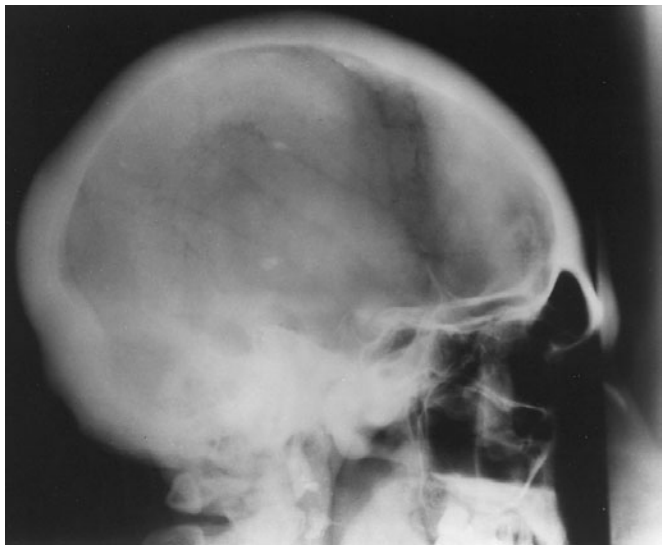
Other findings. Uncommonly described findings are hydrocephaly necessitating drainage (28), Hirschsprung disease (19), and symptoms of neuronal storage disease (38,47,70), indicating further heterogeneity. El Khazen et al (21) described an unusually severe form in which there were in utero fractures, hip dislocation, hydrocephaly, and hypoplasia of the cerebellum. No osteoclasts were found. Monaghan et al (52) described a case with generalized osteosclerosis in infancy that resolved spontaneously within 2 years.

Laboratory findings. Prenatal diagnosis has been accomplished radiologically (54).

Mild autosomal recessive osteopetrosis. This form is rare. It is characterized by short stature, increased upper/lower segment ratio, mandibular prognathism, fractures following minimal trauma, and mild to moderate anemia with extramedullary hematopoiesis, unerupted teeth, and osteomyelitis (4,5,18,32,33,35,40,41,72).

The occurrence in sibs and parental consanguinity indicate autosomal recessive inheritance. Kahler et al (40) have nicely summarized the published cases. This group is probably heterogeneous. Several cases with mental retardation cannot be accurately classified (26,37) but they may represent the disorder discussed below. Horton et al (35) found a decreased number of osteoclasts.

Autosomal recessive osteopetrosis with renal tubular acidosis. At least 30 patients have been reported with short stature (−2 SD to −4 SD), mild to severe mental retardation, basal ganglia calcification, visual impairment, mixed renal tubular acidosis, osteomalacia, extramedullary hematopoiesis, hepatosplenomegaly, pancytopenia, and sensorineural hearing loss (13,31,46,55,59,64,73,78). Improvement of symptoms occurs in time, except for the mental retardation. A deficiency



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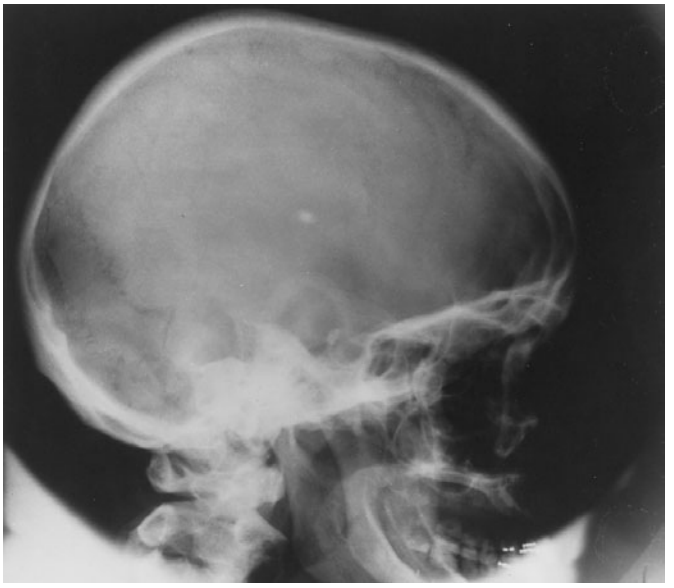

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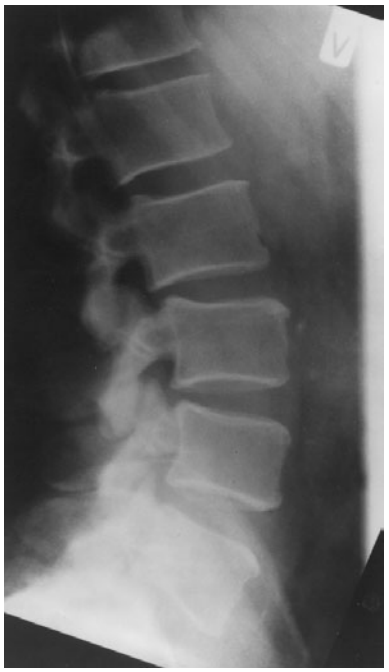

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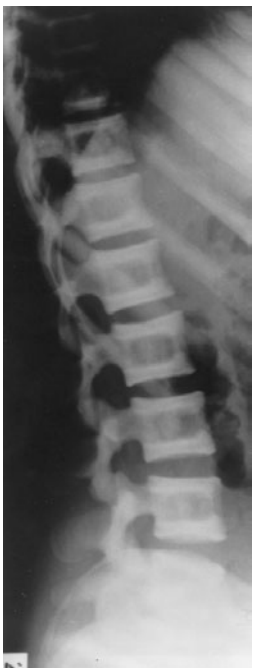

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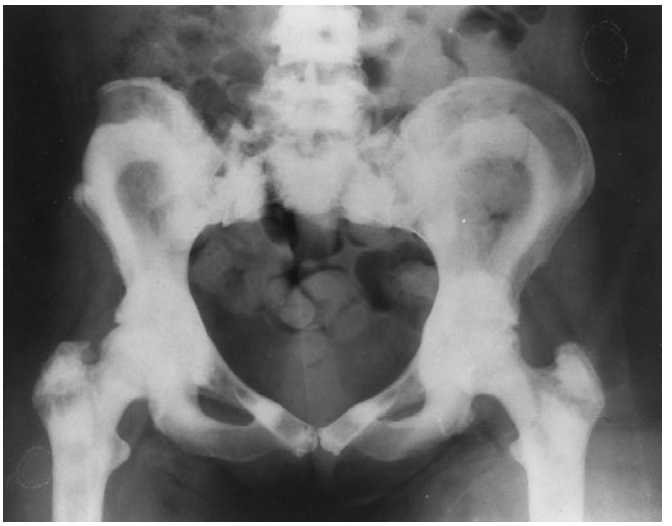

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Fig. 8–6. *Osteopetrosis, autosomal dominant types*. (A) Cranium in type 1. There is pronounced osteosclerosis and enlarged thickness of cranial vault. Trigeminal nerves involved. Conductive hearing loss was common. (B) Cranium in type 2. Osteosclerosis is more pronounced at base. Facial nerves involved. (C,D) Spine. Type 2, in contrast to type 1, has rugger jersey appearance. (E) Pelvis. Endobones in type 2. (A–E from J Bollerslev and PE Anderson, Jr, Bone 9:7, 1988.)

of carbonic anhydrase II has been demonstrated in erythrocytes (64). Heterozygotes have one-half the enzyme levels (67).

The disorder is especially common among Arabs (55,64), but it has been found in Japanese individuals (2,65). The gene has been mapped to 8q22 (53,61). A point mutation is found at an invariant histidine residue His107Tyr (73).

Benign autosomal dominant osteopetrosis. The dominant forms of osteopetrosis are more common than the recessive forms and are not associated with hepatosplenomegaly, anemia, blindness, or mental retardation. At least 40% of cases are asymptomatic, and are diagnosed radiologically (39). The condition has been localized at chromosome 1p21, near M-CSF (74). It usually appears somewhat later in life than the autosomal recessive types (7,11,12), and it appears to be heterogeneous (3,6a,75). Type I is rarely associated with fractures after minor trauma (9,39,43,44,68,83), whereas fractures occur in about 60% of patients with type II (6b,9,24,39). Walpole et al (75) described a family with autosomal dominant osteopetrosis type II, in which an infant had symptoms fitting the severe autosomal recessive type. Thomson (71) described a mentally retarded, blind patient.

Clinical findings. The condition appears silently within the first few years of life, being manifest by increased radiopacity of the skull. Not uncommonly, it is discovered on routine X-ray films of the chest or on radiographic survey of a family of a known patient (Fig. 8–6). In type I there are sclerosis and thickening of the calvaria, no endplate

Table 8–1. Autosomal dominant osteopetrosis

Changes	Type I	Type II
Skull	Thick vault	Dense base
Spine	Variable sclerosis	"Sandwich" vertebrae
Pelvis	No subcrestal sclerosis	Subcrestal sclerosis
Serum acid phosphatase	Normal	Elevated
Osteoclasts	Reduced in size and number	Increased in size and number and in number of nuclei
Fractures	Few %	60%

sclerosis of vertebral bodies, and no "bone-within-bone" appearance in the ilia, whereas in type II, the base of the skull is thickened, and endplate thickening of vertebral bodies ("sandwich vertebrae") and iliac "bone-within-bone" appearance occur (7–12). Osteomyelitis of the mandible occurs in 10%–30% of cases (20,39), as do cranial nerve palsies of cranial nerves II, III, and VII (16,30,39,63,76). In type I there is more often involvement of cranial nerve V with narrowing of the internal auditory meatus (8,51); in type II, cranial nerve VII is far more often affected. Conductive hearing loss is associated with type I (12,30,39) (Table 8–1).

Radiologic findings. Increased density is most marked at the diaphyseal ends of long bones, gradually extending to the epiphyses and to the marrow cavity (39). The times of initiation of calcification and closure of the epiphyses are not altered. There is usually some lack of remodeling, particularly in the femur and tibia. Nearly all bones are ultimately involved. The "sandwich" vertebrae in type II form early in the course of the disease as a result of calcification of the upper and lower surfaces (Fig. 8–6D,E). In the skull, there is thickening of the vault (type I) or base (type II) with clubbing of the anterior and posterior clinoid processes. The sinuses become involved and ultimately disappear. The head is not enlarged.

Elevated levels of serum acid phosphatase have been noted type II (39,44,63) as well as elevated levels of serum creatinine kinase BB (81).

Diagnosis. A contiguous gene syndrome has been described by Zannoli et al (personal communication, July, 2000). It consists of Binder phenotype, obesity, rugger-jersey vertebrae, and Scheuermann disease sign and maps to chromosome 1p21.

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Oculodentoosseous dysplasia (oculodentodigital syndrome)

Although reported as early as 1920 by Lohmann (27) and independently by several other investigators (3,29,35), Meyer-Schwickerath et al (28), in 1957, were the first to fully describe a syndrome characterized by narrow nose with hypoplastic alae and thin nostrils, microcornea with iris anomalies, syndactyly and/or camptodactyly of postaxial fingers, hypoplasia or aplasia of the middle phalanx of the fifth fingers and toes, and enamel hypoplasia. About 150 cases have been reported to date (Fig. 8–7).

The syndrome has autosomal dominant inheritance (9,34,37). New mutations represent approximately 50% of cases (37) or 75% of all reported families (38). Jones et al (23) found advanced age in fathers of isolated cases of the disorder. Although affected sibs with normal parents have been described (10,14), these cases can be attributed to the widely variable expressivity of the disorder also within a family (30,32,37,41). Shapiro et al (41) reported a large pedigree in which genetic anticipation might be present, especially in neurologic symptoms. These authors noted several other reported families who suggest anticipation (1,9,24,30,49) and expressed the view that the entity may be caused by expanded trinucleotide repeat sequences. Brueton et al (5) described a family with cutaneous syndactyly of the fourth and fifth fingers (syndactyly type III), craniofacial symptoms fitting oculodentodigital syndrome, but no ocular or dental anomalies, and suggested that syndactyly type III is part of the same spectrum, possibly being allelic or part of a contiguous gene syndrome. Gladwin et al (16) and Boyadjiev et al (4) mapped oculodentodigital syndrome to 6q22–23 and found the same locus involved in the family described by Brueton et al (5). This finding suggests that isolated syndactyly type III is located in the same region as well (39).

Craniofacial findings. Short, narrow palpebral fissures, epicanthal folds, and long, thin nose with prominent nasal bridge and hypoplastic alae nasi comprise a characteristic physiognomy (Fig. 8–7A). The head circumference may be somewhat reduced (26,37,42) and hyperostosis of the skull has been reported (8,34,37).The pinnae may be somewhat abnormally modeled and/or outstanding. Conduction hearing loss has been described in a number of cases (12,14,23,31,37,44), in part because of recurrent otitis media. Dry, lusterless hair that fails to grow to normal length has been described in about 30% of cases (17,19,26,28,34,42). One author noted microscopic changes of monilethrix and pili annuli (44).

Ocular findings. Striking eye changes consist of short, narrow palpebral apertures, microcornea (6–9 mm in diameter), and epicanthal folds in childhood (9,11,13,25,31). The oft-quoted findings of hypertelorism and microphthalmia are spurious (11,13). The pupil may be eccentric and the iris may consist of fine porous spongy tissue. Between the frill and the pupillary rim are crypts and lacunae, and the iris frill may overlie the pupillary rim. Remnants of the pupillary membrane may be present along the iris margin rather than across the pupil (8,10,17,19,28). A number of patients have exhibited strabismus or secondary glaucoma

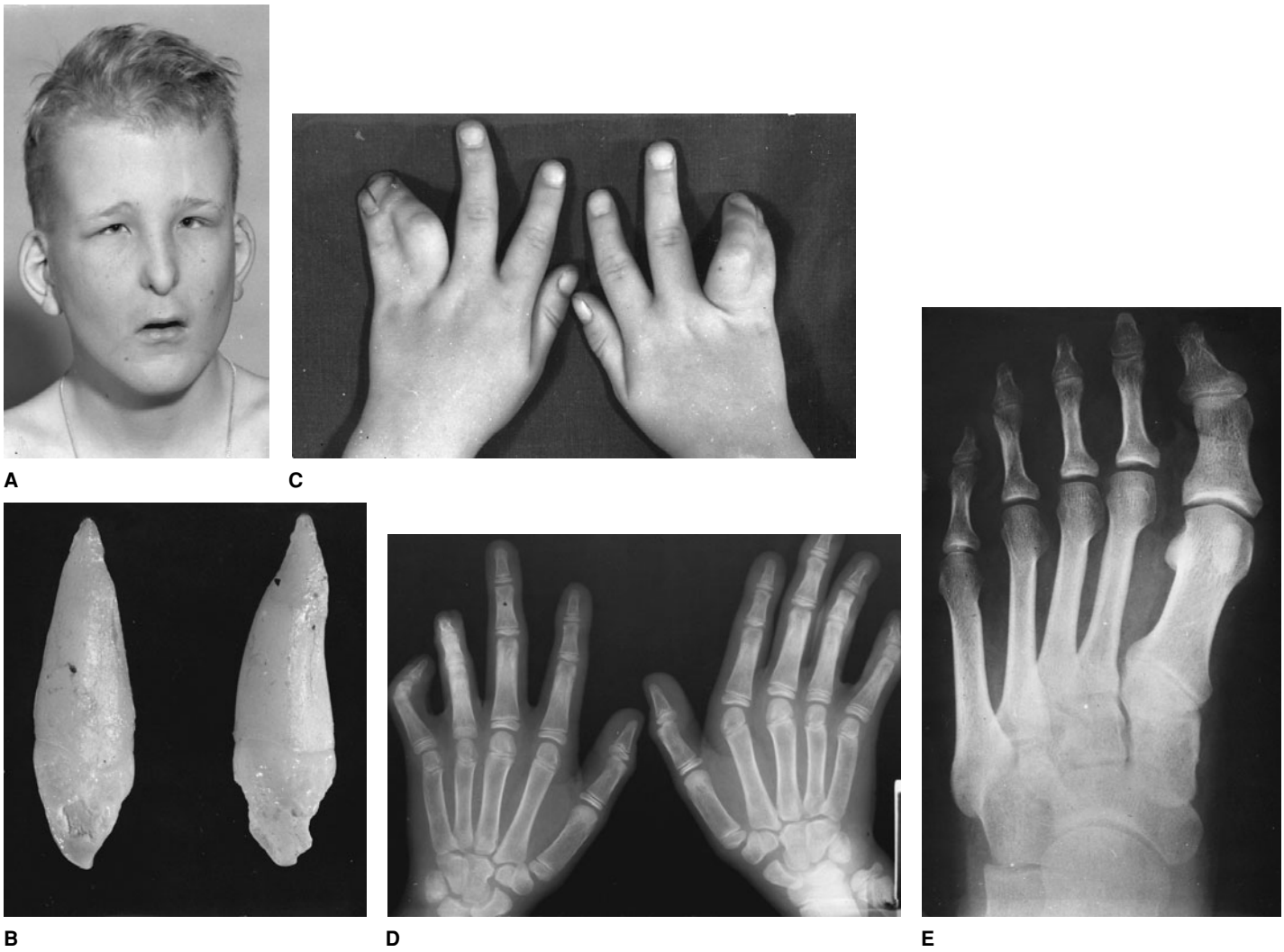

Fig. 8–7. *Oculodentoosseous dysplasia* (*oculodentodigital syndrome*). (A) Characteristic facies showing microcornea and lack of nasal alar flare. (B) Note marked hypoplasia of enamel. (C) Soft tissue syndactyly and ulnar deviation of the fourth and fifth digits. (D) Note poor modeling of metacarpals, abbreviated middle phalanx of fifth finger, and camptodactyly of left fifth finger. There is a mild cone-shaped epiphysis of distal thumb phalanx. (E) Note missing middle phalanges of toes. (A from RJ Gorlin et al, J Pediatr 63:69, 1963. C from SH Reisner et al, Am J Dis Child 118:600, 1969.)

(11,16,24,35,43,46). There may be an increase in the number of disc vessels (24). Persistent hyperplastic primary vitreous has been noted on two occasions (19,45). Radiographically, orbital hypotelorism has been demonstrated in 40% of cases (13). Gutierrez-Dias et al (19) have tabulated the various eye findings in the syndrome.

Musculoskeletal findings. Most patients have a gracile build. Camptodactyly of the fifth or, less often, of the fourth fingers is a common finding (Fig. 8–7C). Clinically, the fifth finger appears to be shortened. Bilateral syndactyly of the fourth and fifth fingers (rarely the third) along with ulnar clinodactyly and syndactyly of the third and fourth toes is often present (35,37,49) (Fig. 8–7E).

Radiographically, the middle phalanx of the fifth finger is cuboid or deltoid or occasionally absent (44) (Fig. 8–7D). The feet, which are clinically normal, exhibit aplasia or hypoplasia of the middle phalanx of one or more toes (Fig. 8–7E). In at least one case, there was postaxial hexadactyly of toes (25). Lack of modeling of the metaphyseal area of the long bones is relatively common (8,9,12,17,26,36).

Oral findings. Generalized enamel hypoplasia has been noted by a number of investigators (10,12,37,38,42) (Fig. 8–7B). The teeth may have a yellowish-brown color (38). Scheutzel (38) described the histopathological changes in the enamel and dentin. The alveolar ridge of the mandible may be wider than normal (6,17,24,36,47). Cleft lip/palate (12,14,30,31,47, RJ Gorlin, personal communication, 2000) and microdontia (11,21,31,47) have been observed by several authors.

Other findings. Cox et al (7) first drew attention to the neurological anomalies. Spastic paraparesis, sometimes progressive (2,4,16,18,20, 30–32,40,42), cerebral white matter anomalies (15,18,20,31,41), basal ganglia calcifications (1), ataxia (37), intention tremor (41), neurogenic bladder disturbances (31,32,41), abnormal visually–evoked and brainstem auditory–evoked potentials (41), epilepsy (32), migraine (31), and learning disabilities (24,31,32) have all been described.

Differential diagnosis. A child with many similar stigmata but with rudimentary dry and brittle nails was described by Whitwell (48). Hypoplasia of the alae nasi can be found in the *oral-facial-digital syndromes* and in *Hallerman-Streiff syndrome*. Although the eye anomalies appear to be similar to those observed in *Rieger syndrome*, there is neither microcornea nor enamel hypoplasia in the latter. Tooth formation is suppressed. Microcornea in combination with glaucoma, epicanthal folds, absent frontal sinuses, and hyperkeratosis of the palms may exhibit autosomal dominant inheritance (22).

References [Oculodentoosseous dysplasia (oculodentodigital syndrome)]

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Frontometaphyseal dysplasia

In 1969, Gorlin and Cohen (11) separated frontometaphyseal dysplasia from other craniotubular dysplasias. The condition consists of pronounced bony supraorbital ridge, mixed hearing loss, and generalized skeletal dysplasia. About 30 cases were subsequently described (1–10,12–21,23–26,28–32). A probable earlier example is that of Lischi (22).

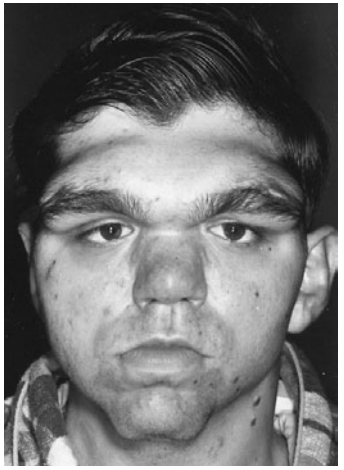
Inheritance appears to be X-linked with variable expression in carrier females (3,9,10,12,14). Although some authors have suggested autosomal dominant inheritance (4,17,32), there has been no male-to-male transmission. No case with a chromosomal anomaly has been described. Verloes et al (30) opined that frontometaphyseal dysplasia, Melnick-Needles syndrome, and otopalatodigital I and II are variants of a single disorder.

Craniofacial features. The marked supraorbital ridge, wide nasal bridge, downward slanting palpebral fissures, and small pointed chin give the patient a striking appearance. Enlargement of the supraorbital ridge becomes evident before puberty (6) (Fig. 8–8). Progressive mixed hearing loss is commonly present (2,11,28,31,32). Missing permanent teeth and retained deciduous teeth have been found (2,6,11).

Musculoskeletal system. There is both primary and secondary wasting of hand muscles (6,8,12). Dorsiflexion of the wrist and extension of the elbows are reduced, with pronation and supination being extremely limited. Flexion deformities of the fingers and ulnar deviation of the wrist are progressive. Finger mobility is essentially limited to the metacarpophalangeal joints. The thumbs tend to be broad. Hammertoes have also been noted (11).

Radiographic findings. A thick, torus-like frontal ridge, absence of frontal sinuses, "Hershey-kiss" or "top-of-the-mosque" defects of supraorbital rims, arched superior border of maxillary sinuses, short maxilla, elongated cranial base, and antegonial notching of the mandible with marked hypoplasia of the angle and condyloid process have been described (2,11,13,16,18,19,28). A mandibular spur has been reported to be characteristic (10).

The foramen magnum is greatly enlarged, and numerous vertebral anomalies have been noted: the odontoid process is located too far anteriorly, the atlas has no posterior arch, the lumbar vertebrae are flattened, the second and third cervical vertebrae are fused, and the third and fourth vertebrae are subluxated. The shoulders may be highly positioned. Scoliosis is usually marked with resultant shortening of the trunk. The long bones manifest increased density in the diaphyseal region, with lack of modeling in the metaphyseal area producing an Erlenmeyer flask deformity. The legs may be laterally bowed. Marked flaring of the iliac bones



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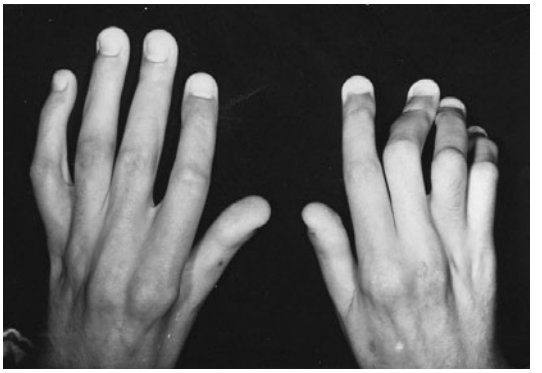

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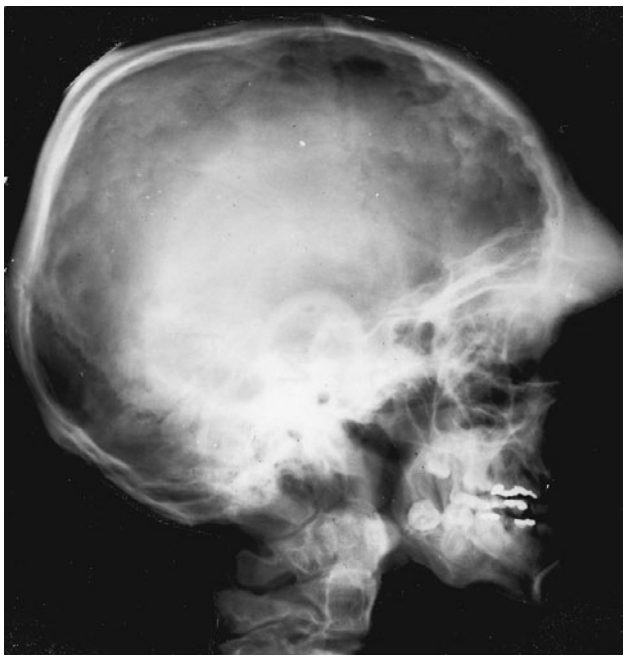

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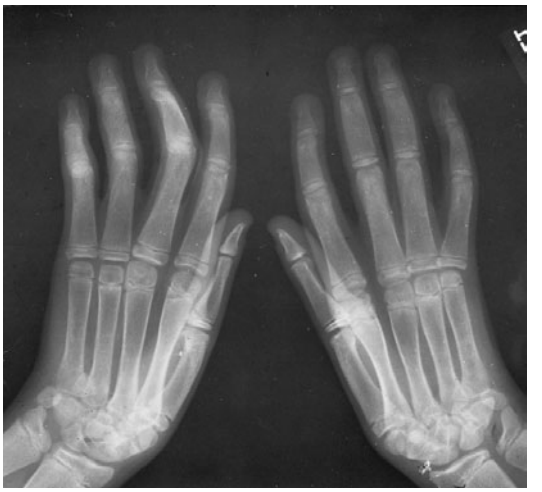

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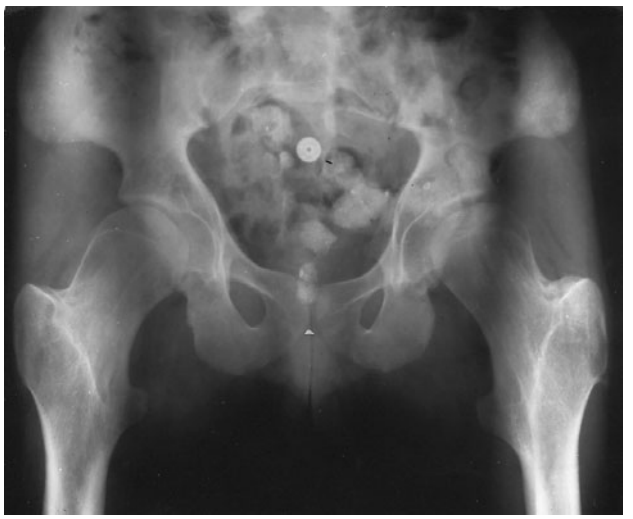

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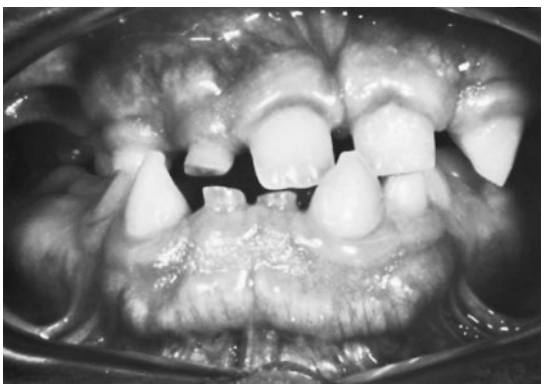

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Fig. 8–8. *Frontometaphyseal dysplasia*. (A) Marked supraorbital ridge, wide nasal bridge, and small pointed chin give patient a striking appearance. (B) Wasting of interosseous muscles of hands, ulnar deviation of fingers. (C) Radiograph showing supraorbital torus, hypoplasia and dysplasia of mandible, and cervical anomalies. (D) Generalized lack of modeling of long bones. (E) Marked flaring of iliac bones, widened femoral necks. (F) Missing permanent teeth, retained deciduous teeth, teeth without conical crown form in 18-year-old patient. (A,D from RJ Gorlin and MM Cohen Jr, Am J Dis Child 118:487, 1969.)

and coxa valga have been noted, as well as fused and eroded carpal bones, wide, elongated middle phalanges, and increased interpediculate distances in the lumbar region of the spine (6,11,14,18,28,32). The ribs and vertebrae are irregularly contoured (13) and the lower ribs are "coat hanger" in form. A characteristic metacarpophalangeal profile has been suggested (14).

Other findings. Urinary tract anomalies, mainly hydroureter and hydronephrosis (8,16,17,28), but also bilateral renal duplication (10) and obstructive airway disease (2,8,11,20,21,28) are common complications. Several patients have had cryptorchidism (3,8). Accompanying heart defects have included atrial septum defects (2,6,10), pulmonary stenosis (2,10), pulmonary and tricuspid atresia (10), and mitral valve prolapse (26). One patient had an esophageal atresia with a fistula (9). Bands of soft tissue extending from the medial edge of the scapula to the vertebral column have also been found (29). Hirsutism of the buttocks and thighs is common.

Differential diagnosis. Frontometaphyseal dysplasia should be distinguished from *craniometaphyseal dysplasia* (27), *craniodiaphyseal dysplasia, otopalatodigital syndrome type I* (6), and *Melnick-Needles syndrome* (5). The diagnosis may be difficult in the newborn period, and rests on the increased bone density, rib configuration, widened metaphyses, and externally rotated iliac bones (10,25).

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Dysosteosclerosis

Dysosteosclerosis, a term first employed by Spranger et al (16) in 1968, was described as early as 1933 by Ellis (2). Additional examples have been described (1,3–5,6,8–12,14,17–20). Affected sibs (2,3,10,17) and parental consanguinity (2,3,5,14,20) indicate autosomal recessive inheritance. However, there appears to be an X-linked recessive form (13), and some of the isolated male cases may be examples of the X-linked form. The patient reported by Ventruto et al (20) as having craniometaphyseal dysplasia surely has dysosteosclerosis.

Craniofacial findings. The anterior fontanel tends to remain open. Frontal and biparietal bossing and a narrow chin are characteristic (Fig. 8–9). Oligodontia, poorly calcified teeth with late eruption and ankylosis, and premature tooth loss have been described (9,13,14,18,19). Natal teeth have also been noted (4). During early childhood, there may be cranial nerve involvement, such as optic atrophy, abducens palsy, and facial paralysis. Some degree of spasticity and exaggerated reflexes have been evident (1–3,8,14). Other patients have manifested progressive mental retardation (1), progressive otosclerosis (8), or intracerebral calcifications (1).

Musculoskeletal findings. The patient is short and there is a tendency to bone fractures (8,16,17). The limbs are disproportionately shortened in comparison to the trunk and somewhat bowed. Pectus carinatum has been noted in several patients. Macular atrophy of the skin has been found in several cases (2,3,13,14,18).

Radiographically, the calvaria and skull base are thickened. There is sclerosis of the orbital roofs, absent paranasal sinuses, and constriction of the foramina. The clavicles, scapulae, and ribs are sclerotic. The vertebral bodies are flattened and irregularly dense. Long tubular bones are bent in the region of the shortened, thickened diaphyses. The metaphyses are bottle shaped. The epiphyses and metaphyses are sclerotic, but the submetaphyseal areas are clear and their trabecular structure is coarse and irregular. Short tubular bones exhibit similar changes. Iliac bones are hypoplastic and sclerotic. Osteomyelitis of the mandible has been noted (11).

Microscopic study of the growth plates suggests that the metaphyses are filled with irregular trabeculae consisting mainly of cartilaginous matrix with few chondrocytes (7).

References (Dysosteosclerosis)

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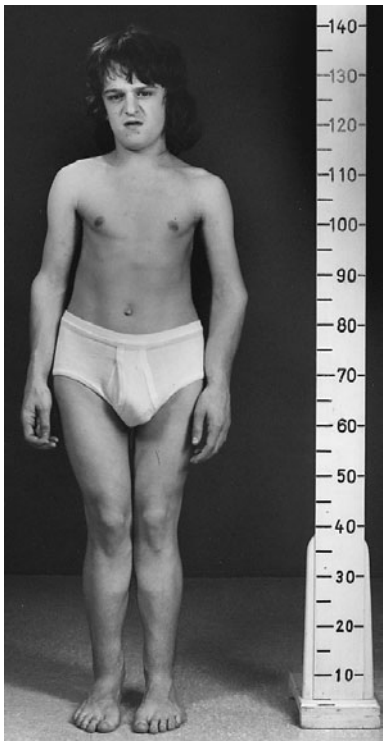

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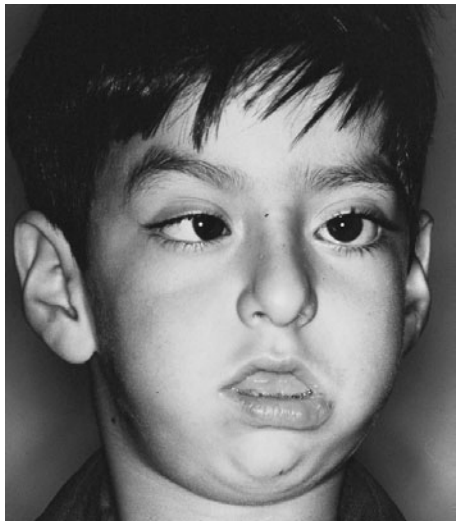

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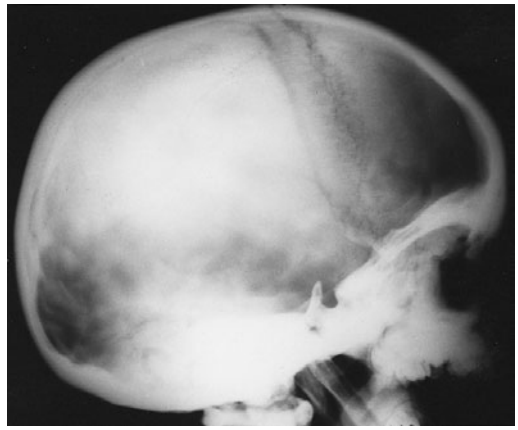

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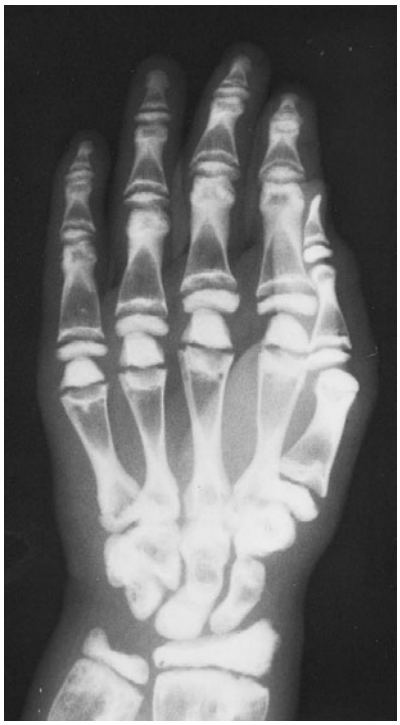

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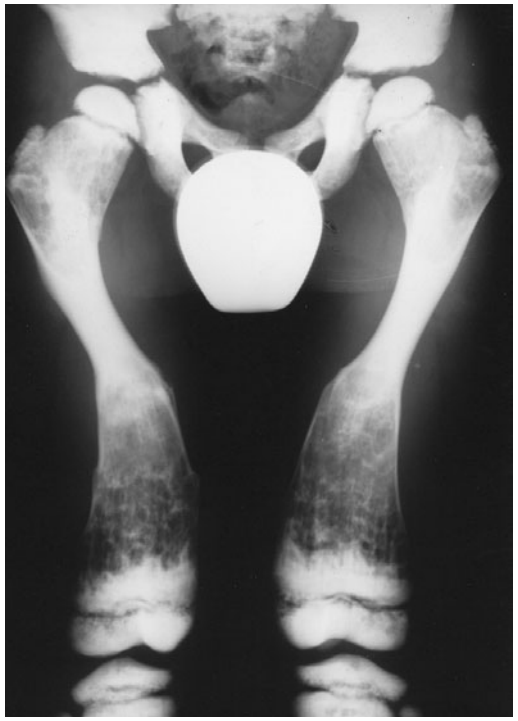

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Fig. 8–9. *Dysosteosclerosis*. (A) Disproportionate short stature. (B) Strabismus, facial nerve involvement, oligodontia, and small chin. (C) Sclerosis of cranial vault and base of skull with underpneumatization in a 10-year-old boy. (D) Epimetaphyseal sclerosis with submetaphyseal radiolucency of short tubular bones, undermodeling with metaphyseal flare; sclerosis of carpal bones and epimetaphyseal parts of radius and ulna. (E) Sclerosis of diaphyses, epiphyses, and adjacent metaphyseal regions; undermodeling and shortening of femora with wide, radiolucent metaphyseal flare, abnormal metaphyseal trabeculation; bowing of femora. [A courtesy of J Spranger, Mainz, Germany. B courtesy of D Rimoin, Los Angeles, California. C–E from RJ Gorlin et al, Birth Defects 5(4):79, 1969.]

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Van Buchem disease and pseudo-Van Buchem disease

Van Buchem disease (generalized cortical hyperostosis) is characterized by osteosclerosis of the skull, mandible, clavicles, and ribs and by hyperplasia of the diaphyseal cortex of the long and short bones. An extensive monograph is the 1976 study by Van Buchem et al (17). The total number of reported patients is 26 (1–3,6–18), with 15 of them belonging to the family originally described by Van Buchem (15,16) (Fig. 8–10A–E).

The disorder exhibits autosomal recessive inheritance. The family described by Dixon et al (4) had a different disorder, one that we have seen in affected sibs and have termed this "pseudo–Van Buchem disease" (Fig. 8–10F–H). Several other patients reported to have Van Buchem disease probably had endosteal hyperostosis, Worth type (5,13). It has been suggested that Van Buchem disease in The Netherlands and sclerosteosis in South Africa are, in fact, the same disorder, the differences being explained by an additional epistatic gene in South Africa (1). A genome-wide search in the original family has shown linkage to chromosome 17q12–q21 (19). The increased bone density is due to a deficiency of a novel secreted protein (SOST)(1).

Craniofacial findings. Facial changes develop slowly, but usually become apparent before the second decade (Fig. 8–10A–E). A most striking finding is a wide and thickened mandible, suggesting acromegaly. Rarely, skull circumference is enlarged. Occasionally there is mild exophthalmos. Patients experience headache, unilateral or, rarely, bilateral facial paralysis, and optic atrophy. Facial palsy may be the initial finding (7). Progressive sensorineural or mixed hearing loss often starts during puberty (18). Surgical decompression has been attempted (13).

Musculoskeletal findings. Radiographic changes include progressive thickening of the calvaria and increased density of the skull base. The body of the mandible is greatly enlarged in all measurements; the angle is obtuse. CT scanning of the skull can be useful in preparation of neurosurgical interventions (3). The long tubular bones exhibit diaphyseal thickening and are rough textured. The cortical hyperostosis is predominantly endosteal in character. In severe cases, the medullary cavity is occluded. The transverse diameter of the diaphysis is normal or increased. Elevated serum alkaline phosphatase levels have been noted in most cases (3,16). An aneurysmal bone cyst has been reported in the para-acetabular area (20).

References (Van Buchem disease and pseudo-Van Buchem disease)

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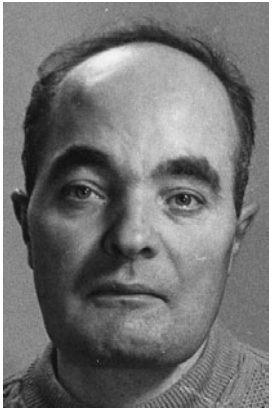
Sclerosteosis

This disorder was described as early as 1929 by Hirsch (16). Several other reports of the disorder (10,11,13,15,17–19,21,22,26,27) antedate Hansen's (14) definition of sclerosteosis. The disorder is characterized by generalized osteosclerosis with hyperostosis of the calvaria, mandible, clavicles, and pelvis similar to that seen in Van Buchem disease. Usually there are syndactyly and other abnormalities of the digits (Fig. 8–11). The disorder appears to be one of osteoblast hyperactivity (23). Beighton (3) provides a good review.

Sclerosteosis has autosomal recessive inheritance. Most patients have been South African of Dutch ancestry (4,7,12,18). The gene has been mapped to 17q12–q21, to the same region as for van Buchem disease (1). Thus, the two disorders are probably allelic. Its frequency there has been estimated to be about 1/60,000 Afrikaners (4). It has been seen in Japan (24), Spain (9), the United States (15,17,23), Senegal (25), and Brazil (21). It is due to loss of SOST gene product (8). Possibly 90 cases have been reported. It has been alleged that heterozygote detection may be possible on the basis of increased calvarial width and density (3,7).

The typical facies, evident by the age of 5 years, is characterized by frontal prominence, hypertelorism, and broad flat nasal root (20). The mandible is prognathic, broadened and squared, and dental malocclusion is frequent. The face may be distorted with relative midfacial hypoplasia. Head circumference is enlarged. In most cases, mixed hearing loss appears in childhood (20). Facial nerve paralysis, transient in infancy, is common in adulthood (10,11). Characteristically, it is unilateral for many years. There is increased intracranial pressure in 80% of cases (5,7,23). Ataxia has been reported (18,23). Exophthalmos, optic atrophy, reduced visual fields, convergent strabismus, nystagmus, chronic headache, and decreased sensory function of the trigeminal nerve have been described in adults. Visual loss occurs in 30%. Only rarely, however, is there total blindness. Several patients have died suddenly from impaction of the medulla in the foramen magnum (5,12).

Body height is over 180 cm in 70% of patients. In about 75%, asymmetric partial or complete cutaneous syndactyly of the index and middle



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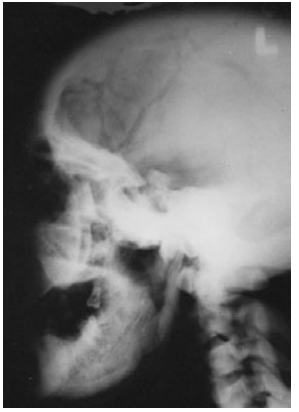

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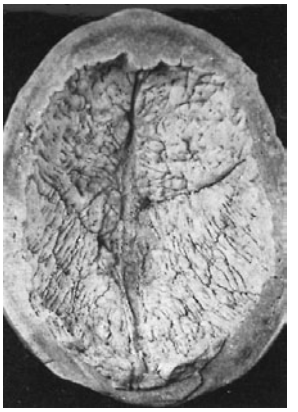

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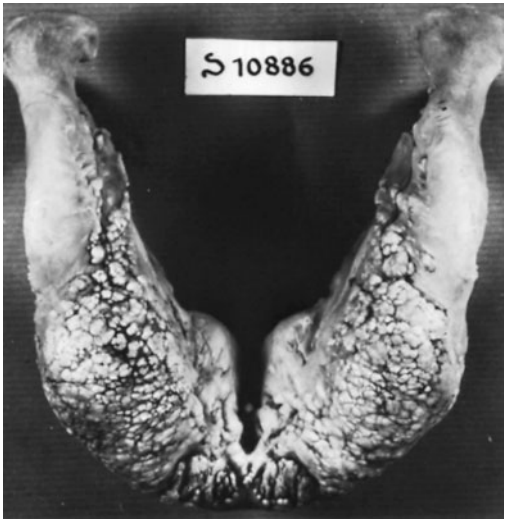

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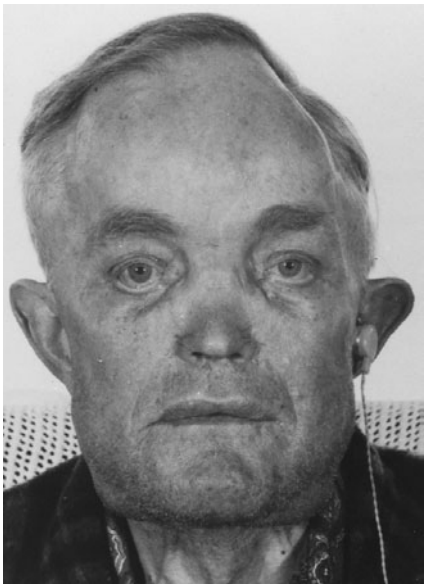

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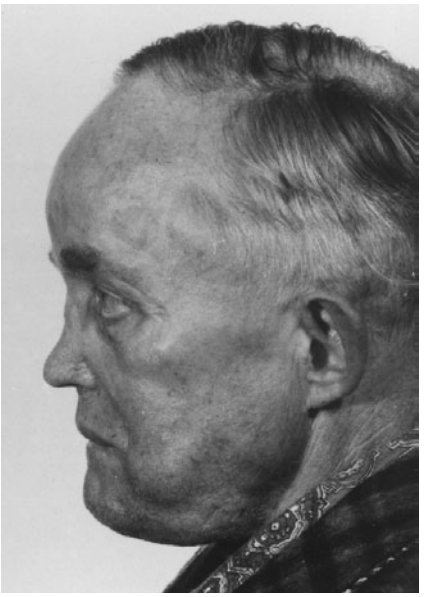

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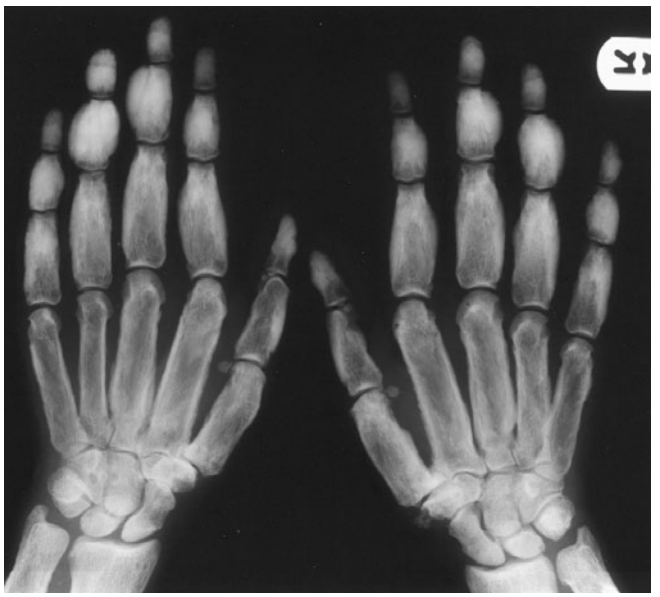

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Fig. 8–10. *Van Buchem disease*. (A) Note wide and thickened mandible. Note bony irregularity of calvaria. (B) Thickening of calvaria, increased density of skull base, and thickening of mandible. (C) Marked thickening of calvaria. (D) Undersurface of mandible showing marked broadening and osteophytic formation. (E) Sclerosis and thickening of long bones with osteophytic formation. *Pseudo-Van Buchem disease*. (F,G) Skull, maxilla, and mandible are irregularly thickened. (H) Radiograph of hands showing marked, predominantly diaphyseal, cortical thickening of metacarpals and phalanges, far more severe than in classic Van Buchem patients. (A,B from FSP Van Buchem et al, Am J Med 33:387, 1962. C from FSP Van Buchem, Acta Radiol (Stockholm) 44:109, 1955. D from FSP Van Buchem and HN Hadders, Schweiz Med Wochenschr 87:231, 1957. E courtesy of FSP Van Buchem, Haarlem, The Netherlands. F–H from JM Dixon et al, J Neurol Neurosurg Psychiatry 45:913, 1982.)

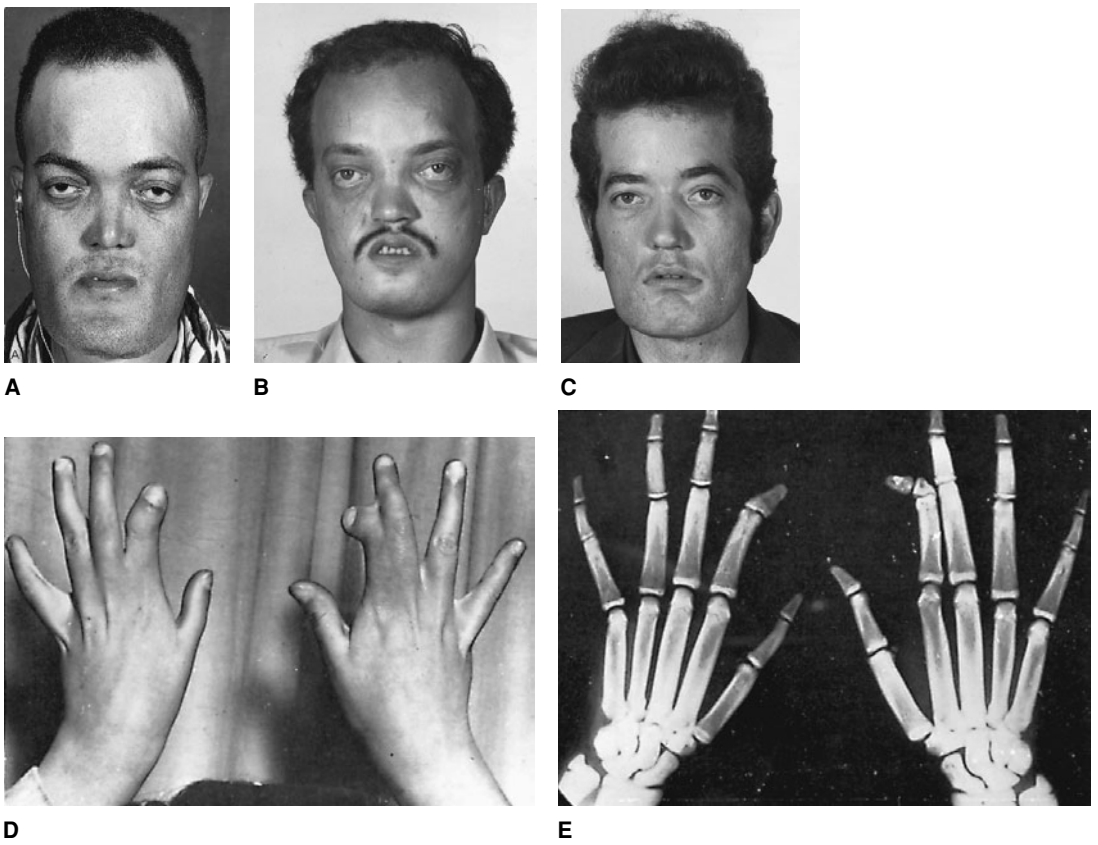

Fig. 8–11. *Sclerosteosis*. (A) There is marked mandibular growth following puberty; mandible assumes square form. Mixed hearing loss, facial palsy, headache, exophthalmos, and blindness are common complications. (B) Exophthalmos and facial palsy. Lips cannot close over teeth. (C) Grossly enlarged cranial vault and mandible. Expressionless facies is due to seventh nerve involvement. (D) Soft tissue syndactyly of second and third fingers was present bilaterally. Third and fourth fingers were partly fused unilaterally. (E) Radiograph shows hypoplasia or absence of middle phalanx of second digit together with radial deviation of terminal phalanx. (A courtesy of CJ Witkop Jr, Minneapolis, Minnesota. B,C from H Hamersma, Laryngoscope 80:1518, 1970. D,E from AS Truswell, J Bone Joint Surg Br 40:208, 1958.)

fingers occurs. There may be radial deviation of the distal phalanx of the index fingers. The nails on the involved digits are hypoplastic in 80% of patients. Height may be is correlated with syndactyly.

Radiographically, the calvaria becomes thickened and sclerotic in infancy. This gradually increases until about the age of 30 years. The base is dense and the foramina obliterated. The mandible is massive, prognathic, and often asymmetric, with an obtuse angle. The clavicles and ribs are broad and dense because of cortical thickening. The scapulae, pelvis, and vertebral endplates and pedicles are uniformly sclerotic. The tubular bones, in addition to having increased density, exhibit a lack of diaphyseal modeling. The index finger may have no middle phalanx or only a small triangular bone (delta phalanx), producing radial deviation. Bony syndactyly may involve the second and third fingers (6).

Microscopic study of the bone reveals only increased density with osteoblastic hyperactivity (23).

Patients with *Van Buchem disease*, most of whom are of Dutch ancestry, tend to be of normal height and never have involvement of digits. Sclerosteosis tends to be more severe in its manifestations. Hearing loss (90%) and raised intracranial pressure (80%) are more common in patients with sclerosteosis than in those with Van Buchem disease. Beighton et al (8), having examined 80 Afrikaners with sclerosteosis in South Africa and 15 patients with Van Buchem disease in The Netherlands, posited that they are the same disorder, the difference being the occurrence of an additional epistatic gene in South Africa.

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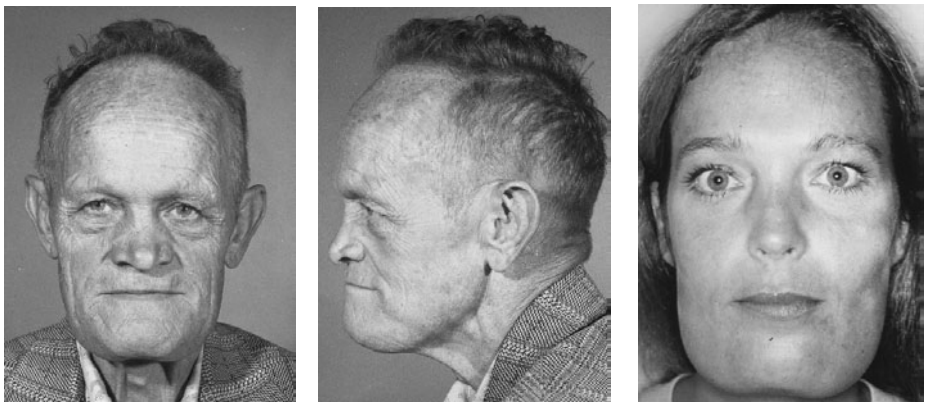

A B C

Fig. 8–12. *Autosomal dominant osteosclerosis*. (A–C) Prominent frontal area and squared jaw. Torus palatinus is often associated. (A,B from RK Beals, J Bone Joint Surg 58A:1172, 1976. C from EW Ruckert et al, J Oral Maxillofacial Surg 43:801, 1985.)

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Autosomal dominant osteosclerosis (endosteal hyperostosis, Worth type)

Clinical manifestation of this disorder is essentially limited to a square jaw—i.e., a widened and deepened mandible with increased gonial angle (1–16,18–20) (Fig. 8–12). We are not certain how to classify the case of Scott and Gautby (17). The changes begin at puberty and plateau with cessation of growth. Possibly, torus palatinus is more frequently associated with the condition (3,10,15,19,20).

Radiographically, endosteal sclerosis of the neurocranium is evident with loss of the diploë, osteosclerosis, and hyperostosis of the mandible as well as absence of the normal antegonial notches, endosteal sclerosis of the diaphyses of long bones (including metacarpals and metatarsals), and osteosclerosis of the pelvis. The vertebral bodies, ribs, and clavicles are involved to a minor degree.

In contrast to *Van Buchem disease*, there is usually no compression of cranial nerves as a result of foraminal encroachment or elevation of serum alkaline phosphatase, but exceptions do exist (1,3,9,11,14). Autosomal dominant inheritance has been reported (7). *Autosomal dominant osteopetrosis* is not associated with enlarged mandible, and furthermore, skeletal involvement is generalized.

References [Autosomal dominant osteosclerosis (endosteal hyperostosis, Worth type)]

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Progressive diaphyseal dysplasia (Camurati-Engelmann disease)

Progressive diaphyseal dysplasia is a sclerotic and hyperostotic disorder of bone. Originally reported by Cockayne (5) in 1920, it was defined by Camurati (3) in 1922 and by Engelmann (9) in 1929. More than 200 cases have been reported (22). The prevalence has been estimated to be lower than 1 in 1,000,000 births (25).

Inheritance is autosomal dominant with considerable variation in expression (4,22,25). There appears to be anticipation (25,25a) and genetic homogeneity (1a,5a). Families with more severely affected parents have been reported (24). The gene has been mapped to 19q13.1–q13.3 (10,16a). Domain specific mutations in the gene for transforming growth factor β-1 (TGFβ1) are responsible (16b). A question has been raised regarding its relation to Ribbing disease (20a). A remarkable example was reported by Clybouw et al (4), who described a fully affected child, a symptomless mother without anomalies on X-rays but with a focus of increased osteoblastic activity at the base of the skull, and a grandfather with all major radiologic features but a normal bone scintigraphy. New

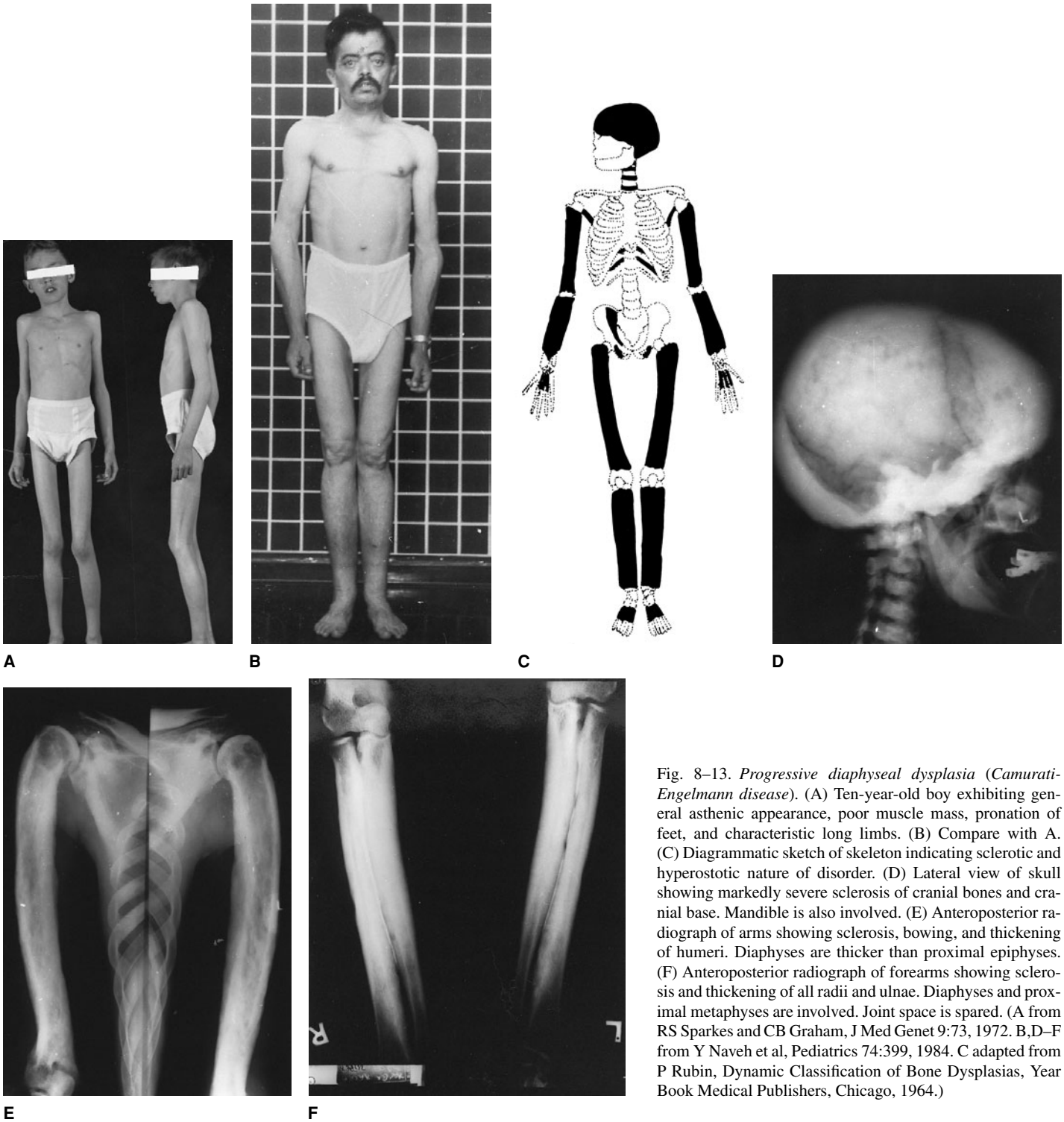

Fig. 8–13. *Progressive diaphyseal dysplasia* (*Camurati-Engelmann disease*). (A) Ten-year-old boy exhibiting general asthenic appearance, poor muscle mass, pronation of feet, and characteristic long limbs. (B) Compare with A. (C) Diagrammatic sketch of skeleton indicating sclerotic and hyperostotic nature of disorder. (D) Lateral view of skull showing markedly severe sclerosis of cranial bones and cranial base. Mandible is also involved. (E) Anteroposterior radiograph of arms showing sclerosis, bowing, and thickening of humeri. Diaphyses are thicker than proximal epiphyses. (F) Anteroposterior radiograph of forearms showing sclerosis and thickening of all radii and ulnae. Diaphyses and proximal metaphyses are involved. Joint space is spared. (A from RS Sparkes and CB Graham, J Med Genet 9:73, 1972. B,D–F from Y Naveh et al, Pediatrics 74:399, 1984. C adapted from P Rubin, Dynamic Classification of Bone Dysplasias, Year Book Medical Publishers, Chicago, 1964.)

mutations have been stated to account for about 50% of cases, but the experience described by Clybouw et al (4) indicates that this may be too high. Hence, a combined radiologic and scintigraphic evaluation of first-degree relatives is needed to investigate whether Camurati-Engelmann disease is present or not. Ghosal et al (11) and, subsequently, Oszoylu (23) and Gümrük et al (13) described diaphyseal dysplasia associated with anemia, which appears to be a separate autosomal recessive entity. Bone marrow suppression and elevated levels of IgG and IgA have been recorded.

The most common clinical findings include delayed ambulation, bone pain, generalized neuromuscular weakness, flat feet, broad-based waddling gait, and thin musculature with disproportionately long limbs and bowed tibiae. Symptoms can manifest as early as the third to fifth year of life, although the mean age for full development of the disorder is about 15–20 years (17,22,25,33). Genua vara, genua valga, lumbar lordosis, or scoliosis may occur. Less often there is hepatosplenomegaly (6) (Fig. 8–13). Secondary sexual development is poor.

Some patients exhibit frontal bossing, exophthalmos, papilledema, epiphora, optic atrophy, and headache (8,18,20,22,31). Luxation of the globe has been reported. Mixed hearing loss has been noted in 5%–7% of patients (6–8,15,21,29,30,32), and sometimes diminishes after decompression procedures (15). Stapes fixation has also been

found (16). The external auditory canals can be nearly occluded by bony overgrowth (27). The vestibular nerve can be compressed (14). Neurological manifestations include cranial nerve dysfunction and pain (1,27,28). Cerebellar herniation into the foramen magnum may be life-threatening (27). Grey et al (12) have reported a remarkable follow-up of 45 years.

Radiographically, symmetric, irregular, spindle-shaped, sclerotic cortical thickening of the mid-diaphyses of the long tubular bones and narrowing of the medullary cavities are evident. With age, the process extends proximally and distally toward the metaphyses, which are rarely involved; the epiphyses are not affected. The base of the skull and calvaria are sclerotic in 70% of cases (Fig. 8–13D). The cervical vertebrae, clavicles, pelvic bones, hand and foot bones, and ribs are affected in about 20%. The mandible is sclerotic in 25% and occasionally is significantly enlarged (6,8,21,24).

Serum alkaline phosphatase and urinary hydroxyproline levels and the erythrocyte sedimentation rate may be elevated (28); carnitine levels may be lowered (2). The scintigraphic changes are striking and do not always correlate with radiographic changes (4,19,26).

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Osteopathia striata with cranial sclerosis

In 1924, the Dutch radiologist Voorhoeve was the first to describe a syndrome of cranial sclerosis with osteopathia striata (32). Approximately 45 individuals have been reported (1–34). Most authors have favored autosomal dominant inheritance for this disorder (2,7,8,10,16,20,22,26,29, 32,34), with male-to-male transmission being poorly documented (16,32). We would opt for X-linked dominant inheritance, as do Pellegrino et al (26), Bueno et al (4), and Behninger and Rott (2a). There is a 2.5:1 female sex predilection (13). Intrafamilial variation in expression may complicate genetic counseling (6,29). The syndrome has been well reviewed by König et al (20).

The cranium is usually biparietally enlarged. This is evident at birth but is frequently mildly progressive so that adult head circumference is often 60–65 cm. The facies appears somewhat squared. Nasal obstruction may be evident in infancy (3,12,16,25). There is frontal bossing, the nasal bridge is broad, and the eyes appear wide set (28) (Fig. 8–14). Ankylosis of the temporomandibular joint has been noted (2a). Hearing loss, present in almost half the cases, is usually mixed and quite variable in degree, and often involves the low frequencies (13,18,20,29). Some patients have facial palsy (12,20,21); other cranial nerves may also be involved (6,10,13). Some investigators have suggested that narrowing of the cranial foramina is the cause of the palsy(10); others have suggested that the often transitional character better fits involvement of other factors such as vascular compromise (20). Mild and sometimes moderate mental retardation occurs in about 20% of cases (2,3,12,16,18,20,25,29,31,33). Brain studies are normal (2) or show atrophy (28), callosal body hypoplasia (26), or hydrocephaly (20,26). It remains uncertain whether the alobar holoprosencephaly found in one of the affected family members described by Savarirayan et al (29) was part of the entity or was a coincidence. Cleft palate or bifid uvula has been noted in 40% of cases (2,3,5,7,12,18,20–22, 26,27,30,31,33). Cataracts and abbreviated tooth roots or unerupted teeth have also been noted (3,12,27; RJ Gorlin, unpublished observations). Radiographically, there is scoliosis and hyperostosis of the cranial vault and a marked increase in density of the cranial base (Fig. 8–14B,C). This may be progressive in childhood (13,20,28) or stationary in adulthood (12).

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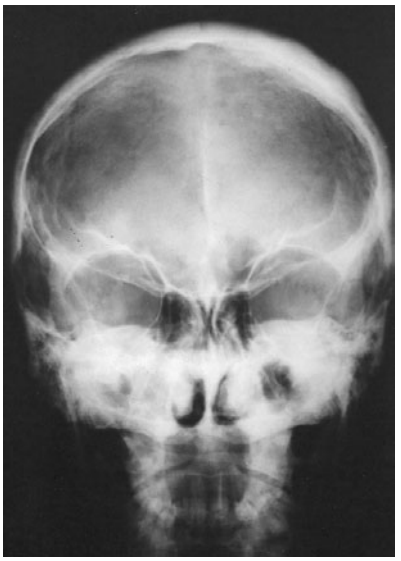

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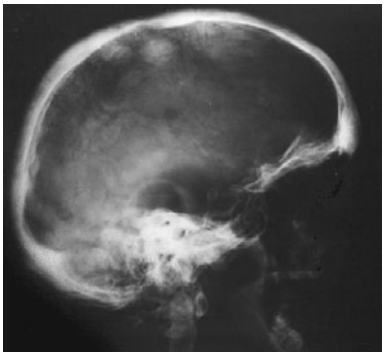

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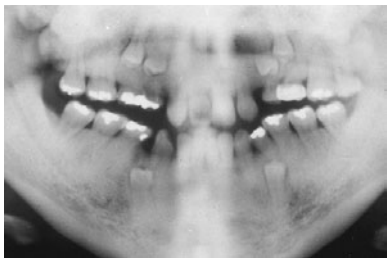

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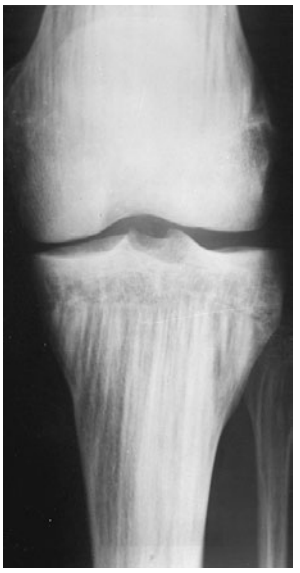

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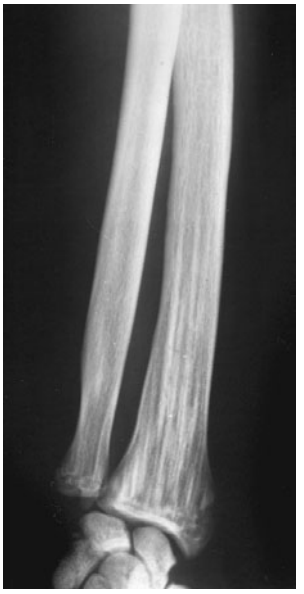

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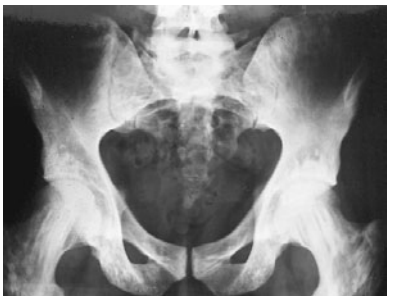

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Fig. 8–14. *Osteopathia striata with cranial sclerosis*. (A) Facies appears somewhat squared with frontal bossing, broad nasal bridge, and the appearance of wideset eyes. (B,C) Markedly thickened sclerotic areas in cranial vault and base with particularly dense petrous portion of temporal bone. Note rudimentary paranasal sinuses and mastoids. (D) Abbreviated tooth roots. (E) Dense linear striations parallel to long axis are present in femur, tibia, fibula. (F) Note combed appearance of radius and ulna. (G) Characteristic striations present in proximal end of each femur and numerous areas of bone condensation are present in acetabula and ischia. (B,C,E–G from PA Schnyder, Skeletal Radiol 5:19, 1980.)

The sinuses may be obscured and the mastoid air cells diminished. The anterior fontanel closes late (7). Radionuclear studies show an increased tracer uptake, suggestive of an active metabolic process (10,13). The long bones and iliac wings appear combed with fine, uniform, linear striation, hence the name *osteopathia striata*. It is particularly clear in the metaphyses (Fig. 8–14E–G). Similar striations may be present in the ribs parallel to the long axis (29). Some have general increased bone density. Spina bifida occulta in the lumbar region is common (16,33). A few patients have scoliosis (16,30,33). The clavicles are sometimes straight with broad endings (13,20,27,34). Nakamura et al (23) described a single case with recurrent fractures and metaphyseal undermodeling.

Ventricular (6,21,24,26,29) or atrial septal defect (20,26), pulmonic stenosis (8), postaxial polydactyly (6), transient cardiac murmurs (31,33), syndactyly between the fourth and fifth toes (6), duodenal web (1), cystic kidneys, micropenis, omphalocele, and malrotation of the gut all occur (20,26,29). Some patients are described as being hypotonic (21,27,33,35).

Prenatal diagnosis has been accomplished (34) through echocardiographic measurement of the head circumference. However, macrocephaly may develop only in the second or third trimester (20,26).

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Hyperphosphatasemia

Variously described under designations such as juvenile Paget's disease, osteochalasia desmalis familiaris, familial osteoectasia with macrocranium, fragile bones with macrocranium, and hereditary chronic hyperphosphatasemia, this disorder was first described by Sorrel and LeGrand-Lambling (20) in 1938 and Choremis et al (5) in 1958. It has been well reviewed by Fanconi et al (12) and Spindler et al (21).

The condition has autosomal recessive inheritance (3,10,11,14,23,24). About half of the patients have been of Puerto Rican origin (1,2,11, 22,24).

The syndrome is characterized by fever, bone pain, and swelling of the extremities during the first year of life (8). Later, enlargement of the calvaria and often numerous fractures and bending of the bones of the extremities occur, particularly anterior bowing of the legs and general broadening of the diaphyseal areas of tubular bones (Fig. 8–15). However, healing is normal. Headache and hypertension are frequent (15,16). Cardiomegaly has been described (14). The sclerae may be blue (11), but are usually normal in color. Intelligence is normal. Progressive mixed hearing loss is commonly diminished and angioid streaking of the retina has been reported (11,16,24). The skin exhibits pseudoxanthoma elasticum (7,9,13,16,19). A single patient developed multiple osteogenic sarcoma of the skull (17).

Histologically, there is intensive metaplastic fibrous bone formation as well as increased osteoblastic and osteoclastic activity that is very similar to that seen in Paget's disease but without typical mosaic or regression lines.

Since chondral ossification is not markedly disturbed (epiphyses are normally formed and the joints are not involved), growth is not seriously diminished. Muscle weakness is frequent, which retards walking, running, and jumping.

Radiographic examination of the skull reveals changes ("cotton ball patches") remarkably like those seen in Paget's disease. There is flattening of vertebral bodies. Long bones exhibit bending, overcylindricalization, and generalized cortical widening. The bone trabeculation is coarse and bone density diminished. Short bones are involved to a lesser degree, mostly on the endosteal side. The facial bones, except in the patient reported by Marshall (15), have not been involved. Scintigraphic changes are striking (14). Teeth are shed early due to root resorption (11).

The blood picture is generally normal, although anemia was described in Swoboda's (23) patients. Serum alkaline phosphatase levels (normal 25) may exceed 500 King-Armstrong units (KAU) (16). Serum acid phosphatase is also elevated (normal 1.5–3.5 KAU) as well as urinary hydroxyproline and leucine aminopeptidase (6).

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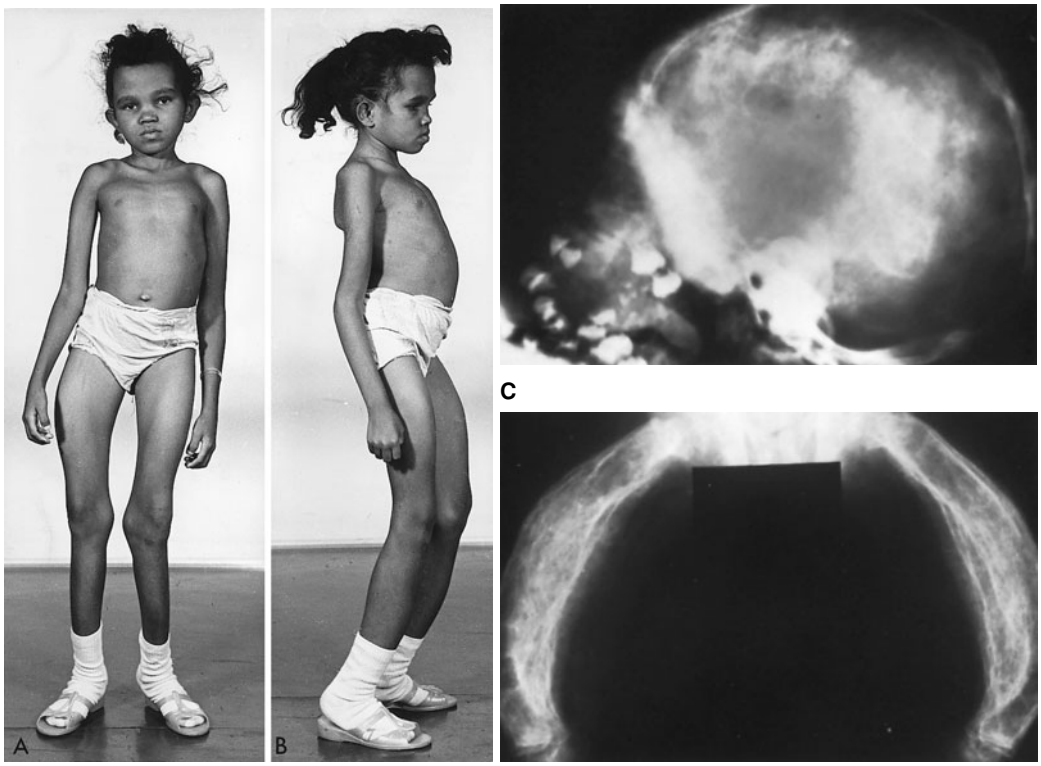

Fig. 8–15. *Hyperphosphatasemia*. (A,B) An eleven-year-old child with enlargment of skull, high forehead, wide face, and bowing of lower extremities. (C) Note changes similar to those observed in Paget's disease of bone. (D) Marked thickening and bending of femora with diaphyseal widening resulting from periosteal new bone formation. (A,B from H Bakwin et al, AJR Am J Roentgenol 91:609, 1964. C,D courtesy of WC Marshall, London, England.)

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Diaphyseal medullary stenosis and malignant fibrous histiocytoma (Arnold-Hardcastle syndrome)

A bone dysplasia characterized by abnormalities of cortical growth including diaphyseal medullary stenosis with overlying endosteal thickening and scalloping, metaphyseal striations, infarctions, and sclerotic areas of bone was first reported by Arnold (1) in 1973. The lower extremities are more often involved than the upper extremities. The skull, axial skeleton, and short tubular bones are spared.

Clinical features include pathologic fractures with poor healing and nonunion with painful debilitation. The legs become bowed. Usually between 20 and 50 years of age, aggressive malignant fibrous histocytoma develops. Other families have been reported (3,6). At least 25 examples are known (6). Presenile cataracts have been noted (1,3). Mental retardation was evident in sisters (3).

Autosomal dominant inheritance with variable expression has been found (1). The gene maps to 9p21–p22 (4,5). The mechanism by which the cancer is produced is not known (2). Thallium scanning has been advocated for diagnosis.

References [Diaphyseal medullary stenosis and malignant fibrous histiocytoma (Arnold-Hardcastle syndrome)]

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Chapter 9
Syndromes Affecting Bone: Other Skeletal Dysplasias

Autosomal recessive mesomelic dwarfism

Reardon et al (1) described a brother and sister, the offspring of second-cousin Pakistani parents. At birth, short angulated lower limbs and forearms with dimpling of the overlying skin were noted, as well as cleft palate and microretrognathia.

Psychomotor development was normal. In addition to marked mesomelic shortness and bowing, there was bilateral camptodactyly of the third, fourth, and fifth fingers. Elbow extension was limited.

Radiographic changes revealed mild generalized platyspondyly with slight irregularity of vertebral endplates of the upper lumbar region with mild posterior scalloping. Flaring of the distal humeral and radial metaphyses was noted. The radius and ulna were short, with marked bowing of the proximal ulna with a bony spur at the apex. The radial head was dislocated, and the distal radial epiphysis was flat. The first metacarpal was abbreviated. Lateral clavicular "hooks" were noted. Flat, irregularly ossified capital femoral epiphyses with broad femoral necks and flared irregular metaphyses were noted. The tibiae and fibulae were short, with anterior bowing and skin dimpling at the apices over the midshaft of the tibiae and fibulae. The talus was unusually formed.

Inheritance is apparently autosomal recessive.

Other mesomelic disorders include Reinhardt-Pfeiffer syndrome, Langer syndrome, Nievergelt syndrome, and autosomal recessive *Robinow syndrome*.

Reference (Autosomal recessive mesomelic dwarfism)

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Calvarial doughnut lesions, osteoporosis, and dentigerous cysts

In 1969, Keats and Holt (8) reported multiple round calvarial radiolucencies surrounded by dense rings of sclerotic bone (doughnut lesions) (Fig. 9–1). Similar examples were described under a variety of names by a number of other authors (1–7,9,10,12,13). Inheritance is autosomal dominant (3,4,10,12). A good review is by Baumgartner et al (4a).

In addition to the calvarial doughnut lesions, there have been osteoporosis, moderate bone fragility, coarse trabeculae, and diaphyseal undermodeling of long bones (1,6,10,12). Multiple fractures occur in early childhood (2,6,13). The calvarial lesions manifest as progressively enlarging skull bumps in adolescence. "Bone within bone" appearance in the vertebral bodies has been noted (2).

Both the jaw and calvarial lesions consist of fibroosseous changes. Colavita et al (6) described dentinogenesis imperfecta with cysts surrounding the roots of several teeth. There may be jaw infection (1).

Histologically, the lesions represent a fibrous nidus surrounded by sclerotic bone, essentially a fibrous dysplasia. Serum alkaline phosphatase has been elevated (1,4,6,10,13).

The disorder should be differentiated from calvarial hyperostosis (11).

References (Calvarial doughnut lesions, osteoporosis, and dentigerous cysts)

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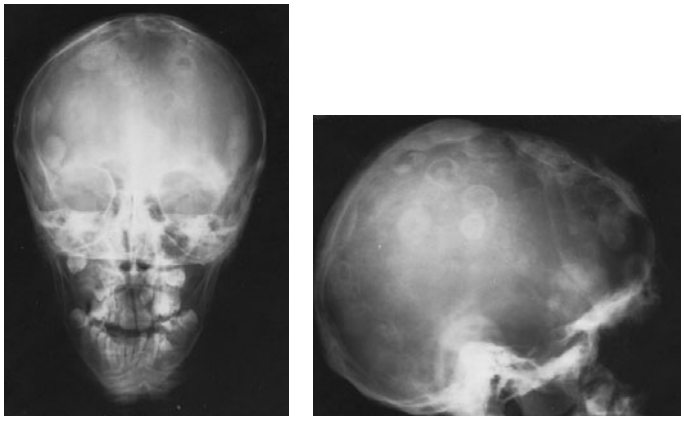

A B

Fig. 9–1. *Calvarial doughnut lesions, osteoporosis, and dentigerous cysts*. (A,B) Note multiple round calvarial radiolucencies surrounded by dense rings of sclerotic bone.

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Campomelia, cervical lymphocele, polysplenia, multicystic dysplastic kidneys, and cleft lip or palate (Cumming syndrome)

Cumming et al (1), in 1986, reported an infant with campomelia, polycystic renal disease, cervical lymphocele, and polysplenia. Additional

cases were presented by Urioste et al (5), Ming et al (3), Dibbern et al (2), and Pérez del Rio et al (4).

In addition to generalized edema and cervical hygroma, all had a short bell-shaped chest. Cystic pancreas (3–5), polycystic liver (1,2,4,5), and cystic kidney disease (1–5) were described. All had short limbs with campomelia and short hands. Some had absent phalanges (3,5). Cutaneous syndactyly of toes (5) was described as well as talipes equinovarus. Cleft palate (1,2) and cleft lip (3,5) have been noted.

Affected female siblings were reported by Urioste et al (5). Inheritance may be autosomal recessive.

References [Campomelia, cervical lymphocele, polysplenia, multicystic dysplastic kidneys, and cleft lip or palate (Cumming syndrome)]

1. Cumming WA et al: Campomelia, cervical lymphocele, polycystic dysplasia, short gut, polysplenia. Am J Med Genet 25:783–790, 1986.
2. Dibbern KM et al: Cumming syndrome: Report of two additional cases. Pediatr Radiol 28:298–301, 1998.
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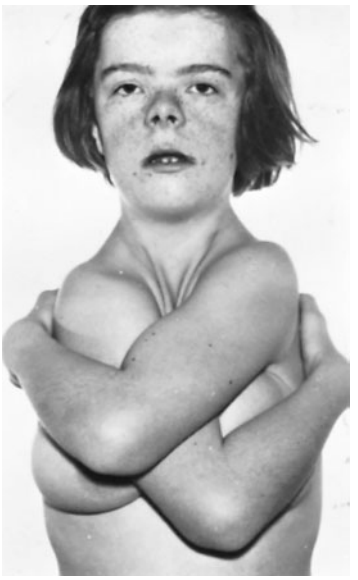


Fig. 9–2. *Cleidocranial dysplasia*. Frontal and parietal bossing, glabellar groove in 13-year-old girl attempting to approximate shoulders. [From M Føns, Acta Otolaryngol (Stockholm) 67:483, 1969.]

Cleidocranial dysplasia

More than 1000 cases of cleidocranial dysplasia have been documented since the reports of Martin (46) in 1765 and Meckel (47) in 1760. It possibly was first manifest in Neanderthal man (24). Scheuthauer (62) accurately described the syndrome in 1871. The Museum of Pathological Anatomy in Vienna harbors a well-preserved skeleton (2). Marie and Sainton (45), in 1897, reported the combination of aplasia or hypoplasia of one or both clavicles, exaggerated development of the transverse diameter of the cranium, and delayed ossification of fontanels. They named the syndrome "cleidocranial dysostosis." The largest known kindred consists of more than 250 affected persons (34,57).

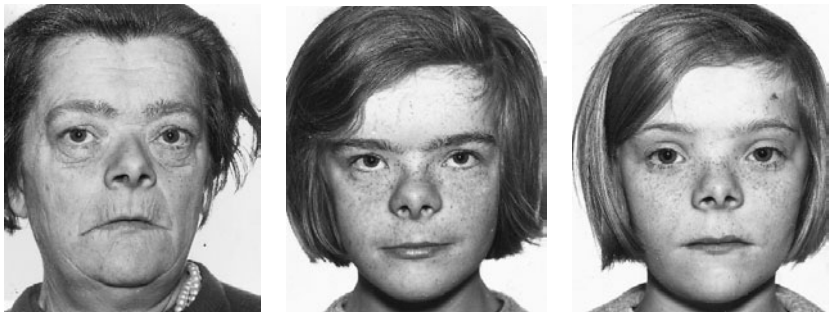
Many extensive reviews and analyses of the syndrome have been carried out, and over 100 associated anomalies have been recorded (9,12,13,15,26,48,49). A classic anatomic study is that of Hultkrantz (32), a good clinical review is that of Schuch and Fleischer-Peters (63), and an excellent historical review was carried out by Soule (68).

The syndrome has autosomal dominant inheritance (5,6,14,15, 48,57,63). It has been suggested that 20%–40% represent new mutations (14,63). Nienhaus et al (53) described a classically affected individual with a de novo pericentric inversion of chromosome 6. Narahara et al (52) found a balanced translocation between chromosome 6p and 18q in another patient. Two groups independently found linkage to 6p21 (13,50), and, in one family, a microdeletion was found (45). After refinement of the localization (21), mutations were found in the CBFA1 gene (51). The CBFA1 gene controls differentiation of precursor cells into osteoblasts (49). The Core-Binding Factor A (CBFA) consists of three different genes, and belongs to the Runt domain gene family (56). In mice, CBFA1 is initially expressed in mesenchymal condensations of the developing skeleton and activity is later restricted to osteoblasts (10), and is important for osteoblast differentiation (55). Mice deficient for CBFA1 showed features comparable with cleidocranial dysplasia in humans (55,65). Hence, the disorder is likely to be caused by haploinsufficiency for the CBFA1 gene, resulting in disturbed terminal differentiation of osteoblasts (56). There may, however, be genetic heterogeneity (3). Some mutations may cause only dental anomalies (56).

There are several reports of affected sibs born to normal parents, which may be explained by germline mosaicism (14,23,75), although this has not yet been proved by molecular studies. Genotype-phenotype correlation has been discussed (76).

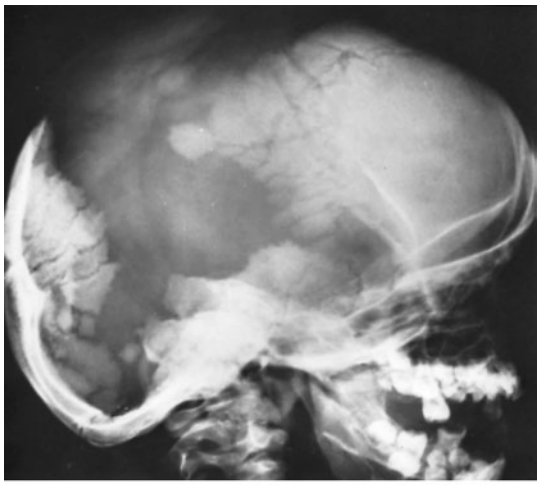
Facies and general appearance. The appearance is generally pathognomonic (Figs. 9–2 and 9–3). Affected individuals are usually short, with males averaging 156.6 to 168.8 cm and females 144.6 to 148.5 cm (32,34,38). The skull is brachycephalic, with pronounced frontal and parietal bossing, and the maxilla and zygomas are hypoplastic; thus, the face appears small. The nose is broad at the base, with the bridge depressed. There is hypertelorism. The neck appears long, and the shoulders are narrow and droop markedly.

Cranium. The skull is large and short with biparietal bossing; the cephalic index is usually in excess of 80. In most patients, a groove, overlying the metopic suture, extends from the nasion to the sagittal suture. Closure of the anterior fontanel and sagittal and metopic sutures is delayed, often for life (70). There is segmental calvarial thickening in the supraorbital portion of the frontal bone, the squama of the temporal bones,

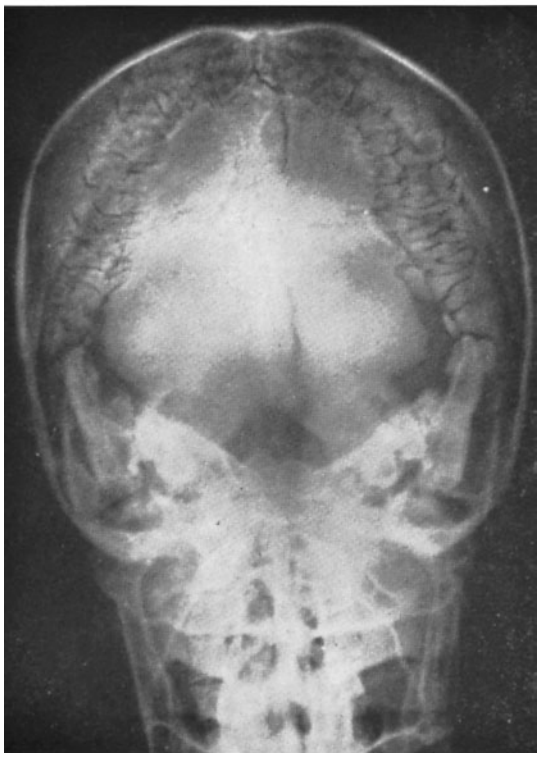


A B C

Fig. 9–3. *Cleidocranial dysplasia*. (A–C) Note brachycephalic skull, frontal and parietal bossing with the appearance of small face. [From M Føns, Acta Otolaryngol (Stockholm) 67:483, 1969.]



A



B

Fig. 9–4. *Cleidocranial dysplasia*. (A) Numerous wormian bones found in lambdoidal sutures, delayed cranial bone formation. (B) Wormian bones in lambdoidal sutures. (A courtesy of F Silverman, Cincinnati, Ohio.)

and the occipital bone above the inion. Secondary centers of ossification appear in the suture lines, and many wormian bones are formed (70,73) (Fig. 9–4). In extreme cases, the parietal bones are not present at birth (69). The cranial base has short sagittal diameter (59). Mandibular length is increased and the maxilla is short vertically (59). The foramen magnum, which is large, often exhibits defects in the posterior wall (68). Paranasal sinuses (5,19,39) and mastoids (73) are often underdeveloped or absent. Cephalometric changes of the skull are carefully described by Jensen and Kreiborg (36–41), Hirschfelder et al (30), and Ishii et al (33).

Clavicle. Clavicles are absent unilaterally or bilaterally in about 10% (67); more frequently, they are defective at the acromial end (26,34). The clavicles of some patients have a central gap (pseudoarthrosis), with bone replacement by fibrous connective tissue (15) (Fig. 9–5A–C). When the defect is unilateral, it is more frequently on the right side (35).

Deficiency of the clavicle is responsible for the long appearance of the neck and the narrow sloping shoulders. The range of shoulder movements permitted by this bony defect is often remarkable, frequently allowing the individual to approximate the shoulders in front of the chest. This ability is not always recognized by the patient, nor are the parents of an affected child necessarily aware of it (Fig. 9–2).

In this syndrome, there are variations in size, origin, and insertion of muscles related to the clavicles, especially the sternocleidomastoid, trapezius, deltoid, and pectoralis major, yet function is remarkably good (14).

Other skeletal deformities. Although cleidocranial dysplasia was originally believed to involve only bones of membraneous origin, involvement of endochondral bones has been recognized since Fitchet's (14) report. The most frequent abnormalities include delayed closure of the pubic symphysis, coxa vara, or (less often) coxa valga with lateral notching of the capital femoral epiphysis (26,35), cone-shaped thorax, spina bifida occulta of the cervical, thoracic, or lumbar regions of the spine, lumbar spondylolysis, pseudoepiphyses at the base of the metacarpal, abnormally pointed terminal phalangeal tufts of the hands and feet, short broad thumbs, long second metacarpal, short middle phalanges and metatarsals/tarsals III–V, and cone-shaped epiphyses of the distal phalanges. Reduced pelvic diameter requires cesarean section in about 35% of affected women (Fig. 9–5D) (35).

Other findings. Conduction hearing impediment (17,18,29,53) has been described. Although mental development is usually normal, several patients with mild delay have been reported (23,53,63).

Oral manifestations. The palate is highly arched. Submucous cleft palate and complete cleft of the hard and soft palates have been described (73). Delayed union at the mandibular symphysis is characteristic. Many patients may show a deficient ossification of the hyoid bone (34,38,58). Development of the premaxilla is poor, and since growth of the mandible is usually normal, relative prognathism results (67). Newborns may have prolonged feeding problems (6).

The literature presents a rather chaotic picture of the dentition, including multiple supernumerary (average−5) teeth (Fig. 9–6A), multiple crown and root abnormalities, crypt formation around impacted teeth, ectopic localization of teeth, and lack of tooth eruption (19,20,54,59, 60,71,73). The extra teeth are most often in the mandibular premolar and maxillary incisor areas (59). It is known that extraction of deciduous teeth does not promote eruption of permanent teeth (73). Rushton (60) and others (4,25,31,67,74) studied teeth microscopically and observed that roots lacked a layer of cellular cementum (Fig. 9–6B). Fleischer-Peters (16) suggested that the greater than normal bone density of the jaws might inhibit tooth eruption. Rushton (60) and Hitchin (31) attributed noneruption of teeth to failure of bone to resorb. Jensen and Kreiborg (36) and coworkers (44) carried out a study of 20 patients (most followed longitudinally), utilizing cephalograms, panorex and intraoral X rays, intraoral photographs, and surgically removed teeth. They found that the dental lamina produced normal primary teeth and permanent tooth crowns. The primary teeth erupted, but not the permanent teeth, except for first molars and occasionally other teeth. Following normal development of the permanent crowns, the dental lamina was reactivated to form supernumerary teeth. These occurred with highest frequency in the maxillary central incisor area and canine regions. The bizarre supernumerary crown and root morphology appeared to be related to spacial crowding. Deciduous root resorption is extremely delayed or arrested, and can probably be explained by diminished bone resorption. Abnormalities of root morphology in the permanent dentition appear secondary to arrested eruption.

Differential diagnosis. Although the facies as well as body habitus are characteristic, brachycephaly and frontal bossing may suggest rickets, prenatal syphilis, *achondroplasia*, hydrocephaly, *osteogenesis imperfecta*, and *pycnodysostosis*. A deficient premaxilla may also be seen in *Apert syndrome* and in *Crouzon syndrome*. Depressed nasal bridge is seen in *hypohidrotic ectodermal dysplasia, Stickler syndrome*, and prenatal syphilis. The appearance of the shoulders is similar to that seen in intrauterine or natal fracture. *Mandibuloacral dysplasia* is characterized by mild cranial and clavicular dysplasia, but lacks the dental abnormalities

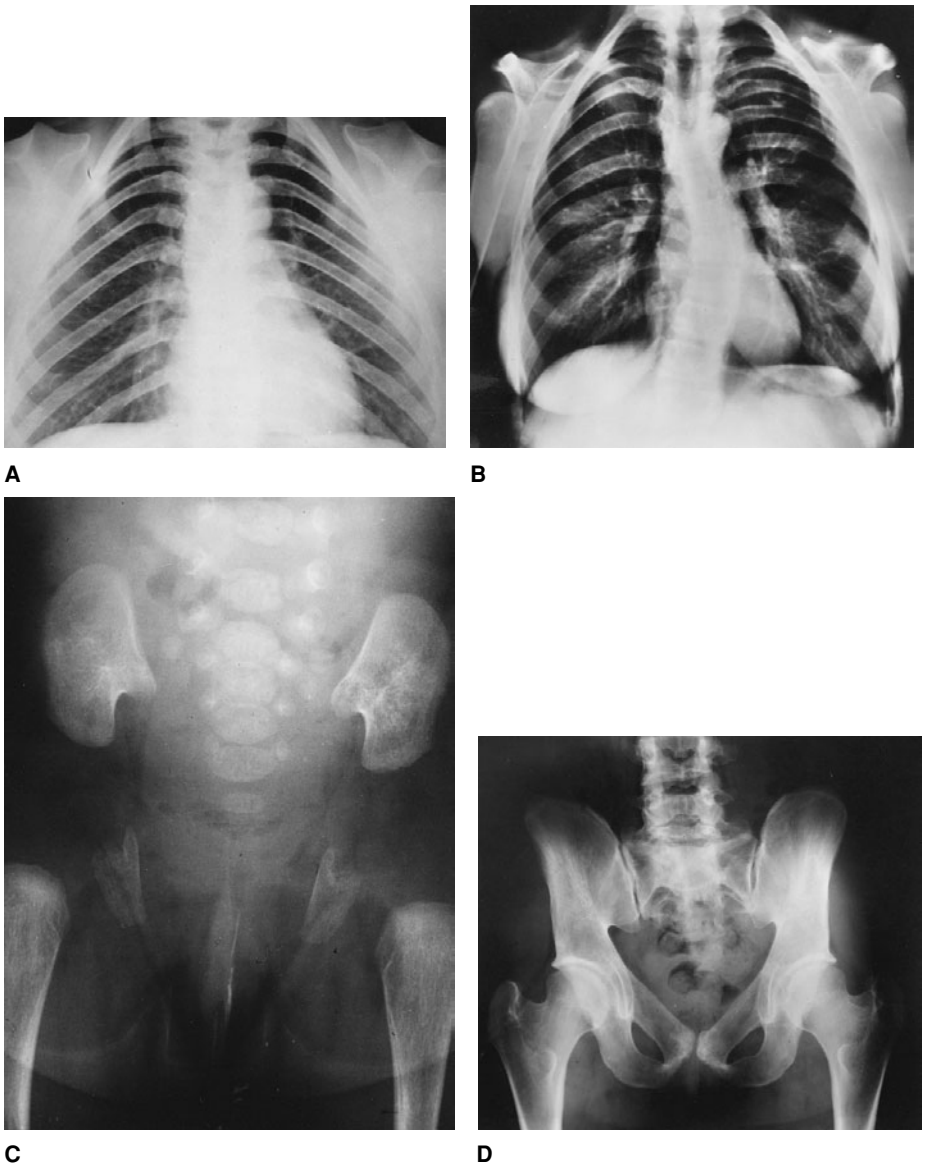


Fig. 9–5. *Cleidocranial dysplasia.* (A,B) Radiographs demonstrating bilateral aplasia of clavicles. (C,D) Pelvic abnormalities (D from M Forland, Am J Med 33:792, 1962.)

seen in cleidocranial dysplasia. In *Hajdu-Cheney syndrome* (acroosteolysis), clavicular demineralization, cranial dysplasia, and severe acroosteolysis occur, but the dental abnormalities found in cleidocranial dysplasia are absent.

Goodman et al (23) reported a disorder resembling cleidocranial dysplasia in three male offspring of two consanguineous matings. These patients had short stature, brachycephaly, open fontanels, bilateral absence of clavicles, wormian bones, nail dysplasia, and radiologic abnormalities of the spine and pelvis. Inheritance was compatible with an autosomal or X-linked recessive disorder.

The *Yunis-Varón syndrome* is characterized by absent clavicles, macrocrania, diastasis of sutures, micrognathia, absent thumbs and distal phalanges of fingers, hypoplasia of the proximal phalanx and absence of the distal phalanx of great toes, pelvic dysplasia, bilateral hip dislocation, and retracted and poorly delineated lips. Inheritance is autosomal recessive. Also, patients with enlarged parietal foramina, macrocephaly, occipital hair tuft, and lateral clavicular aplasia have been described by several investigators (11,22,27); this condition is probably autosomal dominant.

Postnatal clavicular hypoplasia or dysgenesis occurs in *progeria*, disorders of acroosteolysis, and possibly *pycnodysostosis*. Congenital clavicular dysplasia may occur in many disorders reviewed by Hall (27), including *focal dermal hypoplasia, dup(11q) syndrome, dup 20p syndrome, dup8q22 syndrome, Floating-Harbor syndrome*, and *Antley-Bixler syndrome*. Isolated pseudoarthrosis of the right clavicle as an isolated phenomenon is relatively common and largely limited to females. Crane and Heise (8) reported a lethal, autosomal recessive condition characterized by poorly mineralized calvaria, cleft lip and palate, micrognathia, upturned nares, ocular hypertelorism, depressed nasal bridge, and hypoplastic, posteriorly angulated, and low-set helices. In addition, absent cervical vertebrae and clavicles, talipes equinovarus, soft-tissue syndactyly of fingers and toes, short penis, and undescended testes were noted. Barnicoat et al (1) described a fetus with similar features and discussed the resemblance with aminopterin syndrome sine aminopterin.

Wallis et al (71) reported autosomal dominant inheritance of lateral clavicular defects and rhizomelic short stature (cleidorhizomelic syndrome).

Absence of clavicles, anal atresia, and psoriasis-like lesions were reported in sibs by Fukuda et al (20). The affected boy also had hypospadias and urethrorectal fistula. His sister had rectovaginal fistula. The boy's teeth were described as cone shaped with enamel hypoplasia. The parents were normal.

A particular variant, in which there were dolichocephaly, severe lordosis, generalized joint hypermobility, and dystrophic toenails, was described by Winkler (72). RJ Gorlin has seen another patient with the disorder. Patients with cleidofacial dysplasia (42) lack clavicles bilaterally, are microbrachycephalic, have exophthalmos with hypoplasia of lids, and are mentally retarded; inheritance is autosomal recessive.

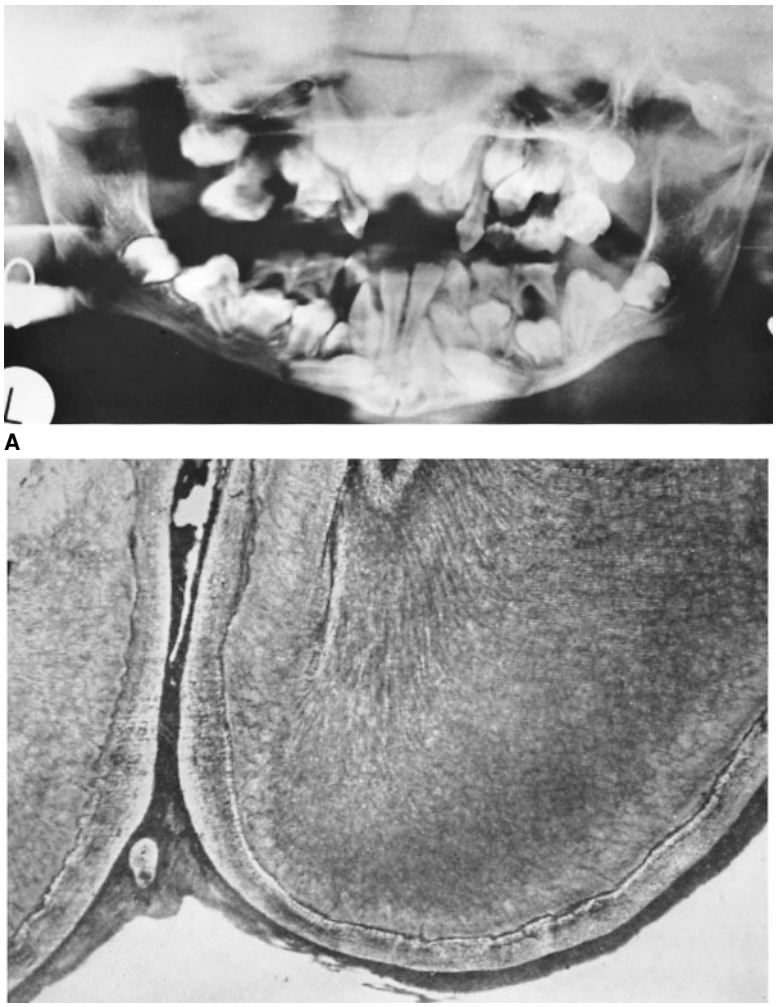


Fig. 9–6. *Cleidocranial dysplasia.* (A) Panorex showing multiple supernumerary, unerupted teeth. (B) Tooth roots, exhibiting complete absence of cellular cementum. (A from A Fleischer-Peters, Stoma (Heidelb) 23:212, 1970. B from M Rushton, Br Dent J 100:81, 1956.)

Silverman and Reiley (66) described spondylomegepiphyseal metaphyseal dysplasia, an autosomal recessive condition similar to cleidocranial dysplasia, but without its cranial and clavicular features.

Delayed ossification of the pubic ramus can also occur in a number of conditions: prematurity, *del(4p) syndrome*, Sjögren-Larsson syndrome, *campomelic dysplasia, spondyloepiphyseal dysplasia congenita* (7), and epispadias.

RJ Gorlin and MM Cohen Jr have seen a girl with congenital absence of both clavicles and sternum and contractures of the fingers. Failure of eruption of most permanent teeth has also been reported as an autosomal dominant trait (64). It also occurs in *GAPO syndrome*.

Clavicular hypoplasia has been seen in combination with zygomatic arch hypoplasia, microcornea, and stellate irides (55a).

Wormian bones are seen in a number of disorders, among them *pycnodysostosis, osteogenesis imperfecta*, hypothyroidism, and *Hajdu-Cheney syndrome*.

Laboratory aids. The disorder has been diagnosed prenatally with ultrasound (28,69a). The advent of molecular studies should allow prenatal studies through mutation analysis of CBFA1.

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Dysplastic clavicles, sparse hair, and digital anomalies (Yunis-Varón syndrome)

Yunis and Varón (13), in 1980, described five children with prenatal and postnatal growth deficiency, hypoplastic clavicles, absence of thumbs and halluces, and distal aphalangia. About 15 cases have been reported to date (2,3,5,6,8–11, RCM Hennekam, unpublished observation, 1999). We are uncertain how to classify the case of Adés et al (1), and the pairs of sibs described by Garrett et al (4) have been compared to the skeletal dysplasia reported by Kozlowski et al (7). The child reported by Hughes and Partington (6) and reviewed by Lapeer and Fransman (8) is mildly affected.

Inheritance is autosomal recessive. Parental consanguinity has been reported, and there have been several affected siblings (4,5,11). Hennekam and Vermeulen-Meiners (5) suggested mild heterozygote expression, but

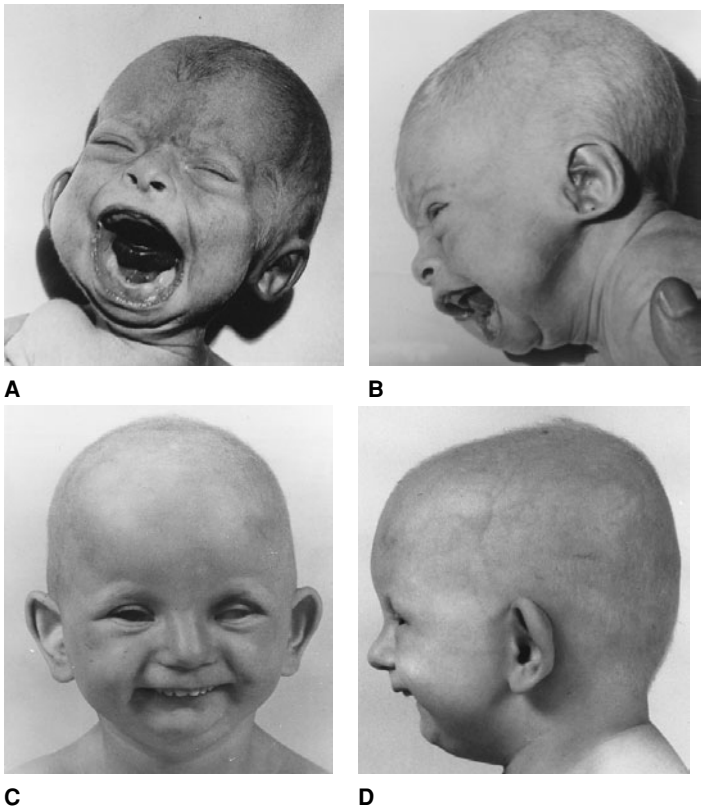

Fig. 9–7. *Dysplastic clavicles, sparse hair, and digital anomalies (Yunis-Varón syndrome).* (A–D) Dolichocephaly with sparse hair, eyebrows, and lashes, outstanding pinnae with wide concha, thin lips, and micrognathia. (A,B from E Yunis and H Varón, Am J Dis Child 134:649, 1980. C,D from HE Hughes and MW Partington, Am J Med Genet 14:539, 1983.)

this has not been found by others (11). In 80% the condition has been lethal before 6 months (11). Walch et al (12) suggested that the syndrome is a lysosomal disorder.

Microcephaly has been found in 40%. Wide sutures and large fontanels are constant features. The facial bones are hypoplastic and the scalp hair is sparse. The eyes tend to be small but proptotic (4,5,12). The pinnae are microtic or dysplastic. One case had severe hearing impairment (11). The nostrils are anteverted. The upper lip is short and the lower jaw small. The skin of the neck appears loose (Fig. 9–7).

The nipples have been absent in a few patients (4,5,12), and pyloric stenosis occurs (11).

The thumbs and great toes are hypoplastic or aplastic (Fig. 9–8). Most have transverse palmar creases. The fingers and toes are short and pointed with hypoplastic or aplastic nails.

Radiographically, there is unusual skull mineralization, wide fontanels and sutures, hypoplastic facial bones, micrognathia, and cystic dental follicles. Clavicles have been missing in 70%. Other skeletal changes include absent sternal ossification, flattened acetabula, and dislocated hips (Fig. 9–9). Constant features are aplasia of thumbs and halluces and distal digits of the toes and middle and distal phalanges of fingers (Fig. 9–10). The diaphyses of long bones have occasionally been thin and constricted. Dworzak et al (3) reported on PAS-positive storage material in vacuoles in heart, muscle, brain, and fibroblasts.

Male infants born to mothers with *Melnick-Needles syndrome* have hypoplastic thumbs and halluces.

References [Dysplastic clavicles, sparse hair, and digital anomalies (Yunis-Varón syndrome)]

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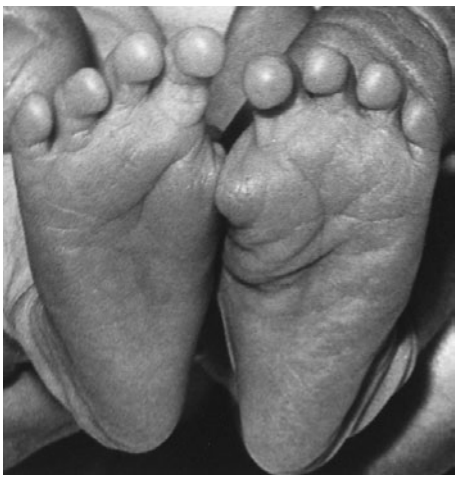

Fig. 9–8. *Dysplastic clavicles, sparse hair, and digital anomalies (Yunis-Varón, syndrome).* Agenesis of halluces. (From E Yunis and H Varón, Am J Dis Child 134:649, 1980.)

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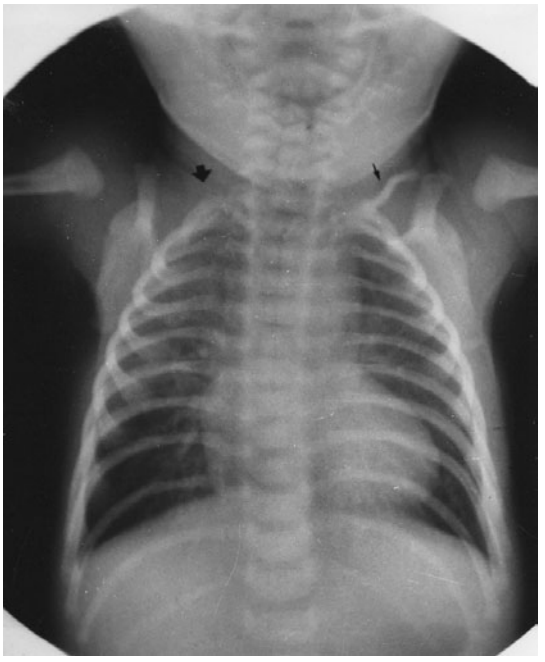
Fig. 9–9. *Dysplastic clavicles, sparse hair, and digital anomalies (Yunis-Varón syndrome).* Agenesis of right clavicle. (From E Yunis and H Varón, Am J Dis Child 134:649, 1980.)



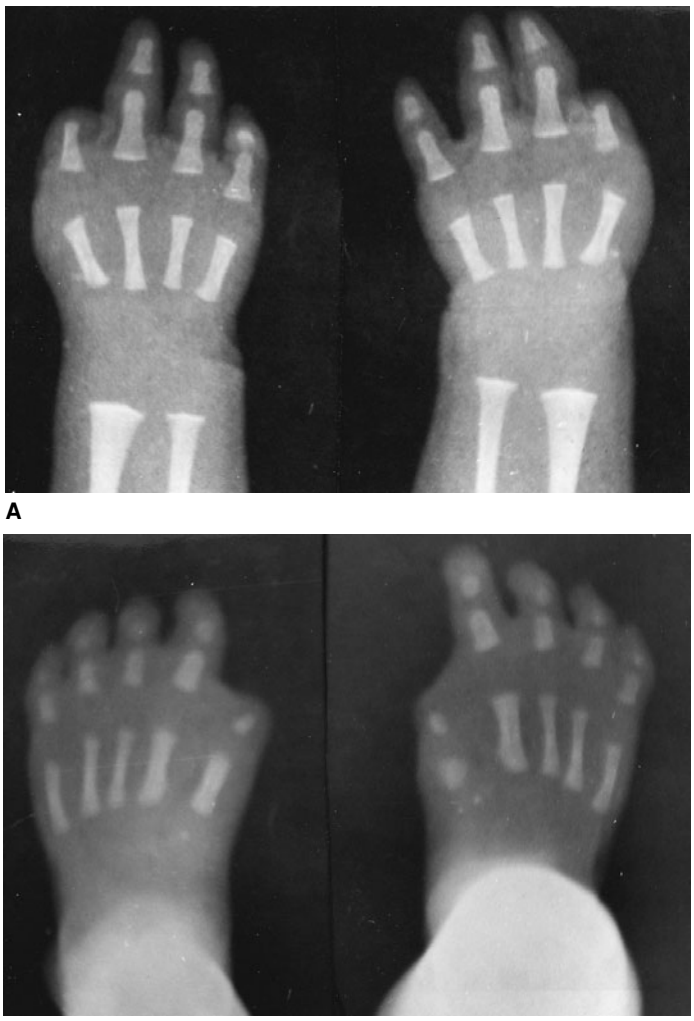


Fig. 9–10. *Dysplastic clavicles, sparse hair, and digital anomalies (Yunis-Varón syndrome).* (A) Absence of entire first ray and distal phalanges, bilateral absence of middle phalanges in second finger. (B) Hypoplasia of phalanges in halluces and of first metatarsals. (From E Yunis and H Varón, Am J Dis Child 134:649, 1980.)

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Fibrodysplasia ossificans progressiva

Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant disorder of connective tissue with progressive ectopic ossification of tendons, ligaments, facial and skeletal muscles, characteristic skeletal malformations including malformations of the hallux and reduction defects of all digits, hearing loss, and baldness. Progressive disability due to ectopic calcification is erratic, but severe restriction of movement eventually occurs, especially in the shoulders and spine. The condition was first recorded by Guy Patin in 1692 (37). The term *myositis ossificans progressiva* is said to have been assigned by von Dusch in 1868 (33). Since connective tissue is primarily affected, especially aponeuroses, fasciae, and tendons, the term *myositis* is no longer appropriate. In 1918, Rosenstirn (42) analyzed 200 cases; by 1982, an excess of 550 instances had been noted (11), and since then more than 150 additional cases have been published (3,4,7,8,14,19–22,35,36,39,45–50). A few large series of cases are available (8,12,33,35,41,49,53). Whites are reported most commonly, but a number of black patients have also been observed (9,46). A racial or ethnic predilection has not been reported.

Genetics. About 95% of the cases are sporadic (12,25,33,41,54). Autosomal dominant inheritance is based on several instances of parent-to-child and male-to-male transmission (5,14,19,20,25) and on concordant monozygotic twins (18,55). A gene called *noggin* has been mapped to 4q27–q31 (18a,31a,56). Most cases arise as new mutations. A significant paternal age effect for new mutations has been demonstrated (11,40,54). Genetic fitness is close to zero, physical disability probably being the main reason (21,53), although infertility has been suggested (54). Other families link to 17q21–q22 (32).

Evidence indicates that when the FOP gene is transmitted through two or more generations, penetrance is complete. However, variable expressivity is observed with respect to skeletal malformations and the extent of ectopic ossification. On occasion, a parent has exhibited only the characteristic skeletal malformations, with the child expressing the full FOP phenotype with ectopic ossification (25,50). There is evidence for genetic heterogeneity (32). The occurrence in two half sisters has been explained by maternal gonadal mosaicism (21). Although a distorted sex ratio has been suggested (33), other studies have not confirmed this, and it seems to be caused by problems of sample size and ascertainment bias.

Connor and Evans (11), attempting complete ascertainment of FOP in the United Kingdom, indicated a point prevalence of 0.61×10^{-6}. They also calculated a direct estimate of the mutation rate: 1.8×10^{-6} mutations per gene per generation, a rate compatible with other known human mutations. A useful review was provided by Buyse et al (6).

Pathogenesis. FOP is a distinctive histopathologic entity that can be differentiated from other soft-tissue lesions that ossify, such as myositis ossificans, extraosseous osteosarcoma, and osseous metaplasia. Early FOP is characterized by multifocal, interconnecting nodules of spindle-shaped, fibroblast-like cells in a distinctive connective tissue matrix with bone spicules occupying the central area. The histologic picture of such an early lesion can be misinterpreted as fibromatosis or sarcoma (26). Foci of chondroid differentiation may sometimes be observed. Lesions evolve to become mature lamellar bone with adipose and hematopoietic tissue in the cancellous spaces; the rim of fibroblast-like cells is no longer evident. Such pathologic features suggest that the spindle-shaped cells, like periosteum, are precursors of the osseous tissue found in FOP lesions (15). In general, lesional biopsies are not needed to reach the diagnosis FOP. In fact, biopsies are contraindicated as these exacerbate the condition (26,41).

Attempts to understand pathogenesis have viewed FOP lesions as a reaction to dystrophic calcification (43,47,48). Biochemical studies have shown normal calcium and phosphate balance, normal levels of parathyroid hormone, normal tubular handling of phosphate, and normal responsiveness to parathyroid stimulation (9,38). Skin fibroblast studies using a fluorometric assay system have shown normal qualitative and quantitative regulation of alkaline phosphatase (10).

Clinical evidence indicates that lesions tend to be located near flat bones that are formed primarily by membranous ossification. Lack of involvement of the abdominal wall, perineum, and internal viscera strongly suggests multifocal rather than truly systemic disturbance.

In 1990, Kaplan et al (24) reevaluated the data on the natural history of FOP and discovered the similarity between FOP and the anomalies induced by mutations in the decapentaplegic (dpp) gene in Drosophila. The Drosophila dpp gene shows strong homology with the human bone morphogenetic protein (BMP) gene (27), which raised the possibility that FOP is caused by mutations in BMP, especially BMP4. The BMPs are potent bone-inducing morphogens that participate in the developmental organization of the skeleton. Overexpression in lymphocytes of BMP4 and its mRNA was found in patients with FOP recently (44), but it remains

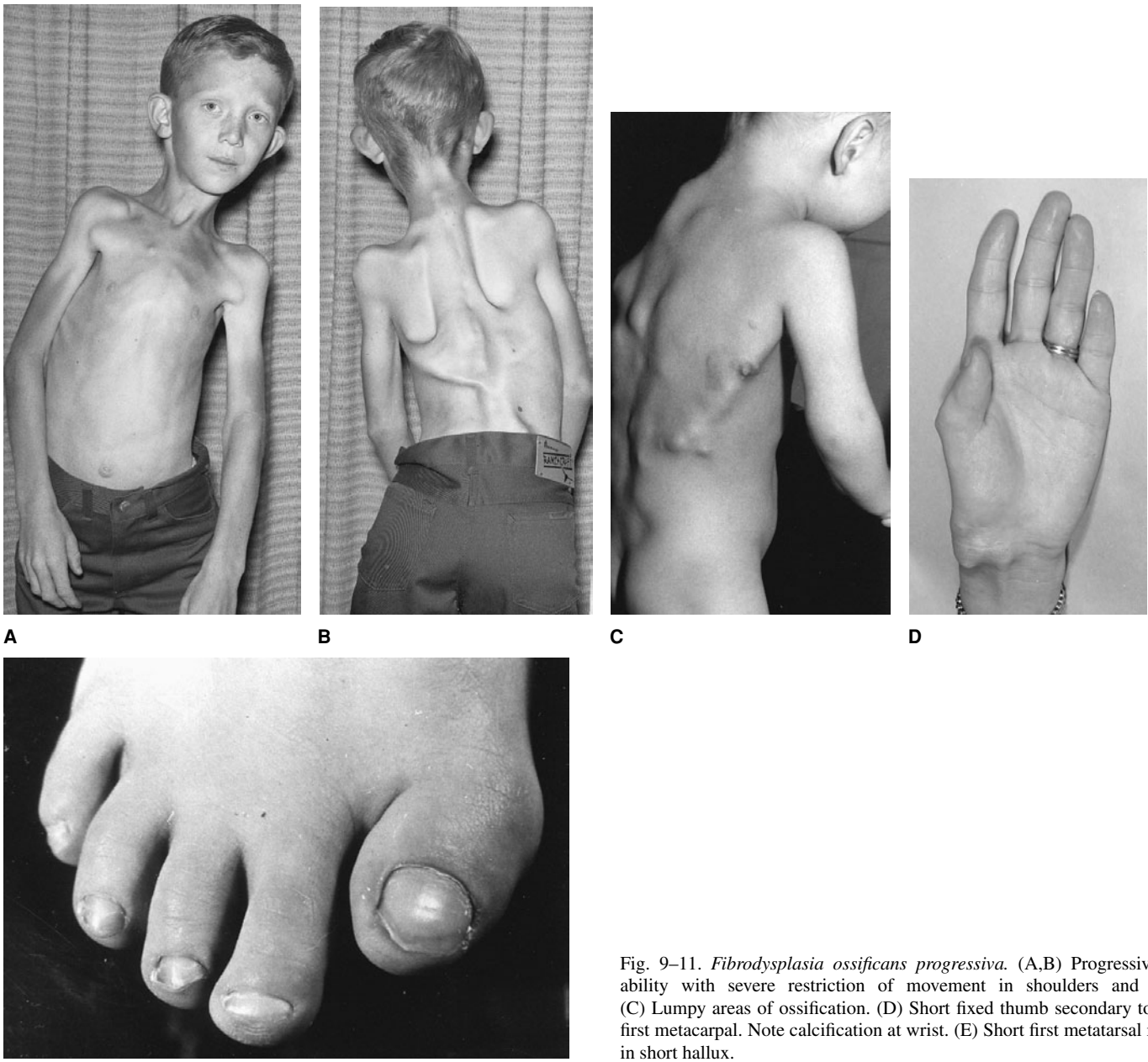
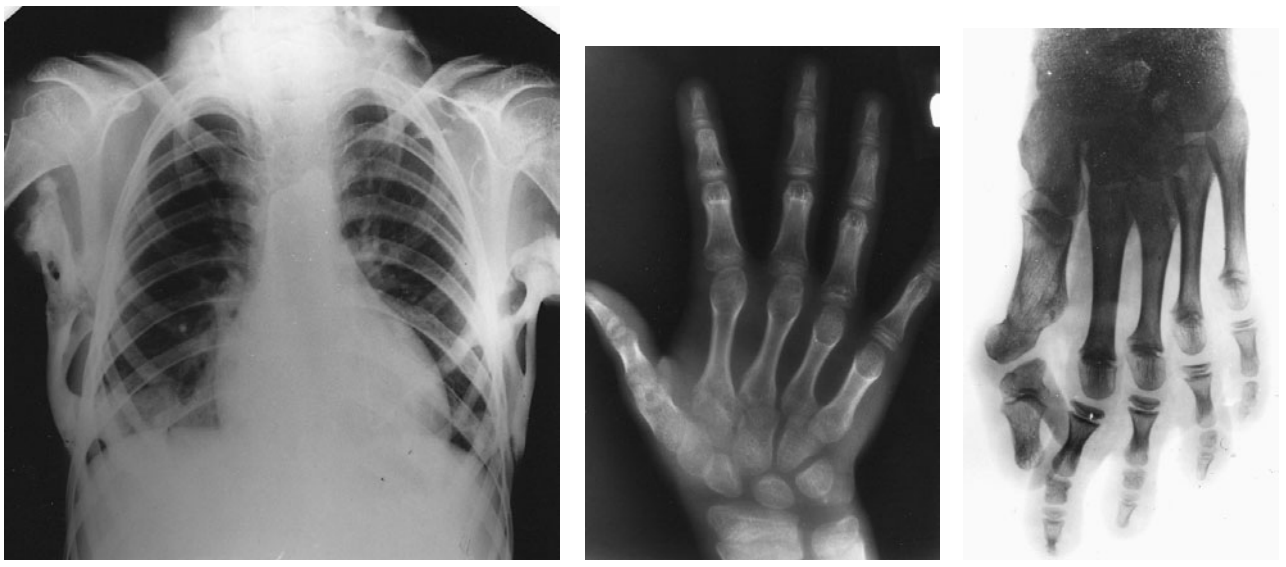


Fig. 9–11. *Fibrodysplasia ossificans progressiva.* (A,B) Progressive disability with severe restriction of movement in shoulders and spine. (C) Lumpy areas of ossification. (D) Short fixed thumb secondary to short first metacarpal. Note calcification at wrist. (E) Short first metatarsal results in short hallux.

uncertain whether this is a primary or secondary event. BMP4 is located at chromosome 14q22–q23.

Musculoskeletal findings. All patients have skeletal abnormalities of the hallux (Figs. 9–11E and 9–12C) that are present at birth and vary from short halluces consisting of a single phalanx, to normal length halluces that are stiff from early childhood and show progressive osseous fusion, hallux valgus, sometimes with osteophytic lipping. Variable other reduction defects have been observed (12,16,52). Other skeletal abnormalities include short thumbs due to short first metacarpals (Figs. 9–11D and 9–12B); clinodactyly of fifth fingers; short broad femoral necks; abnormal cervical vertebrae with small bodies, large pedicles, and large spinous processes; progressive bony ankylosis of the cervical spine (Fig. 9–11A–C); widened metaphyses; and, occasionally, exostoses of the proximal tibiae (12,33,36,41,45). Although regular CT scanning or MRI studies are not indicated, it is important to distinguish the nonspecific findings from those found in soft-tissue tumors, to prevent invasive procedures (7,28) (Table 9–1). Enchondroma has been described (51) but is likely to be coincidental. Limb swelling may be considerable (34).

Ectopic ossification is progressive and begins in early childhood (mean age of 5 years) (8) (Fig. 9–12). The site of onset is most commonly the neck or paraspinal region (spine, shoulder girdle) and less commonly the head or limbs. When new lumps appear, reddening of the overlying skin may occur and pain may sometimes be present. Certain areas within the connective tissue are prone to ossification, especially the paraspinal muscles, limb girdle muscles, and the muscles of mastication. Permanent restriction of mandibular opening has been noted in over 50% and usually presents during adolescence following dental treatment, especially mandibular block anesthesia (7a,31). Involvement of joint capsules, ligaments, and plantar fasciae is common. The progress of ossification proceeds according to characteristic anatomical patterns: dorsal to ventral, cranial to caudal, axial to appendicular, and proximal to distal (8,12). The diaphragm, extraocular muscles, heart, and smooth muscles are spared from ossification. In FOP patients, various factors are known to precipitate ectopic ossification, such as muscle trauma, biopsy, surgical procedures to excise ectopic bone, intramuscular injections, careless venipuncture, and dental treatment (12,29,33,41,46). All patients eventually develop restriction of movement and physical



A B C

Fig. 9–12. *Fibrodysplasia ossificans progressiva.* (A–C). Note calcifications, short first metacarpal and first metatarsal, and fusion of first metacarpal with proximal phalanx.

handicap: by the age of 15 years, 95% of a group of 44 patients had severe restricted mobility of the upper limbs (8). Episodes of ossification and subsequent disability are characteristically erratic. The disorder is known to have long periods of inactivity. Although ectopic ossification is most marked prior to puberty, new lumps may occur during the sixth and seventh decades. Chest wall fixation may lead to diminished pulmonary reserve, and most patients eventually die from respiratory failure (13). Although several treatment strategies have been tried, none has proven to be completely effective (3,4,6). Avoidance of trauma is paramount.

Table 9–1. Features of fibrodysplasia ossificans progressiva[a]

Feature	Percentage
Abnormal hallux	100
Type I (one phalanx)	79
Type II (two phalanges with progressive bony fusion)	9
Type III (two phalanges with osteophytic lipping)	6
Type IV (variable reduction defects)	6
Short thumbs secondary to short first metacarpals	59
Clinodactyly, fifth finger	44
Short broad femoral necks	55
Ectopic calcification, site of onset	
Neck	38
Paraspinal region	32
Head	9
Limbs	12
Joint involvement	
Spine	100
Shoulder	100
Elbow	55
Wrist	7
Hip	59
Knee	38
Ankle	32
Temporomandibular	71
Hearing loss[b]	24
Diffuse thinning of hair[c]	24
Mental deficiency	6

[a] Adapted from data in JM Connor and DAP Evans, J Bone Joint Surg Br 64:76, 1982.
[b] Of these 63% were conductive.
[c] Of these 75% were female.

Other findings. Baldness occurs in approximately 25% of all patients, becoming evident in middle age, and in the majority of females. It appears to be a primary feature of FOP. Mental deficiency is found only as a low-frequency abnormality (12,33). Hearing loss has been reported in at least 25% of patients (10,33,41); in two-thirds, it is conductive; in one-third, sensorineural. It may manifest in infancy to late childhood.

Differential diagnosis. Delayed diagnosis is commonplace in patients with FOP even though they have characteristic skeletal malformations (6,49). Common misdiagnoses are hallux valgus, diaphyseal aclasia, *Klippel-Feil anomaly*, and various forms of arthrogryposis. Swellings, depending upon their site, may be mistaken for lymphadenopathy, sarcoma, or even mumps (9). A number of entities have similarities to FOP, including osseous metaplasia (49), *Albright hereditary osteodystrophy*, extraskeletal osteosarcoma (2,49), dermatomyositis, myositis ossificans with a previous history of trauma (1,35), and bone formation occurring with pilomatrixoma (16).

Laboratory aids. Diagnosis depends on clinical and radiographic demonstration of characteristic skeletal malformations. Routine laboratory tests are usually normal (48); biopsy of lumps should be avoided (26,41), as should careless venipuncture, intramuscular injections, and surgery to excise ectopic bone. Dental treatment should be carried out cautiously and anesthesiologists should be aware of the possibility of atlantoaxial subluxation and also that intubation may be technically difficult because of fixation of the jaws (12,30,31).

CT scanning, ultrasonography, and scintigraphy have all been employed in diagnosis (17).

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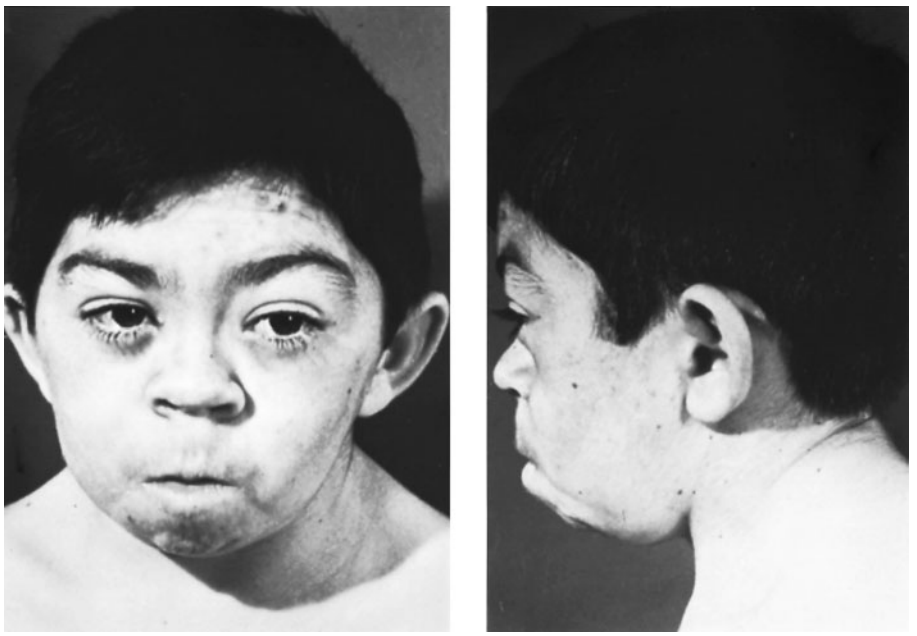
Hajdu-Cheney syndrome (acroosteolysis)

The Hajdu-Cheney syndrome consists of dissolution of the terminal phalanges, bizarrely shaped skull, premature loss of teeth, and short stature (Figs. 9–13 to 9–17). It was first described by Hajdu and Kauntze (18) in 1948. Cheney (6) reported familial occurrence in 1965.

The syndrome has autosomal dominant inheritance with very variable expressivity (6,11,35,54,60), but the vast majority have been isolated examples. About 50 patients have been described (1–6,8–14,17,18,20–22, 24–26,28,35,36,38–43,45,46,49,50,52–55,57,58,60–63). A few examples are less certain (34,37). We cannot identify some presumed cases (48). No patient with a chromosome defect has been described, nor is there any clue regarding the gene(s) involved. Crifasi et al (8) provide a useful tabulation of patients.

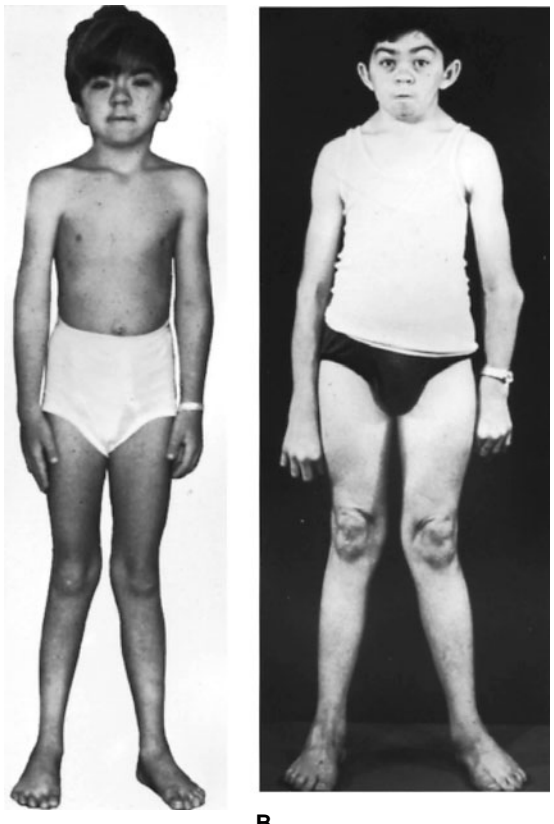
Facies. The face is characteristic (Figs. 9–13 and 9–14). The head appears disproportionately large. The scalp hair and eyebrows are thick and coarse with synophrys. The hair is low on the forehead and nape. The outer supraorbital ridges are often enlarged. There may be mild exophthalmos and hypertelorism. The midface is somewhat hypoplastic and the philtrum is long. The lower third of the face is shortened, probably in large part due to premature loss of teeth. The mouth tends to be small and the chin usually recedes, although prognathism has been described (18). The neck is often short. The ears are low-set. Conduction



A B

Fig. 9–13. *Hajdu-Cheney syndrome*. (A,B) Unusual facies marked by midface hypoplasia, fullness of outer supraorbital ridges, mild hypertelorism, small mouth, and receding chin. (A,B from A Matisonn and F Zaidy, S Afr Med J 47:2060, 1973.)

Fig. 9–14. *Hajdu-Cheney syndrome*. (A) Ten-year-old boy exhibiting shortness of stature, hirsutism, genua valga, unusual facial appearance. (B) Compare with 18-year-old boy. Note similar, somewhat more square-appearing face, bushy eyebrows, and subluxation of radial head. (A from J Herrmann et al, Z Kinderheilkd 114:93, 1973. B from A Matisonn and F Ziady S Afr Med J 47:2060, 1973.)



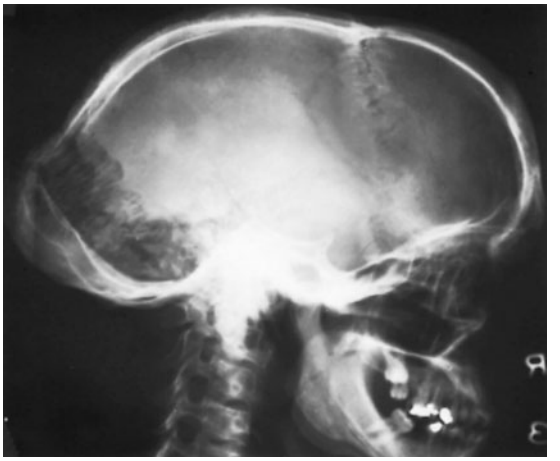
A B

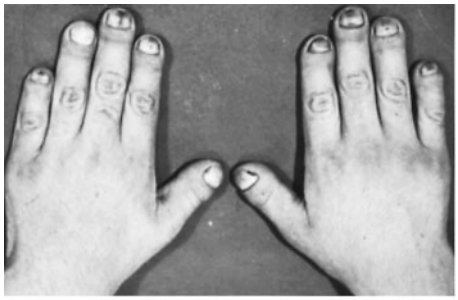
(1,8,9,18,49,54,57,58,60) and sensorineural (14,20,55) hearing loss have been noted in a number of cases. Myopia, epicanthal folds, nystagmus, reduced visual fields, abducens palsy, disk pallor, morning glory pupil, and optic atrophy have been found (1,2,14,18,22,57,60). One patient had cataract (25).

Skin. Generalized hirsutism is relatively frequent. The skin may be somewhat more elastic than normal (22,37). The nails are often wider than they are long and may become coarse and curved (1,2,11,25,37). Prominent sweat pores in axillae, groin, and neck have been reported (1). Kaler et al (24) described concomitant psoriasis; Nishimura et al (39) described the skin as being coarse and scaly.

Central nervous system. A serious complication can result from impaction of the cerebellum into the foramen magnum (18,22,27,35,45, 49,60). This can cause occipital headache, hydrocephaly, and progressive neurologic deterioration with involvement of the lower cranial nerves (gruff or low-pitched voice, paralyzed palate, anesthesia of pharynx)

Fig. 9–15. *Hajdu-Cheney syndrome*. Bathrocephaly with many wormian bones in suture lines, depressed anterior fontanel, and basilar impression. (From WD Cheney, Am J Roentgenol 94:595, 1965.)





A

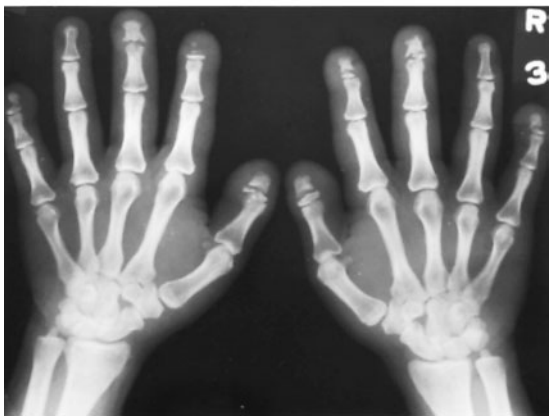


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Fig. 9–16. *Hajdu-Cheney syndrome.* (A) Abbreviated terminal phalanges. (B) Lytic alterations of terminal phalanges. (A from A Matisson and F Ziady, S Afr Med J 47:2060, 1973. B From WD Cheney, Am J Roentgenol 94:595, 1965.)

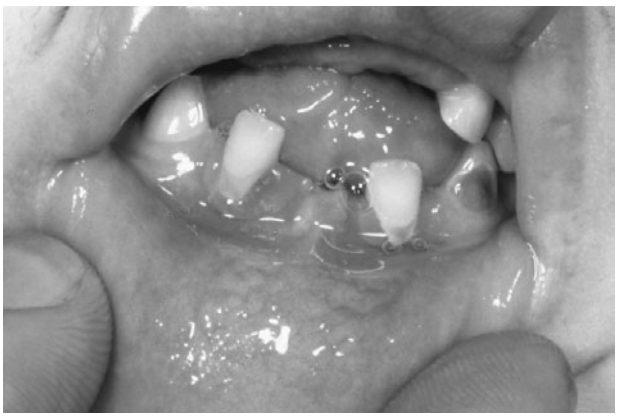
and cerebellar dysfunction (1,2,8,20,22,25,27,28,43,45,57,58,60). Seventh nerve palsy has also been noted (2), as were anosmia (8), trigeminal neuralgia (38), vocal cord paralysis (14), and syringomyelia (50).

Musculoskeletal alterations. Progressive basilar invagination, dolichocephaly, and unusual protuberance of the squamous portion of the occipital bone (bathrocephaly) are striking. Widening of the metopic, coronal, and lambdoidal sutures with multiple wormian bones and depression at the anterior fontanel are evident in most patients (Fig. 9–15). The frontal sinuses are absent and the maxillary antra underdeveloped. The sella turcica is enlarged, elongated (J-shaped), and wide open with slender clinoids (Fig. 9–15). The anterior nasal spine resorbs (54). The mandibular condyles are positioned anterior to the glenoid fossae and there may be resorption of the condylar heads (2) or mandibular rami (16). The mandibular chin button is often missing.

Adult height has ranged from 140 to 157 cm but decreases with age (11). This is in part due to progressive kyphosis and/or scoliosis, marked osteoporosis (40), and compression of thoracic vertebrae. There is associated pain (5,6,18) due, in part, to compression fractures of the spine. Extension and flexion of the neck are often limited (21). The superior and inferior surfaces of the vertebrae are concave, assuming a "fish-bone" shape (60). The cervical spine is often straighter than normal (4,52). Syringohydromyelia has been reported (1,39). Intervertebral disks may appear denser than the vertebral bodies.

Shortening and clubbing due to resorption of the distal portion of fingers and toes, primarily the former, begin around the third or fourth year of life. In severe cases, the middle phalanges can be involved (6,10,11). The terminal portion of the thumb is especially abbreviated (6,42,54) (Fig. 9–16). All joints are somewhat hyperflexible, especially the interphalangeal joints. Hip dislocation has been reported (3). Pain or paresthesia may be experienced in the joints, especially on motion (49). Genua valga is frequent. Long bones, metacarpals, and metatarsals often fracture (4,6,10,39,42,45,47). The metaphyseal area of metapodial bones tends to undergo dissolution. Narrowing of the metacarpophalangeal and/or metatarsophalangeal spaces (6,9,17,18,47) and osteolysis of the radial head (18,55) have been documented. The tibiae and fibulae may be somewhat curved, and some patients have a proximal anterior tibial groove. Some patients have exhibited fusion of the dorsal processes of the third to fifth cervical vertebrae. Radial dislocation has also been noted (1,14,25,35,41,61). Clubfeet (1,2,8,37,47,57) and umbilical and/or inguinal hernia (1,25,49,57) have been reported in a few cases.

Fig. 9–17. *Hajdu-Cheney syndrome*. Early loss of teeth due to periodontal disease.



Genitourinary findings. Anomalies have included renal cortical cysts (2,8,13,14,25,32,45,61), glomerulonephritis (45), urinary reflux (14,25,58), hypogonadism (1,2,35,41), cryptorchidism (1,22,25), and hypospadias (8,61). The polycystic kidneys may lead to hypertension and early chronic renal failure (13,14,25,45).

Other findings. VSD (1,8,49,54), patent ductus arteriosus (1,3, 25,61), aortic and mitral regurgitations and aortic stenosis (24), and malrotation of the bowel (25,43,54) have been reported.

Oral manifestations. Early loss of teeth due to periodontal disease with marked resorption of the alveolar ridges within 6 months after loss of teeth is an almost constant feature (2) (Fig. 9–17). Permanent teeth are often impacted. Malocclusion is constant. Molar roots may be resorbed (2,10,42). Cleft palate, cleft uvula, and velopharyngeal incompetence have been mentioned (4,8,25,27,45,49,60). The mandible, small in childhood, may become relatively prognathic with age (57).

Differential diagnosis. The term "acroosteolysis" is used nonspecifically to refer to dissolution of the terminal phalanges of the hands and feet. Acroosteolysis may also be seen in *pycnodysostosis, progeria, mandibuloacral dysplasia, epidermolysis bullosa, Murray-Puretić-Drescher syndrome, Winchester syndrome*, Gorham disease, scleroderma, syringomyelia, leprosy, syphilis, psoriasis, trauma, dominant acroosteolysis, neurogenic ulcerative acropathy, manual exposure to polyvinyl chloride intoxication, and a host of other disorders (7,11,15,19,23,26,29–33, 48,59).

The *serpentine fibula syndrome* (12) has been suggested to be allelic to Hajdu-Cheney syndrome (13,25,44). There is also resemblance with *Melnick-Needles*, and *Ter Haar syndrome* (51,56). Rosser et al (46) provide a useful comparison with the latter entities. A very severe case of massive osteolysis, in part, resembled Hajdu-Cheney syndrome (31).

Laboratory aids. Several investigators (4,22,35,55) described somewhat elevated serum alkaline phosphatase levels but others have noted normal values (11,57). Vanek (55) found elevated acid phosphatase. Brown et al (4) noted elevated plasma beta-glucuronidase activity. Growth hormone deficiency has been found but needs confirmation (47).

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Infantile cortical hyperostosis (Caffey-Silverman syndrome)

Although infantile cortical hyperostosis was originally described by Röske (36) in 1930, it was not until 1945–1946 that the clinical and radiographic studies of Caffey and Silverman (11) and of Smyth et al (42) called attention to it. The disorder affects infants under 6 months of age and is generally a benign and self-limited disorder. Its most constant features are bilateral swelling over the mandible or other bones, radiographic evidence of new bone formation in the area, hyperirritability, and mild fever. At least 250 cases have been recorded. A number of large series have been published (10,18–20,22,38) and, although sporadic cases have far outnumbered familial cases, autosomal dominant inheritance with incomplete penetrance and variable expression has been repeatedly demonstrated (1,4,15,17,19,20,34,38,43,46). It has been stated that the sporadic form has occurred less frequently during the last decades (32).

Saul et al (38) and MacLachlan et al (32) indicated that familial infantile cortical hyperostosis differed in several respects from sporadic examples, the former having an earlier onset of disease (24% at birth),

less frequent mandibular, ulnar, and clavicular involvement, no involvement of ribs and scapulae, and more frequent lower extremity involvement. Onset in the sporadic form is at 10 weeks, a bit later than the 7 weeks in the familial form (32). The disorder has been observed as late as 20 months after birth (20,25,27). Blank (6) indicated that some unexplained episodes of pain and cortical thickening in older children may represent recurrences in patients in whom the infantile phase of the disease has not been severe enough to call attention to it. A severe prenatal form is likely to exist (2,14,28,30,31,48), characterized by polyhydramnios, extensive skeletal involvement but with relative sparing of the clavicles, hands, and feet, edematous and sometimes short extremities, and frequent intrauterine or early neonatal death (48). Most cases with this form are sporadic, but familial occurrence has been described (14,48) and autosomal recessive inheritance can not be excluded. In one case (31), elevated IgA and C-reactive protein levels at cordocentesis pointed to an infectious cause.

Cayler and Peterson (12) estimated that the disorder was present in 3 of every 1000 registered patients under 6 months of age. It has been suggested that pathogenesis is based on congenital abnormality of the vessels supplying the periosteum of the involved bones, hypoxia effecting focal necrosis of the overlying soft tissue, resulting in new subperiosteal bone formation (40,41). A dog model exists (32).

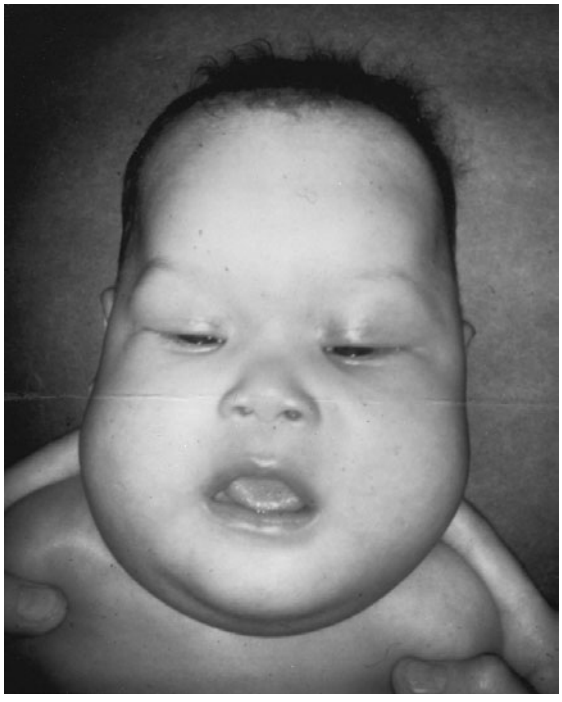
Here the sporadic and autosomal dominant cases will be described collectively.

Facies. Because of the swelling, the facies is so striking that the condition may be diagnosed with considerable assurance even prior to confirmatory X-ray evidence (24). The swelling is symmetric and located over the body and ramus of the mandible (Fig. 9–18). Pallor is often observed as well.

Soft tissues. The condition is initiated by tender, soft-tissue swelling over the face, around the orbits, thorax, or extremities; this swelling often undergoes remission and exacerbation (33). It is firm, brawny, and often so painful as to cause pseudoparalysis of an extremity (41). It is not accompanied by redness or increased heat.

Fever and irritability. Pain, fever of mild degree, and hyperirritability are seen in at least two-thirds of the patients (10,41). These signs commonly precede the appearance of the swelling and bone involvement. One or all may, however, be absent. Anemia, leukocytosis, and elevation of the sedimentation rate occur in more than half the patients (22,50).

Fig. 9–18. *Infantile cortical hyperostosis*. Note bilateral swellings over ramus of mandible.



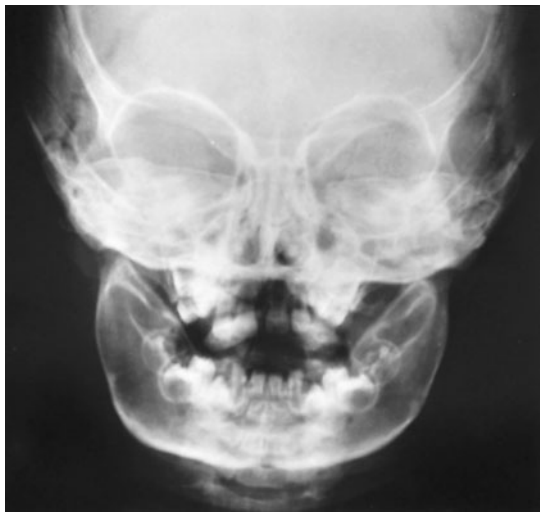
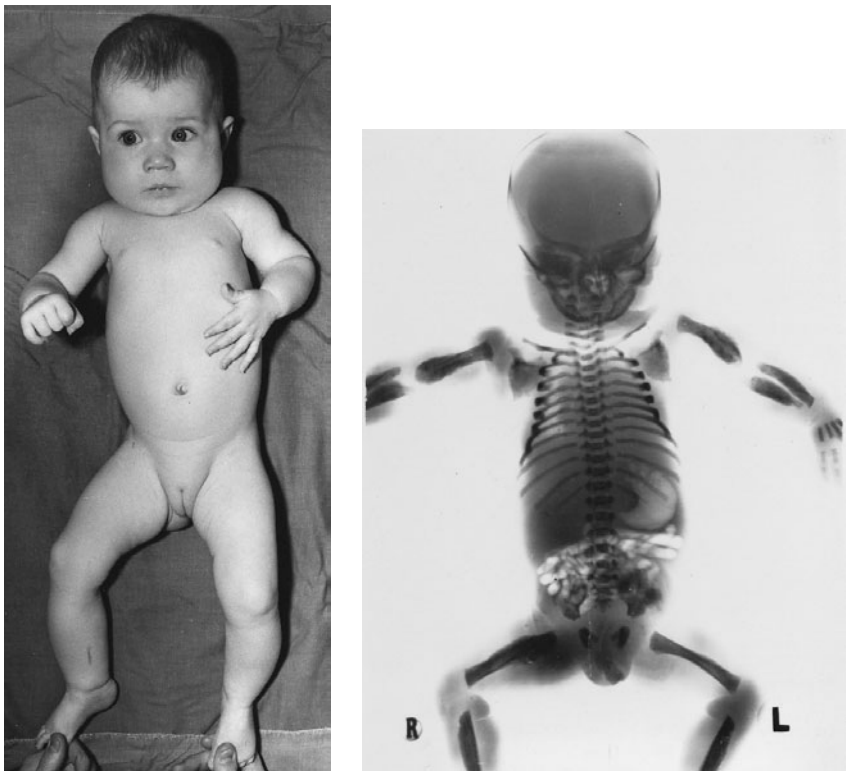


Fig. 9–19. *Infantile cortical hyperostosis.* Symmetric mandibular enlargement 6 months after onset of the disorder. (From PM Burbank et al, Oral Surg 11:1126, 1958.)

Skeletal system. The most frequently affected bone is the mandible, at least three of every four patients experiencing mandibular enlargement (Fig. 9–19). Less commonly involved are the clavicle, tibia, ulna, femur, rib, humerus, maxilla, and fibula (10,21–23,41,45,50). MRI studies have not had additional value (37). Usually several bones are affected at the same time (Fig. 9–20). As noted above, in the autosomal dominant form, the mandible, ulna, and clavicle are less often involved than in the sporadic form and the ribs and scapulae almost never (32). Lachaux et al (29) described sibs in whom the lesions were largely confined to the skull, sparing the mandible. New periosteal bone formation, appearing most often during the ninth week, undergoes resolution slowly. Though complete clinical resolution takes place within 3 to 30 months (average, 9 months), radiographic evidence may persist for many years (11,35). Bone bridges between the radius and ulna and between ribs have been described (11). Leg length inequality (11,23) and forward bowing of the tibia (20,25,32,49) are common. Pleural effusion has been reported in cases in which there has been rib involvement (11). Later recurrences of the disorder, although uncommon, have been described (6,8,22,35).

Oral manifestations. The oral findings have been discussed, in part, above. Involvement of the mandible was formerly thought to be necessary for diagnosis of the condition, but analysis of large series of cases has revealed that this is not so (41). Nevertheless, swelling of the jaws is the most common presenting sign. In a follow-up survey of 11 cases, Burbank et al (10) demonstrated that in six cases the mandible was the only bone involved. Follow-up showed that the fever had no effect on the enamel or on the eruption sequence. However, 8 of the 11 patients had radiographic evidence of residual bony asymmetry of the mandible at the angle and ramus, and some had severe malocclusion. Dysphagia has been noted (39).

Pathology. Several microscopic studies have been performed (8,9,35), the most comprehensive being that of Eversole et al (16), and are characterized by periosteal reactive bone formation associated with resorption of the immediate underlying cortex. In the early stages, foci of polymorphonuclear neutrophilic leukocytes are seen within the periosteum. The periosteum is swollen and mucoid in appearance, losing its well-defined limits and blending into the muscle, fascia, and tendons. At this stage, there is some resemblance to osteosarcoma, and erroneous diagnosis and treatment may result. The small arteries of the periosteum



A B

Fig. 9–20. *Infantile cortical hyperostosis.* (A) Involvement of mandible and lower extremities. (B) Thickening of periosteum and new bone formation in long bones. (A from JW Gerrard et al, J Pediatr 59:543, 1961.)

and overlying soft tissue show intimal proliferation. In the later stages, poorly vascularized and incompletely structured new bone is laid down. Neither hemorrhage nor inflammation is seen at this stage (22).

Differential diagnosis. Bocian et al (7) reported a newly recognized skeletal dysplasia that simulates infantile cortical hyperostosis, but differs in absence of induration, redness or tenderness over affected bones, absence of fever, and presence of transient neonatal cholestatic jaundice. Bowing of the lower extremities persisted after infancy. Inheritance is probably autosomal recessive. Also to be considered are epidemic parotitis (mumps), vaccinial and pyogenic osteomyelitis, parotid tumor, rickets, congenital syphilis, *osteogenesis imperfecta*, subperiosteal hematoma, scurvy, and vitamin A intoxication (13,25).

Kozlowski and Tsuruta (26), in 1989, described a seemingly new form of lethal neonatal dwarfism, which they called *dysplastic cortical hyperostosis*, that resembles the severe perinatal type of Caffey-Silverman syndrome. It was characterized by generalized symmetric cortical thickening and sclerosis of the long bones. The ribs appeared somewhat wavy. To be excluded are *I-cell disease* and G_{M1} *gangliosidosis.*

Laboratory aids. Radiographic study not only of the mandible but of the chest and long bones confirms the clinical impression. Serum alkaline phosphatase is elevated in cases with marked bone deposition (22). In over 80%, the sedimentation rate is elevated. Anemia and leukocytosis are common. Elevated IgM and thrombocytopenia have also been noted (44,47). Prenatal diagnosis by radiography (2,3,5,28,30) and echography (31,43), using bowing of the tibia and an irregular cortex of the long bones as indices, has been accomplished. The variable severity and onset possibly only late in the third trimester make prenatal studies less reliable.

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Kenny-Caffey syndrome (tubular stenosis, Sanjad-Sakati syndrome)

Kenny and Linarelli (15) and Caffey (5) first described the syndrome of proportional growth retardation with macrocephaly, low birthweight, and episodic hypocalcemia with hyperphosphatemia leading to tetany. About 50 cases have been reported (1–25,27,28). Genetic heterogeneity appears likely (23). Vertical transmission was described three times (15,19,25), but multiple affected children born to normal parents (10,16,21,22) and consanguinity in 17 families (1,3,10,16,21,22) point to autosomal recessive inheritance. In one family, deletion at chromosome 22q11 was detected both in the four affected sibs and in their clinically unaffected mother (15). The finding was not confirmed in another, unrelated patient (28). The autosomal recessive form, known as Sanjad-Sakati syndrome, probably originated from the Mediterranean area. It maps to 1q42–q43 (2,6,20). Diaz et al (7) indicated that Sanjad-Sakati syndrome and recessive Kenny-Caffey syndrome are allelic. Patients with the recessive disorder show mental retardation, more obvious prenatal growth retardation, microcephaly, severe micrognathia, large low-set pinnae, deep-set eyes, small hands and feet, cryptorchidism, and micropenis (12,14,24), compared to those with the dominant form with normal intelligence, only postnatal growth retardation, macrocephaly, and dense bones. Patients with the recessive disorder are usually identified by neonatal seizures, tetany, or apnea due to hypocalcemia. Some exhibit immune deficits that result in neonatal sepsis or repeated infections. We cannot agree that the patient described by Wilson et al (27) has the disorder. Khan et al (16) provide a useful review.

The facies is only mildly dysmorphic. There are frontal bossing, high hairline, and diminished eyebrows and lashes (Fig. 9–21A,B). Ocular findings, found in 80%, have ranged from uncomplicated microphthalmia and hyperopia to extreme pseudopapilledema, vascular tortuosity, optic atrophy, and macular clouding (9). Corneal and retinal calcification has been seen on autopsy (4,18). Intracranial calcifications have been reported (4,22). Delayed tooth eruption and extensive caries can be present (16,22).

Adult height has ranged from 121 to 152 cm (18). The shafts of the long bones are narrow, with cortical thickening and stenosis of the medullary cavities (17) (Fig. 9–21C–E). Bone age is delayed in about 60%. There is mild brachymetacarpalia. Delayed closure of the anterior fontanel is very common in Western cases (90%) but rare in cases from the Middle East. Wide metopic suture with absent diploic spaces can be seen in about 80%. The patients of Majewski et al (19) lacked medullary stenosis. Mental development is usually normal, except in cases from the Middle East (16).

Episodic hypocalcemic tetany has been noted in about 70% (8,16,26), usually in cases with hypoparathyroidism. Anemia has been documented in about 30% (10). Growth hormone studies have been normal (18,19,22). Hoffman et al (13) reported two cases with microorchidism, of whom one patient had elevated levels of follicle-stimulating hormone with normal testosterone, and the other had Leydig cell hyperplasia.

References [Kenny-Caffey syndrome (tubular stenosis, stenosis, Sanjad-Sakati syndrome)]

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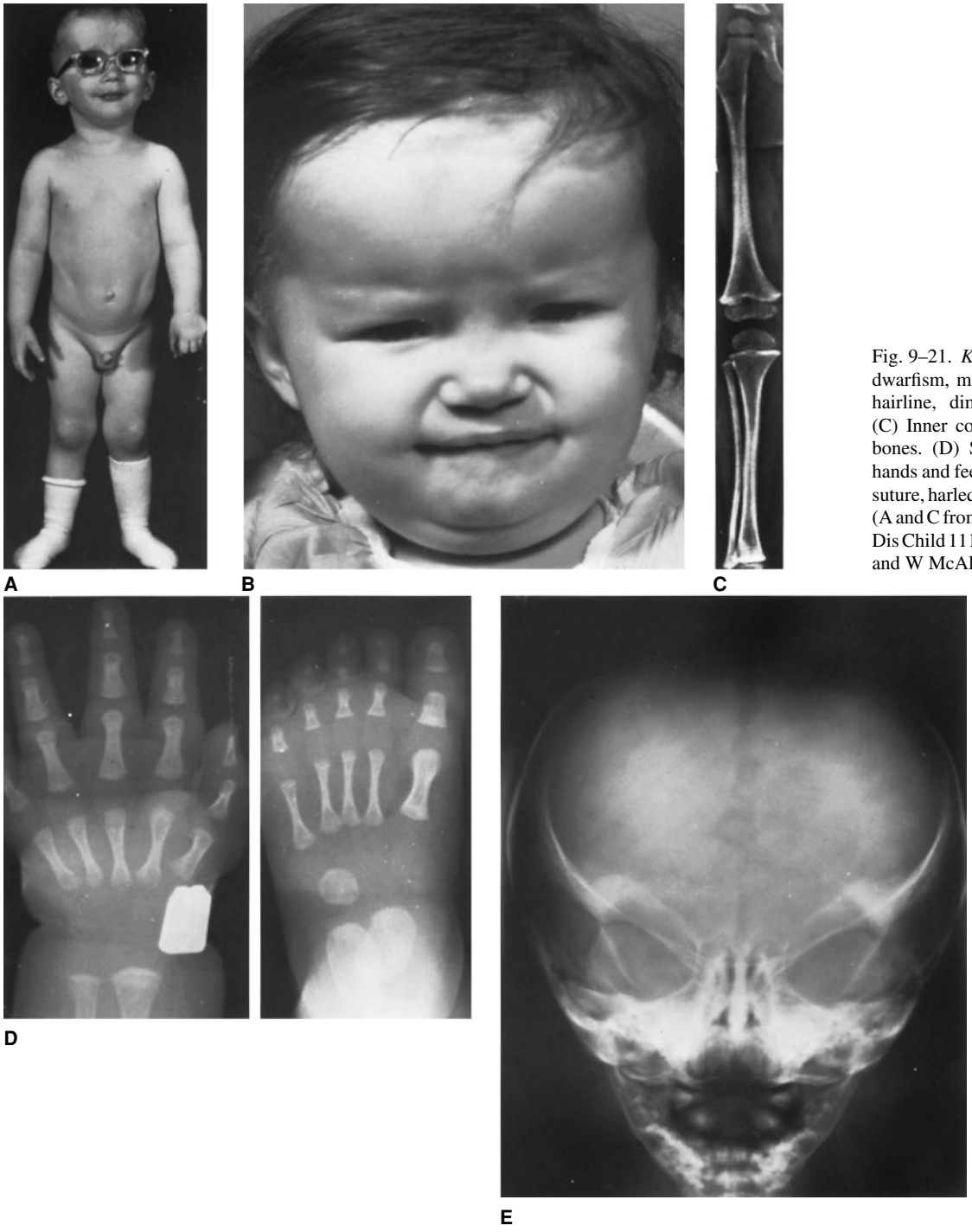

Fig. 9–21. *Kenny syndrome*. (A) Proportional dwarfism, myopia. (B) Frontal bossing, high hairline, diminished eyebrows and lashes. (C) Inner cortical thickening of thin tubular bones. (D) Similar appearance in bones of hands and feet. (E) Wide fontanel and metopic suture, harlequin configuration of orbital roofs. (A and C from FM Kenny and L Linarelli, Am J Dis Child 111:201, 1967. D and E from R Frech and W McAlister, Radiology 91:457, 1968.)

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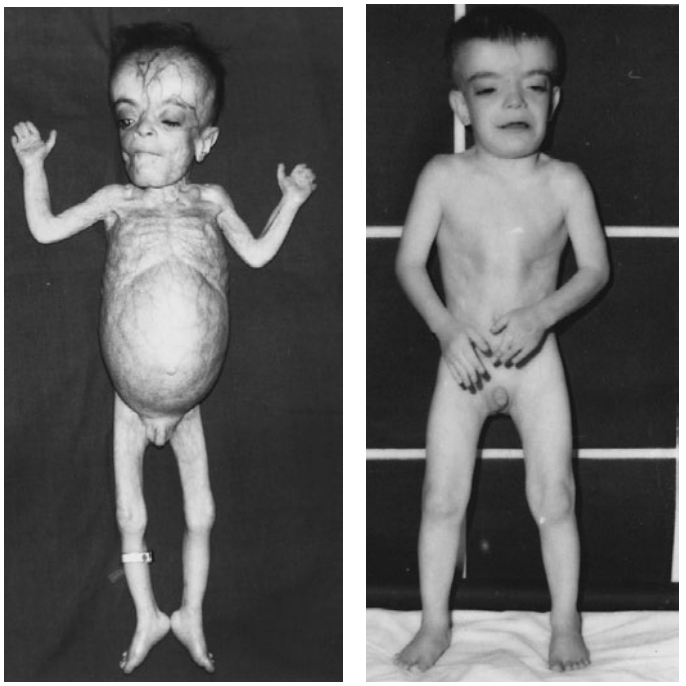


A B

Fig. 9–22. *Lenz-Majewski syndrome*. (A,B) Note disproportionately large head contrasting with reduced trunk and limbs. Note prominent veins and syndactyly in A. (From M Robinow, J Pediatr 91:417, 1977.)

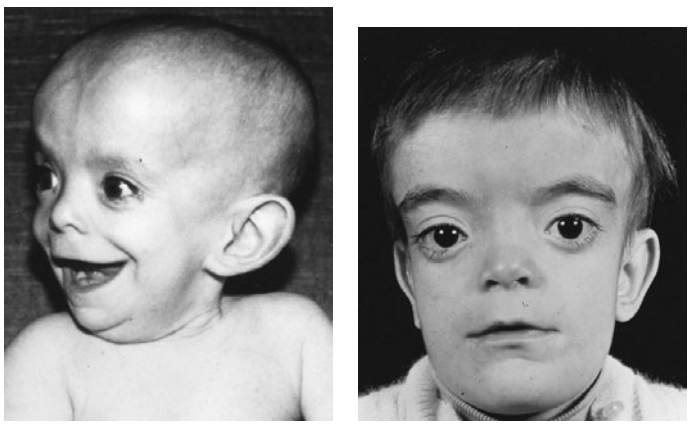
Lenz-Majewski syndrome

The syndrome characterized by large head, characteristic facies, loose skin, mental retardation, and skeletal findings (Figs. 9–22 to 9–25) was first reported by Braham (1) in 1969. This report went largely ignored until the entity was rediscovered by Lenz and Majewski (7) in 1974 and updated in 2000 (8). Eleven reported examples were reviewed in 1983 by Gorlin and Whitley (4). Additional examples are those of Elefant et al (3) and Chrzanowska et al (2).

All cases have been isolated. Paternal age appears advanced (4). Chromosome studies have been normal.

Facies. The head appears disproportionately enlarged with large fontanels and widely separated sutures that close late. The size of the head contrasts sharply with the reduced trunk and limbs (Figs. 9–22 and 9–23). Prominent veins, especially in the scalp, are evident. The ears are very large and floppy. Choanal atresia or stenosis and nasolacrimal duct obstruction are common. Hypertelorism is evident.

Fig. 9–23. *Lenz-Majewski syndrome*. Disproportionately large craniofacies. (A) Age 8 months. Note thin atrophic skin with prominent veins. (B) Note hypertelorism. (B from M Robinow, J Pediatr 91:417, 1977.)



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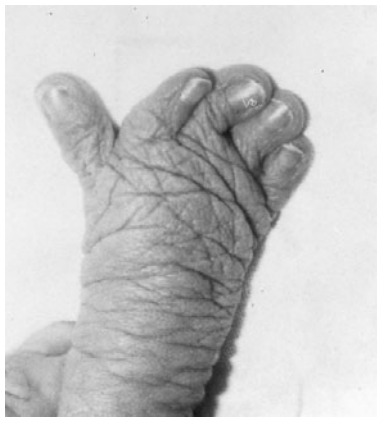

Fig. 9–24. *Lenz-Majewski syndrome*. Loose and wrinkled atrophic skin of hands with short digits and partial syndactyly.

Musculoskeletal. Inguinal hernia is common. The digits are hyperflexible and there may be generalized hypotonia (5). Radiographic features include progressive sclerosis of the skull (especially at the base), facial bones, and vertebrae. The clavicles and ribs are broad. The middle phalanges are short or absent. The long bones exhibit diaphyseal undermodeling and midshaft cortical thickening. However, there is marked hypostosis of the metaphyses and epiphyses. In general, skeletal maturation is retarded (Fig. 9–25).

Genitourinary. Cryptorchidism has been a uniform finding in affected males. Hypospadias and/or chordee have been noted (6,11). The anus may be anteriorly displaced.

Central nervous system. All children with the disorder have been mentally retarded, intelligence quotients ranging from 20 to 40. Sensorineural hearing loss is frequent. Agenesis of the corpus callosum has been seen (11).

Skin. The skin is thin, loose, wrinkled, and atrophic (Fig. 9–24). Veins, especially in the scalp, are prominent and cutis marmorata is evident (5). Proximal interdigital webbing of the fingers is frequent (4).

Oral manifestations. Tooth enamel has been defective in all patients. No microscopic studies have been carried out.

Differential diagnosis. Radiographically the disorders most often mistaken for Lenz-Majewski syndrome are *craniometaphyseal dysplasia* and *craniodiaphyseal dysplasia*. In contrast to those disorders, there does not appear to be any impairment of cranial nerves. One example was thought to represent *Camurati-Engelmann syndrome* (1). Nishimura et al (9) described a boy with a disorder that overlapped Lenz-Majewski syndrome, who lacked the diaphyseal hyperostosis and had, in addition, proximal symphalangism.

Laboratory aids. While alkaline phosphatase levels have been elevated in some cases (4,10), the significance is not known.

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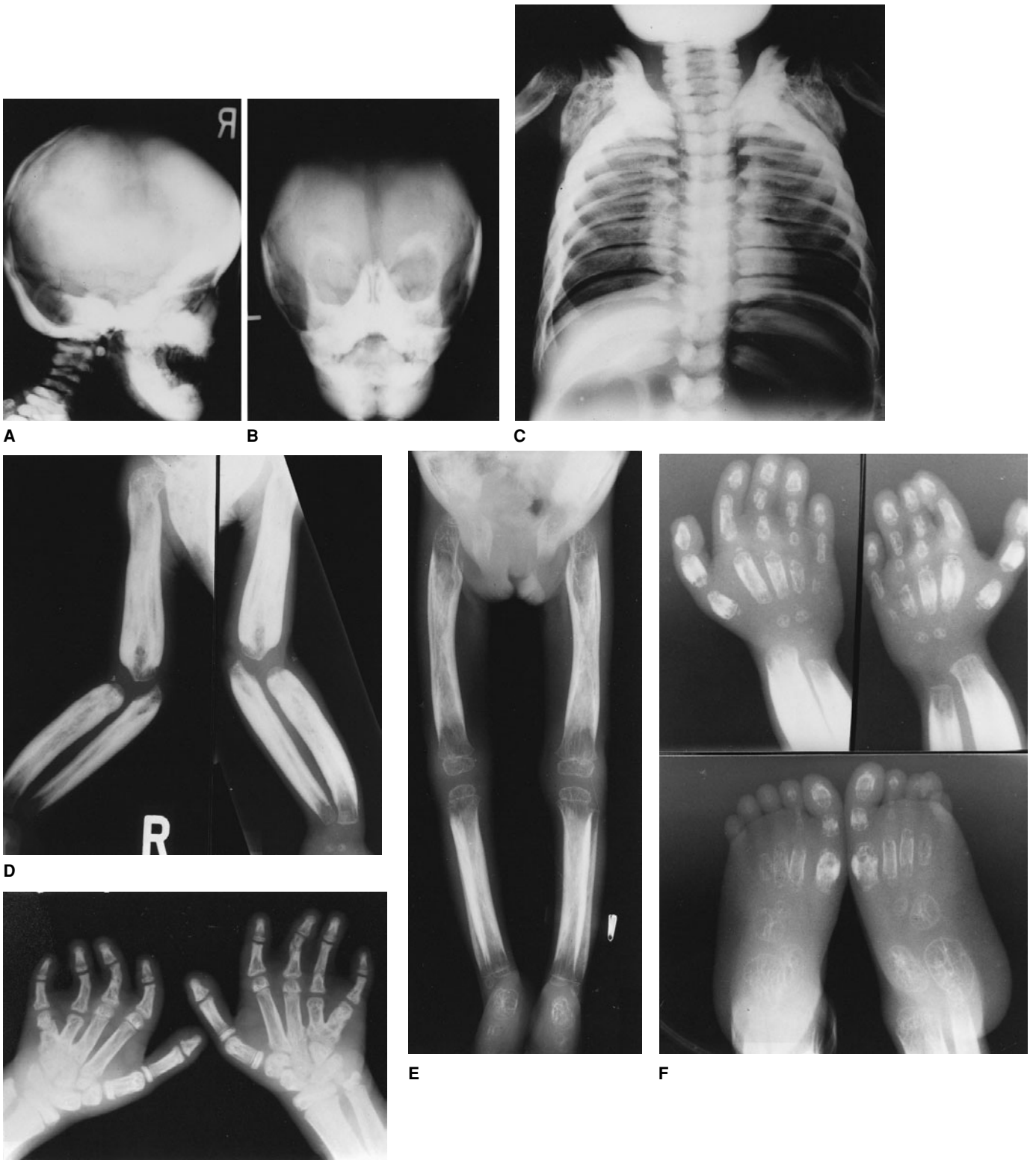

Fig. 9–25. *Lenz-Majewski syndrome*. Radiographs. (A,B) Hyperostosis of facial bones, cranial base, mandible, and proximal cervical spine; paranasal sinus and mastoids obliterated. (C) Hyperostosis of ribs, clavicles, scapulae. (D,E) Diaphyseal hyperostosis of long bones. (F) Hands and feet showing hypoplasia of bones on medial aspects of hands and lateral aspects of feet as well as diaphyseal hyperostosis. (G) Note abbreviated digits, absent middle phalanges, and clinodactyly. (A–F from RI Macpherson, J Can Assoc Radiol 25:22, 1974.)

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Mandibuloacral dysplasia

Cavallazzi et al (1), in 1960, were probably the first to report a syndrome characterized by short stature, delayed cranial suture closure, mandibular hypoplasia, dysplastic clavicles, abbreviated club-shaped terminal phalanges, acroosteolysis, and atrophy of skin over the hands and feet (Figs. 9–26 to 9–28), as an atypical form of cleidocranial dysplasia. Others reported cases but did not associate the disorder with that in Cavallazzi's patient or mistakenly classified their patients as examples of Werner syndrome (2,15), acrogeria (10,13), geroderma osteodysplastica (20), pycnodysostosis (14), and Hutchinson-Gilford progeria (3,16,18,26). Young et al (30) coined the name for this disorder. Danks et al (5) employed the term *craniomandibular dermatodysostosis* to describe the same condition. A total of 30 cases has been published (6a,19,24,27,28). The patient reported by Schrander-Stumpel et al (23) has an unusual severe presentation and may have another entity, possibly a collagen disorder. Toriello (27) provides a good review. The occurrence of the disorder in sibs strongly suggests autosomal recessive inheritance [12(sib mentioned in 24),16,17,19,21,25,27a,29,31]. Reports describe possible consanguinity (19,25,31). The disorder has an apparently high frequency in Italians (25). Onset of symptoms is usually between 3 and 14 years, but neonatal lethal cases are known (12,24). In some cases, the phenotype is unusually severe (5,20,23,27). Intelligence is normal.

Facies. The eyes are prominent. The nose is sharp or pointed (Fig. 9–26A–C). With age, the face becomes pinched. The scalp hair becomes sparse and lusterless, usually without graying, by the third decade, revealing the scalp veins. Some patients have alopecia (17,18). The mandible becomes progressively smaller and more recessed. Cataracts (6), hearing loss (6), and a high nasal voice (17,23) are unusual features.

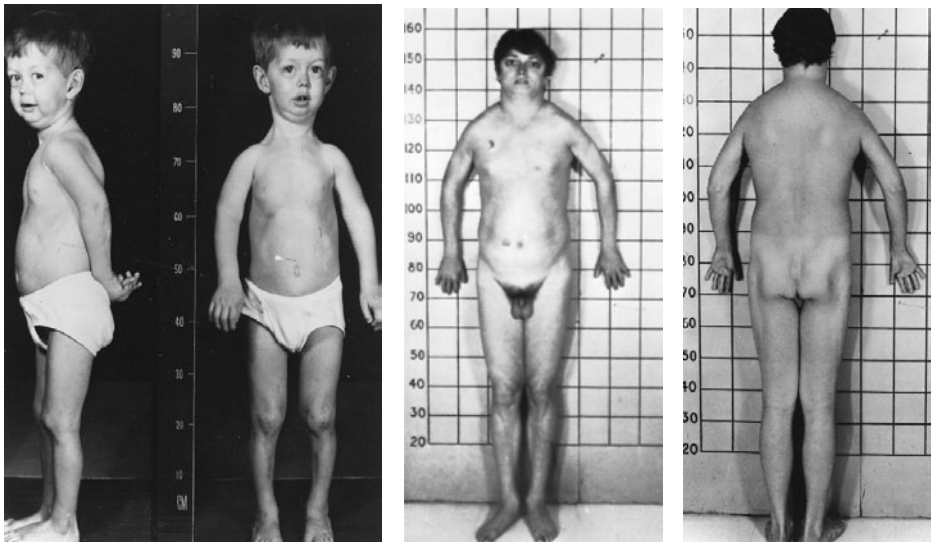
Musculoskeletal. Stature is usually reduced by 3 SD, although this is not always the case (6,17,23,29). There appears to be progressive stiffness of joints and swelling, and redness may occur. The shoulders become narrow, usually by the end of the first decade (Fig. 9–26A–D). The hands and feet appear small. The terminal phalanges are short and club-shaped, which, together with cutaneous atrophy, cause them to appear spatulate (Fig. 9–28).

Radiographic changes include slow osteolysis of the mandibular body and ramus, resulting in micrognathia with antegonial notching, delayed cranial suture closure and fontanel, numerous wormian bones, and acroosteodysplasia of fingers and toes (27) (Fig. 9–27). Clavicular osteolysis is progressive, eventuating in severe hypoplasia or aplasia. Delayed ossification of carpal bones is evident.

Variable findings include abnormal modeling of femur, humerus, and tibia with patchy thickening of cortex, hypoplasia of first through fourth ribs (25,29,31), coxa valga (21), avascular necrosis of femoral head (21), fish-mouthed vertebral bodies, and scoliosis (30). In one patient, MRI studies showed cortical atrophy (6). A follow-up of the patient reported by Danks et al (5) showed striking metaphyseal changes (27).

Skin. The skin over the hands and feet becomes atrophic and mottled giving a poikilodermatous appearance at about two years of age (Fig. 9–28). A mottled brown skin rash may extend over the trunk and extremities (6,9,14,17,20,23,29,30). Subcutaneous fat is diminished over the distal extremities, causing the veins and tendons to become evident. Fat deposits are marked over the abdomen (14,29). Calcium deposits frequently extrude from the scalp, ears, elbows, and, especially, fingertips. Plantar hyperkeratoses have been noted (15). The nails become brittle.

Oral manifestations. Mandibular hypoplasia with inability to open the mouth widely has been a common feature. Crowding of the mandibular teeth with absence of cellular cementum has been demonstrated (5). The roots are hypoplastic. The teeth are lost during adolescence (17,25,29,31).



A B C D

Fig. 9–26. *Mandibuloacral dysplasia*. (A–D) Short stature, sloping shoulders, thick trunk and neck, micrognathia. [A,B from DM Danks et al, Birth Defects 10(12):99, 1974. C,D from VA McKusick et al, Birth Defects 7(7):291, 1971.]

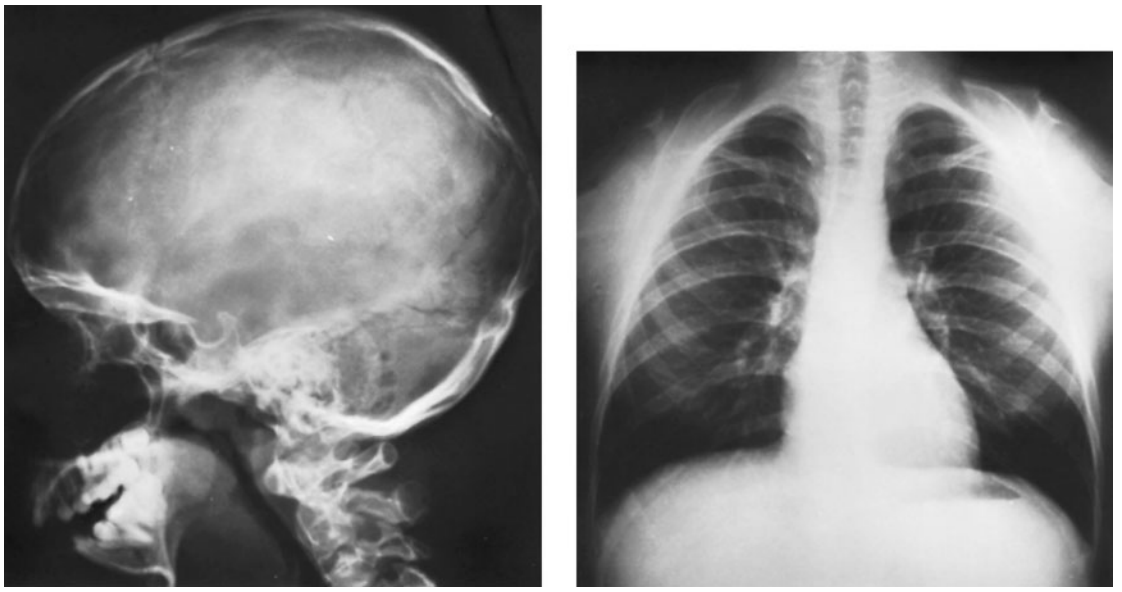


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Fig. 9–27. *Mandibuloacral dysplasia*. Radiographs. (A) Wide sagittal sutures and hypoplastic body and ramus of mandible. (B) Hypoplastic clavicles. [A,B from VA McKusick et al, Birth Defects 7(7):291, 1971.]

Other findings. Renal failure due to focal sclerosis (5,27) or focal tubular atrophy (6), hepatomegaly (6), anemia (31), glandular hypospadias (24), and delayed or absent sexual maturation (2,17,25,30) have been reported. At follow-up (27), one patient (5) proved to need a tracheostomy for airway difficulties.

Differential diagnosis. Similar cutaneous changes are seen in *progeria* and *Werner syndrome. Cleidocranial dysplasia* should easily be excluded. Acrometagyria (7,8) is probably a still different disorder (27).

Laboratory findings. Diabetes mellitus has been described (6,15). More extensive glucose metabolism studies showed a severe insulin resistance, which placed mandibuloacral dysplasia in the group of partial lipodystrophies (4,6). However, this seems not to have been present in other patients (25,29). It has been suggested that type III collagen anomalies may be present (3). Premature adrenocortical dysfunction has been found in one patient (16a).

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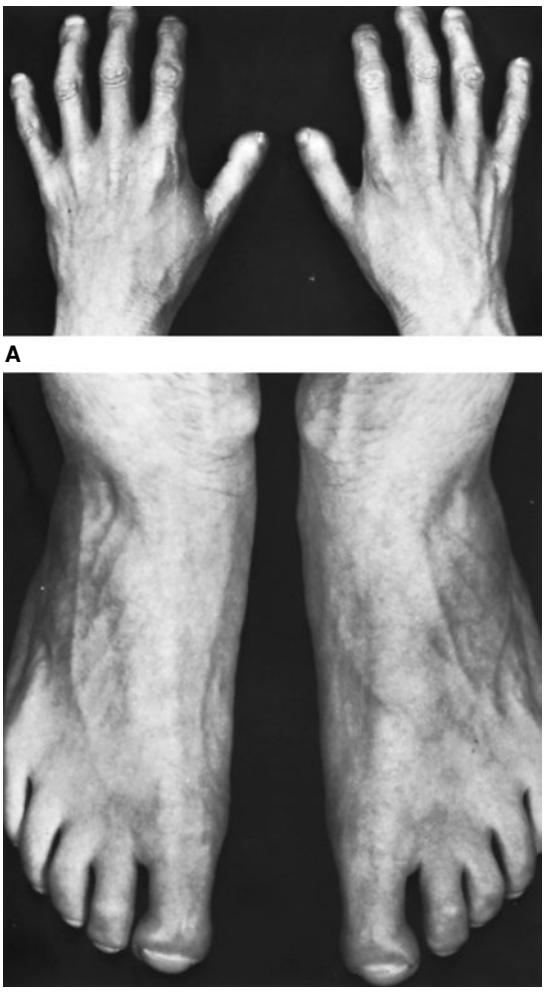
Fig. 9–28. *Mandibuloacral dysplasia*. (A) Short terminal phalanges and stiffness of interphalangeal joints. (B) Similar acroosteolytic alterations in toes. [A,B from VA McKusick et al, Birth Defects 7(7):291, 1971.]



A

B

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Marfan syndrome

The main features of Marfan syndrome include disproportionate skeletal growth with dolichostenomelia, ectopia lentis, and fusiform and dissecting aneurysms of the aorta. Marfan syndrome was first mentioned in the fifth century in the Babylonian Talmud. The French pediatrician Antoine-Bernard Marfan described a 5-year-old girl with skeletal manifestations of the disorder that now bears his name (89). It has been suggested that Abraham Lincoln had Marfan syndrome (56). Lincoln was known to have a Marfan-like habitus, and his son, Tad, had a flat face with cleft palate, raising the possibility of Stickler syndrome (64). A case has been made for Marfan's original patient having cystathionine synthase deficiency (homocystinuria) (13), but the most convincing argument has been made for congenital contractural arachnodactyly (9). The famous violin virtuoso Nicolo Paganini had long fingers and hyperextensible joints that were said to be attributable to Marfan syndrome (132). In 1986, the U.S. volleyball star Flo Hyman died from a ruptured aortic aneurysm associated with Marfan syndrome. This tragic event focused widespread public attention on the syndrome for the first time (60). The Dutch ophthalmologist Weve (159) was the first to demonstrate the autosomal dominant pattern of inheritance, and also suggested it to be a disorder of mesodermal tissues. A major contribution was made in 1955 by McKusick (94), who established the nosology of the heritable disorders of connective tissue.

Marfan syndrome has autosomal dominant inheritance with extremely high penetrance. Indeed, not a single case with nonpenetrance has ever been reliably documented. A patient who was asymmetrically affected is probably an example of somatic mosaicism (19). An example of gonadal mosaicism has been published (122). Affected sibs born to unaffected parents may well be explained by insufficiently detailed investigations of the parents, although genetic heterogeneity cannot be discarded (21,47). The homozygous state is lethal (21,133). The reported number of sporadic cases varies from 25% to 35% (88,103,106,115,116). Advanced paternal age at the time of conception was found to be associated with sporadic cases (88), although this was not found in another study (106). The earlier estimate of the prevalence of 4–6 per 100,000 (116) is probably an underestimate (115). The frequency is now estimated to be about 1 per 10,000 (60,114,115).

In 1990, the disorder was mapped to chromosome 15q21 (72). In that same year, Godfrey et al (53) and Hollister et al (67) reported diminished amounts of microfibrils in the skin of Marfan patients. Eventually, Dietz et al (39) reported that mutations in fibrillin type I gene cause the disorder. Fibrillin is a large glycoprotein and a major component of microfibrils, which interacts with elastin in elastic fibers and has anchoring functions in other tissues (97,109). Microfibrillin assembly is disturbed in Marfan syndrome (74,124a). The structure of the fibrillin gene is complex (110 kb, 65 exons, 10 kb of coding sequence) and has epidermal growth factor (EGF)-like domains and transforming growth factor (TGF)-like domains. Multiple mutations of all sorts have been found (38,73), confirming intragenic heterogeneity. No clear genotype–phenotype correlation exists (5,12,38), with the exception of mutations in the EGF domain 24–26, which are mainly found in severe, neonatal, sporadic Marfan patients (73,98). Two "hot spots" have been found in the fibrillin 1 gene in neonatal Marfan syndrome. The mutations often involve exons 24–27 with skipping of exons 31 or 32 (16).

Fibrillin-1 mutations are not restricted to patients with Marfan syndrome but can also be found in patients with familial aortic aneurysms, familial ectopia lentis, Shprintzen-Goldberg syndrome, the Mass phenotype (38,73), autosomal dominant Weill-Marchesani syndrome (160), and even familial tall stature (99). The so-called neonatal Marfan syndrome is not a separate entity, but is also caused by fibrillin-1 mutations (18,62,73,98). Hence, the presence of a mutation in the fibrillin-1 gene in itself is not a proof for the existence of Marfan syndrome.

In a related protein, fibrillin-2, located at chromosome 5q (151), mutations give rise to congenital contractural arachnodactyly (Beals syndrome) (112).

It still remains possible that Marfan syndrome has a heterogeneous cause: in a large French family with skeletal and cardiovascular anomalies fitting the diagnosis, but without the characteristic eye symptoms, linkage with the fibrillin genes was excluded (14), and a possible second locus has been mapped at 3p24.2–25 (28). Bonneau et al (15) described a neonate with a Marfan phenotype and cutis laxa, who had recurrent chromosome breaks at 7q31.3–32, possibly disrupting laminin B1. In another neonate with a Marfan phenotype, a mitochondrial complex I deficiency was found (23).

Animal models of the Marfan syndrome are available (12).

Criteria. In 1986, criteria for the diagnosis of Marfan syndrome were published (10). Over time, both emerging weaknesses in these criteria and molecular progress urged revision, which was published as the Ghent criteria (Table 9–2) (34). In general, at least two specific studies are required for the diagnosis: careful cardiac evaluation, including echocardiography, and slit-lamp examination of the eyes (114,117). In cases in which the diagnosis remains doubtful, radiographs of the pelvis to ascertain protrusio acetabulae, and (especially) MRI or CT of the lower vertebral column for lumbosacral dural ectasia, can be useful to establish diagnosis. In children, the criteria may not be met on first investigation, and establishing the diagnosis may need follow-up of years (85). Although many authors have tried to establish a radiographic criterion for arachnodactyly (metacarpal index), this is of very limited value and precision (149). The thumb (Steinberg) sign (the entire nail of the thumb projects beyond the ulnar border of the hand when the hand is clenched without assistance) and wrist (Walker-Murdock) sign (the thumb overlaps the terminal phalanx of the fifth digit when grasping the contralateral wrist) are more simple and more helpful, but are also subject to interpretation and are of limited value in differentiating Marfan syndrome from other hypermobility conditions (116,156) (Fig. 9–31C,D). In any patient, homocystinuria should be ruled out.

Table 9–2. Diagnostic criteria for Marfan syndrome

Family History

Major criteria
Having a parent, child, or sib who meets these diagnostic criteria independently:
Presence of a mutation in FBN1 known to cause the Marfan syndrome; or
Presence of a haplotype around FBN1, inherited by descent, known to be associated with unequivocally diagnosed Marfan syndrome in the family.

Minor criteria
None

For the family history to be contributory, one of the major criteria must be present.

Skeletal System

Major criterion—Presence of at least four of the following manifestations:
Pectus carinatum
Pectus excavatum requiring surgery
Reduced upper to lower segment ratio or arm span to height ratio greater than 20°
Positive wrist and thumb signs
Scoliosis or spondylolithesis.
Reduced extension of elbows (<170°)
Medial displacement of the medial malleolus causing pes planus
Protrusio acetabulae of any degree (ascertained on X ray)

Minor criteria
Pectus excavatum of moderate severity
Joint hypermobility
Highly arched palate with dental crowding
Facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)

For the skeletal system to be involved, at least two components comprising the major criterion or one component comprising the major criterion plus two minor criteria must be present.

Ocular System

Major criterion
Ectopia lentis

Minor criteria
Abnormally flat cornea (as measured by keratometry)
Increased axial length of globe (as measured by ultrasound)
Hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis

For the ocular system to be involved, at least two of the minor criteria must be present.

Cardiovascular System

Major criteria
Dilatation of ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva; or
Dissection of the ascending aorta

Minor criteria
Mitral valve prolapse with or without mitral valve regurgitation
Dilatation of main pulmonary artery, in absence of valvular or peripheral pulmonic stenosis or any other obvious cause, below the age of 40 years;
Calcification of the mitral annulus below the age of 40 years; or dilatation or dissection of the descending thoracic or abdominal aorta below the age of 50 years

For the cardiovascular system to be involved, a major criterion or only 1 of the minor criteria must be present.

Pulmonary System

Major criteria
None

Minor criteria
Spontaneous pneumothorax, or
Apical blebs (ascertained by chest radiography)

For the pulmonary system to be involved, one of the minor criteria must be present.

Table 9–2. (*cont.*)

Dura

Major criterion
Lumbosacral dural ectasia by CT or MRI

Minor criteria
None

Skin and Integument

Major criteria
None.

Minor criteria
Striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy or repetitive stress, or
Recurrent or incisional herniae
For the skin and integument to be involved, the major criterion or one of the minor criteria must be present.
Requirements of the diagnosis of Marfan syndrome
For the index case
Major criteria in at least two different organ systems and involvement of a third organ system
For a family member
Presence of a major criterion in the family history and one major criterion in an organ system and involvement of a second organ system.

Adapted from A De Paepe et al, Am J Med Genet 62:417, 1996.

Extensive long-term study of the natural history was reported by Marsalese et al (92) and Sun et al (144). The frequencies of major symptoms are shown in Table 9–3. A health supervision scheme has been proposed (36).

Craniofacial features. Dolichocephaly usually occurs with prominent supraorbital ridges (Fig. 9–29). This can result in a characteristic long face with deeply set eyes (due to decreased retrobulbar tissue) (104), prominent brows, downslanting palpebral fissures, hypoplastic malar eminences, and retrognathia (34,111) (Fig. 9–30).

Although earlier authors estimated the prevalence of a high palatal vault to be between 15% and 40%, some have observed this condition in all their patients (88,156). Cleft palate or bifid uvula has been reported in several instances (88). The teeth have been noted to be long and narrow and frequently maloccluded (31,156). Mandibular prognathism is common and temporomandibular joint disease is found more frequently than expected. Large maxillary sinuses may be noted radiographically (7).

Table 9–3. Characteristics of Marfan syndrome[a] ($n = 50$)

Clinical feature	%
Ocular	70
Ectopia lentis	60
Myopia	34
Cardiovascular	98
Prosthetic aortic valve	10
Aortic enlargement	84
Mitral valve prolapse	58
Musculoskeletal	100
Arachnodactyly	88
Upper/lower segment at least 2 SD below mean for age	77
Pectus deformity	68
High, narrow palate	60
Height greater than 95th centile for age	58
Hyperextensible joints	56
Vertebral column deformity	44
Pes planus	44
Striae distensae	24
Inguinal hernia	22
Family history	85
Additional documented cases of Marfan syndrome	85
Sporadic cases (new mutations)	15
Unclear or unknown pedigree	6

[a] From RE Pyeritz and VA McKusick, N Engl J Med 300:772, 1979.

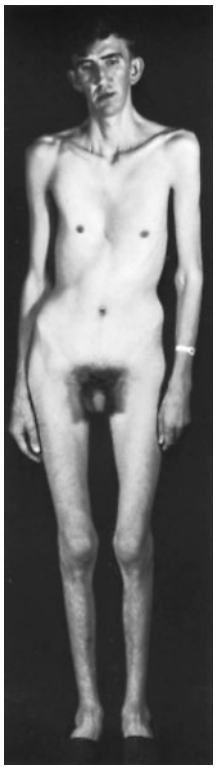


Fig. 9–29. *Marfan syndrome*. Patient has dolichostenomelia, arachnodactyly, scoliosis, pectus excavatum, and bilaterally subluxated lenses. (From N Tuna and AP Thal, Circulation 24:1154, 1961.)

Musculoskeletal system. Dolichostenomelia, defined by an upper segment–to–lower segment ratio (US/LS) of at least 2 SD below the mean, or arm-span-to-height ratio of at least 1.05, is found in 76% (116). Arachnodactyly occurs in 88% (Figs. 9–29 and 9–31A,B). Pectus excavatum, especially when asymmetric with the left costochondral junction more anterior, is most characteristic. Other features include pectus excavatum (6) and weakness of joint capsules manifested by pes planus (44%) and hyperextensibility of joints (56%) with recurrent dislocation (mainly first metacarpal-phalangeal joint and patellae) (108) (Fig. 9–31C,D). As joint hypermobility is common in the general population, it has by itself little diagnostic specificity. The elbows may show a limited extension in late childhood or thereafter (140). In coexistence with joint hypermobility elsewhere, this sign is more specific. Joint complaints are common at all ages. In later life, secondary arthritic changes occur commonly. Scoliosis may develop in childhood and worsen during periods of rapid growth, such as puberty (124,141), and can be accompanied by a thoracic or thoracolumbar kyphosis. More often, however, the physiologic thoracic kyphosis has disappeared or even a thoracic lordosis occurs. Spondylolisthesis is found in about 6% (141,146). Enlarged vertebrae and widened spinal cord have also been noted (116). The frequency of osteoporosis in older patients remains uncertain (59). An abnormally deep hip socket is very frequent (81) but is generally asymptomatic. The skull shows often dolichocephaly.

Fig. 9–30. *Marfan syndrome.* Enophthalmos, downward-slanted palpebral fissures, malar hypoplasia, narrow maxilla, retrognathia.

Ocular changes. Ectopia lentis, resulting from lax suspensory ligaments, is found in 50%–80% and is almost always bilateral and symmetrical (22,32,77,93). Dislocations are not found at birth, but are noted first at 10–14 days of age. They tend to progress in infancy and early childhood, and in early puberty. The direction of dislocation is upward in about 75% (93,104,106,116). The zonular fibers remain intact, permitting normal accommodation. Some degree of backward dislocation is frequently found. Anterior dislocation may cause glaucoma, but most cases of glaucoma are the result of surgical extirpation rather than acute blockage of the anterior chamber. Subluxation of the lens often causes the iris to flutter as the lens accommodates (iridodonesis). An enlarged axial diameter (especially above 25 mm) is responsible for the increased tendency to myopia that occurs most often in the first two decades.

An increased corneal diameter occasionally gives the appearance of megalocornea. The radius of curvature of the cornea can be studied by keratometry, and mostly shows corneal flattening. The degree of reduction in curvature is positively correlated with the presence of ectopia lentis (93). Hypopigmentation of the posterior iris epithelial layer permits transillumination of the iris in 10% (120). Dilatation of the pupil is often difficult because of hypoplasia of the ciliary muscle. Increased size of the eyeglobe accounts for choroid thinning, apparent microphakia, and blue sclerae. Ocular changes are also found in the anterior chamber angle, ciliary body, and pupil (3). The most frequent cause of visual loss is amblyopia from delayed refraction or inadequate correction of myopia; the visual loss is usually reversible. More than 80% of patients have normal vision, even with dislocated lenses. Rarely, Rieger anomaly has been noted (61). It is still uncertain whether early nuclear cataract and open-angle glaucoma occur more frequently in Marfan syndrome (34,70).

Cardiovascular abnormalities. Cystic necrosis of the vascular media leads to diffuse, progressive dilatation of the ascending aorta (123). The resulting aneurysm can be associated with increasing aortic regurgitation and congestive heart failure or dissection and rupture (43). Together, these constitute the leading causes of death in affected individuals. Before the development of an effective procedure for presymptomatic, elective repair of the aorta, the average age of death was 32 years (17,57,102), but during the last decades a considerable improvement in life expectancy has been reached, mainly due to prophylactic medication (136), prophylactic surgical interventions (138), and better survival after cardiosurgery (4,11,30,58,84).

Echocardiographic evidence of mitral valve prolapse is found in 68% (37,51,52,90,91,117). Valvular abnormalities may be present at birth and aortic dilatation is detectable by echosonography from early infancy (140). Mitral valve prolapse is also found in the majority of children (50%–80%) (117,140). Progressive mitral valvular dysfunction and potentially malignant ventricular dysrhythmias do occur in children (22,100,138). Exceptionally, aortic dissection has been reported to occur already at 5 years of age (128).

In adults, significant auscultatory signs are found in only one-third to one-half of cases, whereas abnormal echocardiograms are found in the majority (80%–95%). Characteristically, the aortic root diameter is above the upper limit of normal (approximately 38 mm) and there is mitral valve prolapse and left atrial dilatation (65). Nomograms for the upper normal limits for age and body size have been developed (125–127). Symptomatic aortic regurgitation, which is found in less than 25% of patients, and aneurysmal dissection are both associated with dilatation of the aortic root beyond 55 mm (29,110,116,117,129). The strongest

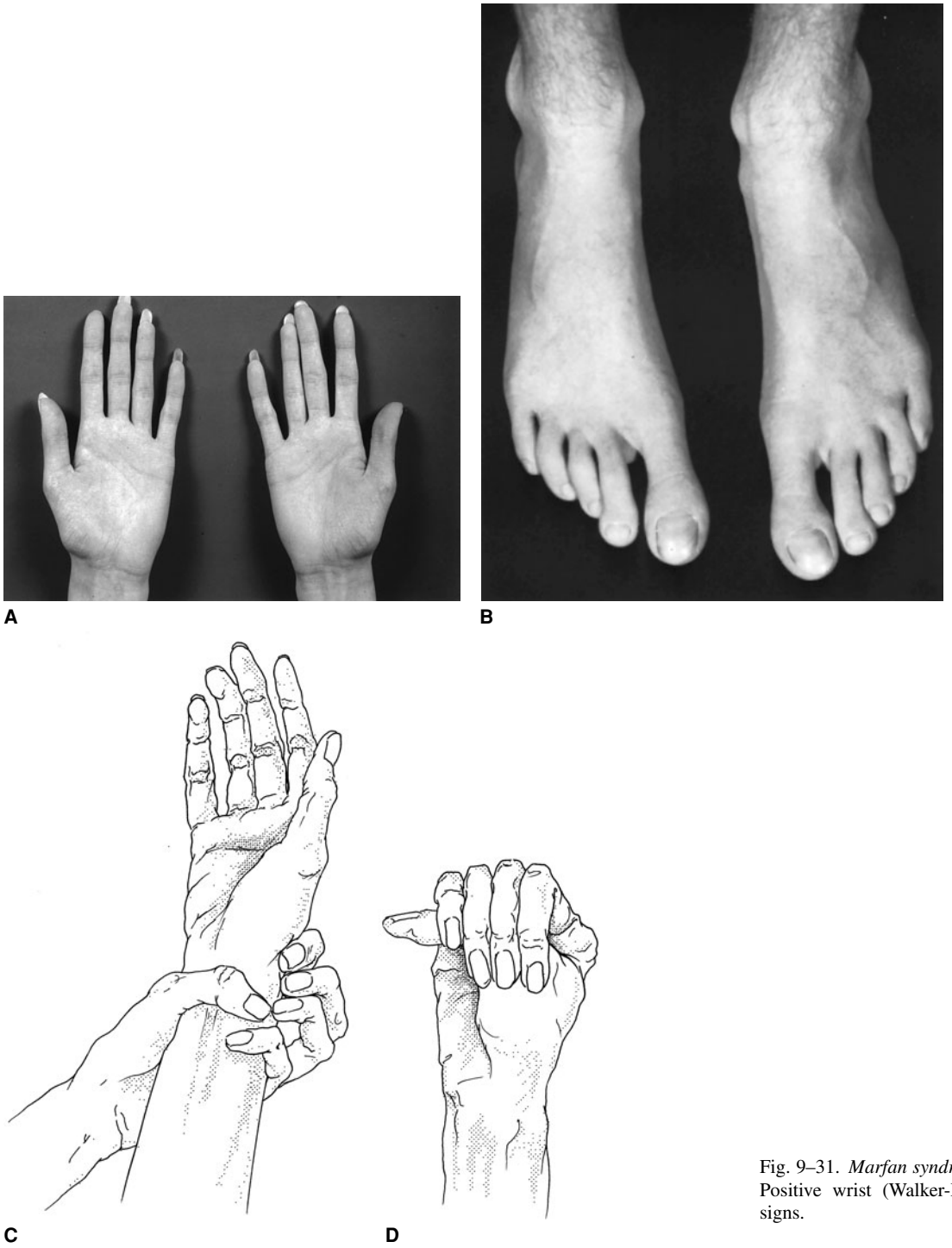


Fig. 9–31. *Marfan syndrome*. (A,B) Arachnodactyly. (C,D) Positive wrist (Walker-Murdock) and thumb (Steinburg) signs.

predictors of dissection of the ascending aorta are the actual size of the aortic diameter and a history of dissection in a relative (106,115). DeSanctis et al (35) published an excellent review of aortic dissection. Serious cardiovascular complications during pregnancy are also more likely with dilatation greater than 40 mm (45,69,80,86,101,113,115). The risk is greatest during the last trimester of pregnancy and first weeks after delivery.

Obstetric complication are otherwise not more frequent (86).

Other reported cardiovascular complications include acute aortic valve prolapse (20), bicuspid aortic valve (50), aneurysms of the descending aorta or pulmonary artery (40), renal vein thrombosis (2), and aneurysms of the abdominal aorta (82,153). As with all patients with valvular disease, there is an increased risk of bacterial endocarditis. Although an increased risk for intracranial aneurysms has been reported, this was not confirmed in a larger study (152).

Pulmonary pathology. Because of the connective tissue defect, the tall asthenic habitus, and the frequency of thoracic cage deformities, affected individuals are at increased risk for spontaneous pneumothorax. Although the frequency is low (4.4%), recurrence is likely unless the underlying lesion, usually an apical bulla, is resected. Pulmonary infections and chronic emphysematous changes occur with increased frequency (41,147). The pulmonary vital capacity is generally reduced even in patients without thoracic distortion, adding significantly to the anesthetic risk (63,143,154,161).

Skin and integument. Connective tissue involvement leads to increased frequency of striae distensae (24%), arising around puberty, and mainly on the shoulders, lumbar region, and thighs (27). Striae gravidarum can be masked in women with Marfan syndrome (115). Inguinal herniae (22%) and recurrence after standard surgical therapy are common. Hernias of other structures have also been described (135), including paraesophageal hernias in newborns (107). Miescher elastomata, especially on the neck, may also be found (116).

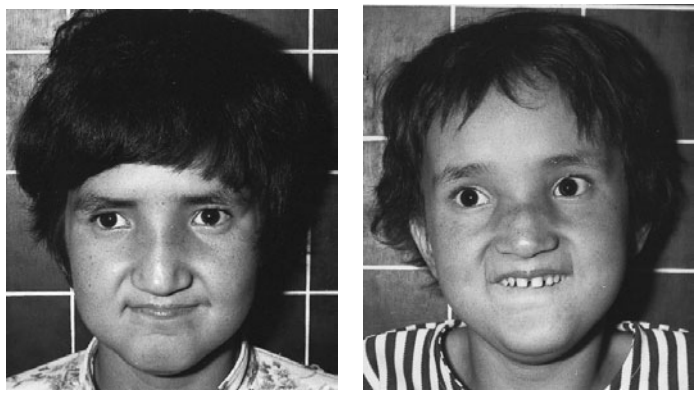
Miscellaneous findings. Abnormalities of the central nervous system, presumably of connective tissue origin, include dural ectasia, sacral meningocele, and dilated cisterna magna, but neurological manifestations are rare (24,66,114). Dural ectasia in the lumbosacral region is very common in Marfan syndrome, but may be found in disorders such as *neurofibromatosis, Ehlers-Danlos syndrome*, and ankylosing spondylitis (1a,119).

Other symptoms in Marfan syndrome are nephrotic syndrome (2,130), possibly due to glomerular basement membrane alterations, medullary sponge kidney (131), hematologic abnormalities (44,68), primary hypogonadism (50), myopathic symptoms due to a diminished amount of skeletal muscles (55), sleep apnea (25), diminished amount of subcutaneous fat (106,115), biliary tract anomalies (96), and alopecia (162). Neuropsychological studies showed problems with sustained visual attention and visual construction abilities, which could not be explained by reduced visual acuity, but otherwise normal intelligence (83). The meaning of the report of schizophrenia in five Marfan patients is uncertain (139).

Differential diagnosis. A Marfan-like habitus may be observed in *homocystinuria* (cystathionine synthase deficiency), congenital contractural arachnodactyly (9), Marfanoid hypermobility syndrome (155), eunuchoidism, *Klinefelter syndrome, XXY syndrome*, sickle-cell anemia, *multiple endocrine adenomatosis, type IIb*, and occasionally in *nevoid basal cell carcinoma syndrome.* Marfan-like habitus may also be a feature in some cases of *Stickler syndrome* (64). Other symptoms of Marfan syndrome may also be seen in other disorders. In *Shprintzen-Goldberg syndrome* (137), arachnodactyly is associated with craniosynostosis, mental deficiency, ocular proptosis, micrognathia, and other features. Furlong et al (49) reported a patient with typical characteristics of Marfan syndrome, but additionally had craniosynostosis, hypospadias, spondylolisthesis, and absence of ectopia lentis. Clunie and Mason (26) described three sibs, products of a consanguineous union; Marfan-like habitus and multiple inguinal and femoral hernias were described. Jaffer and Beighton (71) noted a patient with arachnodactyly, pectus carinatum, spondylolisthesis, joint laxity, and mental deficiency. Lujan et al (87) and Fryns and Buttiens (48) reported an X-linked disorder characterized by Marfan-like habitus, large head, mental retardation, long narrow face, highly arched palate, small mandible, atrial septal defect, and other anomalies. Tamminga et al (145) reported an infant with a Marfan-like phenotype, congenital contractures, microspherophakia, optic nerve colobomas, prolapse of mitral and tricuspid valves, cerebral white matter hypoplasia, and spinal axonopathy. Currarino and Friedman (33) reported a severe form of congenital contractural arachnodactyly associated with unusual histopathologic changes in the metaphyses and epiphyses together with other anomalies such as ankyloblepharon, esophageal atresia with tracheo-esophageal fistula, duodenal atresia, and vertebral malformations. They suggested that congenital contractural arachnodactyly may be etiologically heterogeneous.

Fragoso and Cantú (46) described four sibs with psychomotor retardation, flat and coarse facies, dolichocephaly, low posterior hairline, synophrys, hypertelorism, broad nose with bifid columella, malar hypoplasia, small mouth, and large ears (Fig. 9–32). Musculoskeletal alterations included pectus excavatum, muscle hypoplasia, dolichostenomelia, osteopenia, and thin metapodial bones, phalanges, and ribs. Inheritance is probably autosomal recessive.

Thieffry-Kohler syndrome (148), a dubious entity, has been characterized by Marfan-like appearance, frontal bossing, micrognathia, mild scoliosis, pes cavus, overlapping toes, and plantar cysts. Bone destruction of the wrists and ankles, beginning with the carpal and tarsal bones and spreading to involve adjacent bones, occurred during childhood and progressed, with painless, at times asymmetric, osteolysis. Serum alkaline phosphatase and hydroxyproline levels were elevated.



A B

Fig. 9–32. *Coarse facies, Marfanoid habitus, and mental retardation*. (A,B) Facies of two of four affected sibs. In addition to mental retardation, all have flat coarsened facies, synophrys, hypertelorism, esotropia, broad nose, short philtrum, somewhat small mouth. (From R Fragoso and JM Cantú, Clin Genet 25:187, 1984.)

The Mirhosseini syndrome is characterized by microcephaly, severe mental deficiency, pigmentary retinal degeneration, cataracts, hyperextensible joints, arachnodactyly, and mild scoliosis (95). Inheritance is autosomal recessive.

Ectopia lentis may occur in Weill-Marchesani syndrome, congenital contractural arachnodactyly (8), *Ehlers-Danlos syndromes*, *homocystinuria*, *osteogenesis imperfecta*, and as an isolated autosomal recessive trait. In homocystinuria, the lens tends to dislocate, nasally, inferonasally, or inferiorly (32). Shawaf et al (134) reported a Lebanese family with ectopia lentis, spontaneous filtering blebs, and mild craniofacial dysmorphism. Aortic dilatation is also seen in Erdheim's cystic mediconecrosis and in tertiary syphilis (150). Joint hypermobility is seen in a number of disorders, including *osteogenesis imperfecta,* the *Ehlers-Danlos syndromes, homocystinuria, Stickler syndrome*, and Marfanoid hypermobility syndrome (64,155).

Mitral valve prolapse may occur in *cutis laxa syndromes, Ehlers-Danlos syndromes, osteogenesis imperfecta, Stickler syndrome, fragile X syndrome*, contractural arachnodactyly, and a host of other conditions reviewed in the third edition of this text.

Laboratory aids. Preimplantation (75) and prenatal (54,121,157) diagnosis by molecular studies have been accomplished. During the third trimester, diagnosis can be strongly suspected on the basis of ultrasonographic analysis of limb lengths (78). Some parents may benefit from emotional preparation for the birth of an affected child (68).

Lumbosacral dural sac dimensions can be measured by MRI. Dural ectasia is a good marker for Marfan syndrome (106a).

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McCune-Albright syndrome

The McCune-Albright syndrome is characterized by (a) polyostotic fibrous dysplasia, (b) multiple areas of cutaneous light brown pigmentation or café-au-lait spots, and (c) autonomous hyperfunction of one or more endocrine glands, especially gonads and thyroid (Figs. 9–33 to 9–35). The syndrome was delineated by McCune (48) and McCune and Bruch (49) in 1936 and 1937 and by Albright et al (2,3) in 1937 and 1938, although it was described as early as 1922 by Weil (72). It has been suggested that cases 5, 6, and 7 of von Recklinghausen may possibly represent examples of this syndrome rather than neurofibromatosis (18). Because of multiple endocrine gland dysfunctions, the syndrome has been included as one of the multiple endocrine adenomatoses. The most extensive review is that of Danon and Crawford (18). Cohen and Howell (15a) describe the molecular aspects of the syndrome.

Virtually all cases described to date have been isolated examples. Hibbs and Rush (36) reported a woman with skin pigmentation, possible sexual precocity, and bone lesions consistent with fibrous dysplasia; a daughter had multiple cystic bone lesions, but no endocrine or skin manifestations. Firat and Stutzman (25) described a mother and daughter with hyperparathyroidism, cystic lesions of bone, but no skin or other endocrine abnormalities. Bone biopsy in the mother was consistent with fibrous dysplasia. Alvarez-Arratia et al (4) described a woman with bone lesions, skin hyperpigmentation, and diabetes mellitus and thyroid enlargement, who had 11 relatives with café-au-lait spots and, in some, mild skeletal symptoms. The syndrome has also been observed in one of monozygotic twins (21,40). An analysis of 32 cases was published by De Sanctis et al (19a) in 1999.

Happle (34) postulated an autosomal dominant lethal gene as the cause, resulting in loss of the zygote in utero. Mutated cells are thought to survive only when occurring together with normal cells in the mosaic state. The disorder may result from a gametic half chromatid mutation or from an early somatic mutation. Danon and Crawford (18) suggested that functional failure of receptor complexes might underlie the syndrome. Weinstein et al (73) proved this by showing activating missense mutations at codon 201 of the *GNAS1* gene encoding the α subunit of the stimulatory G protein, located at chromosome 20q13.2, in a mosaic state. The G (guanine nucleotide binding) proteins form a superfamily of signal-transducing proteins that mediate numerous transmembrane hormonal and sensory processes (42). The proteins have a heterotrimeric structure, of which the alpha subunits have intrinsic GTPase activity and probably allow for functional specificity of each G protein (74). The (stimulatory) Gs alpha protein couples receptors causing activation of adenylate cyclase and thereby increases the synthesis of cyclic AMP (Fig. 9–33). Mutations in the Gs alpha protein are found in various degrees in different tissues (13,20,61,62,64,65,73), and somatic mosaicism can account for the great clinical variation in the disorder (69). Possibly, similar isolated organ defects can be explained this way (45,52,60). Studying bone marrow, Bianco et al (8) found two different genotypes within single fibrous dysplastic lesions, which is in accord with the hypothesis put forward by Happle (34). The same *GNAS1* mutations occur in isolated fibrous dysplasia (8a).

Features of the syndrome occur with variable frequency. Diagnosis is made with certainty if all three principal features are present, but should

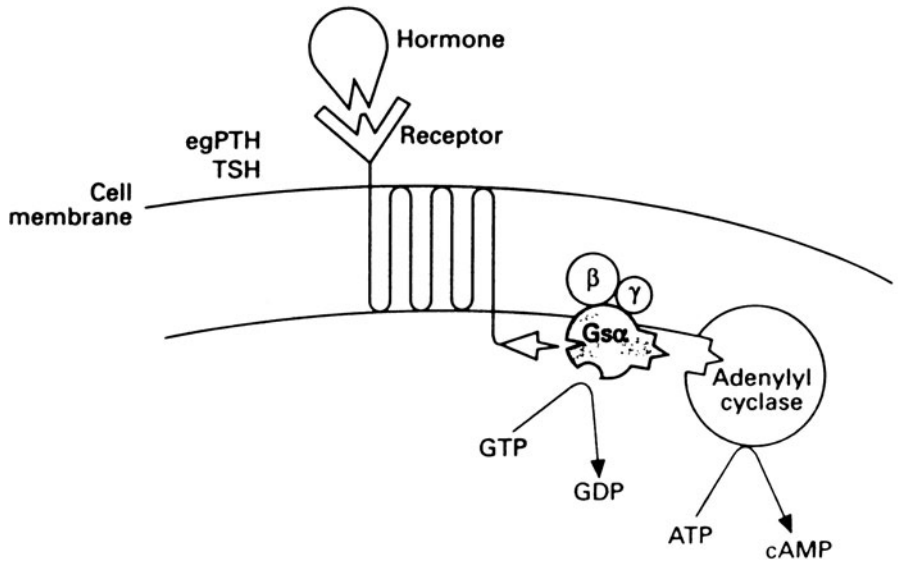


Fig. 9–33. *Hormone receptor-Gs-adenylyl cyclase pathway.* Parathormone, like TSH and several other hormones, exerts its effects by stimulating adenylate cyclase to produce a second messenger cAMP. The receptor is coupled to adenylate cyclase by a signal-transducing protein, Gs, one of a large family of heterotrimeric GTP binding G Proteins. Note that Gs is composed of α, β, and γ subunits, the subunit determining both effector and receptor specificity. (From LC Wilson and RC Trembath, J Med Genet 31: 779, 1994.)

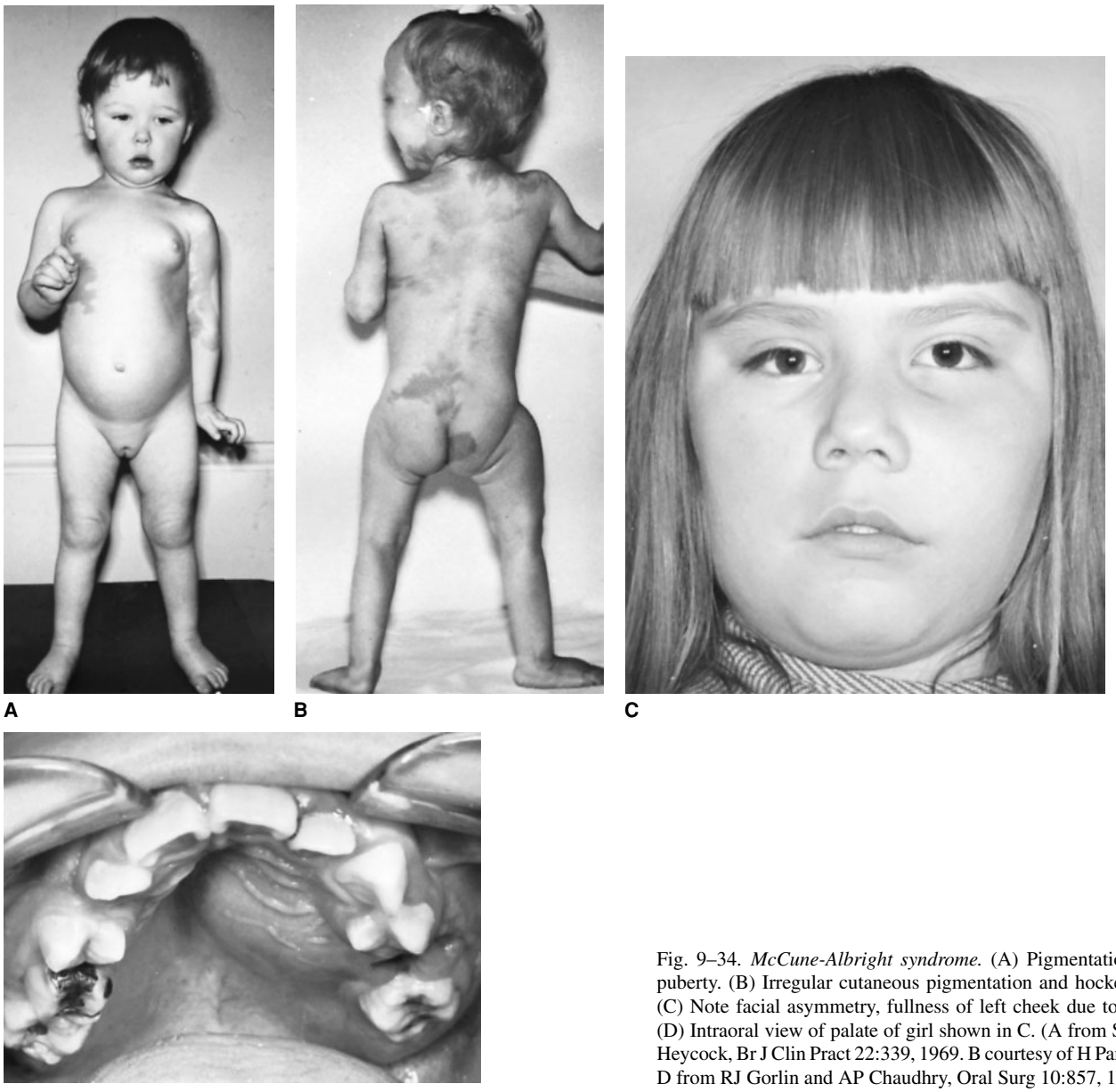


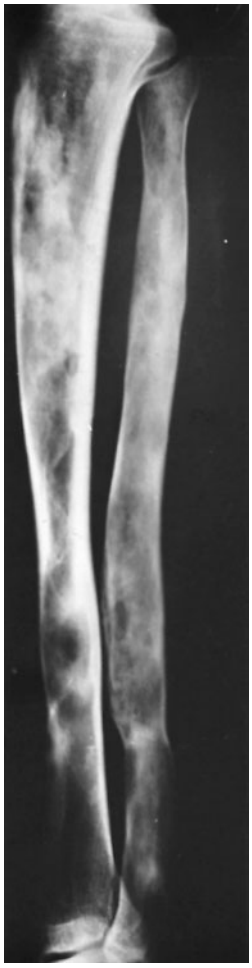
Fig. 9–34. *McCune-Albright syndrome.* (A) Pigmentation and precocious puberty. (B) Irregular cutaneous pigmentation and hockey-stick deformity. (C) Note facial asymmetry, fullness of left cheek due to fibrous dysplasia. (D) Intraoral view of palate of girl shown in C. (A from S Agarwala and JB Heycock, Br J Clin Pract 22:339, 1969. B courtesy of H Pande, Oslo, Norway. D from RJ Gorlin and AP Chaudhry, Oral Surg 10:857, 1957.)

also be considered with two features because each has special characteristics seldom encountered in other disorders. The presence of any one of the three features should prompt a search for one or both of the other features of the syndrome. In the series of Harris et al (35), about 38% had bone involvement alone, 40% had two features, and 22% had the full-blown syndrome. Pritchard (53) found cutaneous pigmentation in 43% ($n = 181$). Approximately 45% of affected females exhibit sexual precocity, but only 6% of affected males have this feature. Of patients referred for sexual precocity, only 8% have McCune-Albright syndrome (56) and only 3% of patients with polyostotic fibrous dysplasia have McCune-Albright syndrome (18).

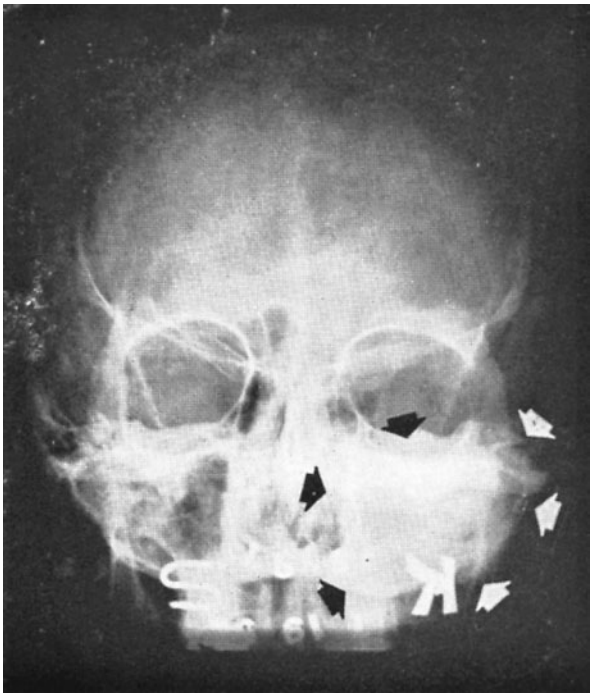
Skeletal manifestations. Although any bone may be involved, the long bones are most frequently affected, especially the upper end of the femur. Bowing resembling a hockey stick may be produced, resulting in leg-length discrepancy (Fig. 9–34A,B). Limp, leg pain, or fracture is the presenting complaint in about 70% (35). Other bones affected, in descending order of frequency, are the tibia, fibula, pelvis, humerus, radius, and ulna. Bilateral involvement occurs in about half the cases (9,22) (Fig. 9–35A,B). Occasionally, a single bone is involved. Incipient bowing of the legs may be seen as early as the first year of life and nearly always appears before the end of the first decade (48,49). The process may be asymptomatic or accompanied by pain and fracture. Fractures may be multiple and recurrent. At least 85% have one fracture, and over 40% have three or more (5,35). Occasionally, bones on only one side of the body may be involved (53). Scintigraphic studies have been reported (51).

Bone is replaced by a yellowish to red-brown fibrous tissue, its composition varying greatly in different parts of the body. It may be rich or poor in cells. The stroma may vary from a finely fibrillar one with a loose whorled arrangement to one that is densely collagenous. Some areas appear edematous, with numerous small cystic spaces. Foci of hemorrhage and multinucleated giant cells may be observed. The trabeculae are irregular in form, and occasionally a few fragments of cartilage are present (Fig. 9–35C).

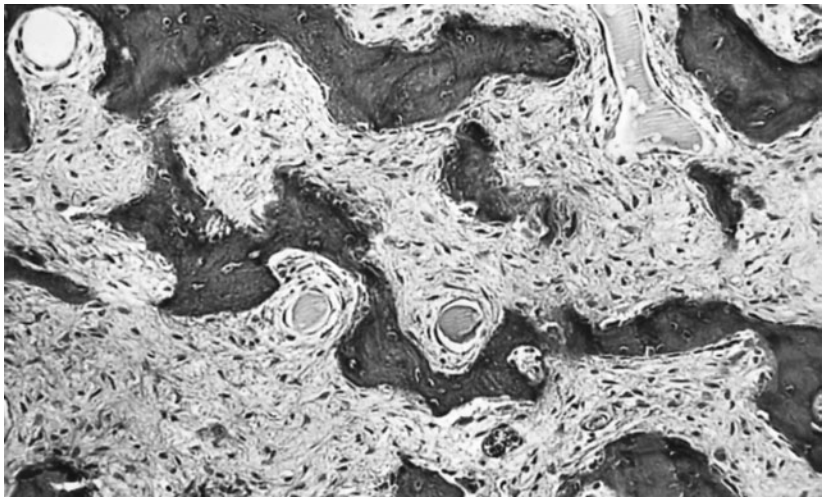
Facial asymmetry occurs in about 25% (Fig. 9–34C,D) and may be accompanied by protrusion of an eye with associated visual disturbances in some instances (22,53,69). The bony lesions of the skull and facial skeleton, in contrast to the cystic lesions of long bones, are hyperostotic (Fig. 9–35B). The skull base becomes thickened and dense, bulging upward into the cranial cavity (17). The calvaria may also become



A



B



C

Fig. 9–35. *McCune-Albright syndrome.* (A) Thickening and pseudocystic involvement of tibia and fibula. (B) Hyperostotic involvement of maxillary sinus by fibrous dysplasia. (C) C-shaped trabeculae composed of metaplastic woven or fiber bone in fibrous connective tissue stroma.

thickened, with marked occipital and frontal bulging. Bossing may be asymmetric, with unilateral, and occasionally bilateral, obliteration of the sinuses and nasal passages. Overgrowth of bone around foramina may result in deafness and blindness. Furin et al (28) reported an intracranial frontoethmoid mucocele.

The jaws may be enlarged, expanded, and distorted (14). Radiographic examination may show a dense mass, especially in the maxilla, extending into and obliterating the sinuses and expanding the buccal plate in the tuberosity areas, or there may be a radiolucent area, more common in the mandible, similar to that seen in long bones. Often there is loss of trabeculae and a "ground-glass" appearance on radiographic examination (18,35,53,77).

Cutaneous manifestations. Pigmentation is of the café-au-lait type (7,55,58). Well-defined, generally unilateral, irregular macular spots are scattered over the forehead, nuchal area, and buttocks. Only rarely are the face, lips, or mucosa affected (10,30,57) (Fig. 9–34A,B). The hyperpigmentation may follow Blaschko's lines (55).

There appears to be a correlation between the amount of pigmentation and the degree of bone involvement (7). It has been stated that

pigmentation is more frequent on the side of unilateral bone involvement, although this has been denied (36). The pigment appears from the fourth month to the second year of life. In a few patients, it has become evident a few weeks postnatally (6). In one patient, symptoms resembling epidermal naevus syndrome were found (76).

Endocrine manifestations. Endocrine abnormalities, reviewed elsewhere (3,9,15,18,19,24,29,32,36,46–50), are characterized by autonomous hyperfunction and, to date, no instances of extraglandular trophic influences mediating hypersecretion have been identified. In affected patients, any given endocrine gland may function normally. At autopsy, characteristic endocrine nodular hyperplasia may be found that did not give rise to clinical signs of hyperfunction during life. In fact, endocrine organs, in spite of autonomy, may function so nearly normally that their independence is not recognized until appropriate tests have been performed. Sexual precocity is the most common endocrine manifestation, especially in females (Fig. 9–34A). It is generally manifest earlier in girls than in boys. Menarche is reached between 1 and 5 years of age in 50% and between 6 and 10 years in another 33% (9). However, vaginal bleeding may occur within the first few months or even the first few days of life (2,3,6,32). It is usually irregular, lasts from 2 to 4 days, and may, on occasion, be profuse. Breast development and pubic and axillary hair appear after menarche, usually from the fifth to the tenth year, but may be manifest as early as birth (48,49). Hypertrophy of the internal (26) and external (2,3) genitalia occurs. It is remarkable that affected women can be fertile (18,32). In males with sexual precocity, enlargement of the penis and testes is accompanied by growth of pubic hair, suggesting hyperfunction of both spermatic tubules and Leydig cells (18,32). Precocious puberty in males may be accompanied by gynecomastia (22,53). Acromegaly or gigantism has been described (1,37,69).

Hyperthyroidism is present in about 20%, occurring at an early age (3,49,53,57,59,78). The sex distribution is approximately equal. Thyrotoxic manifestations such as irritability, poor weight gain, and growth failure have been described during infancy, as early as 3 months in one instance (59). With untreated sexual precocity or hyperthyroidism, skeletal maturation is often rapid and premature closure of the epiphyses may result, producing short stature in adulthood.Various other endocrine disorders have also been noted, including Cushing's syndrome, hypersomatotropinism, hyperprolactinemia, hyperparathyroidism, thyroid storms after surgery, and hypophosphatemic vitamin D–resistant rickets or osteomalacia without hypercalcemia or elevated parathyroid hormone levels (15,18,22,24,33,39,56).

Central nervous system. Although the overwhelming majority of patients have normal intelligence, mental deficiency has been reported in a few instances (2,15,18). It may be secondary to factors such as prematurity, hypercorticalism, or grossly malformed skull. The significance of mental retardation in others remains unclear. In the original description of Albright et al (2), an accessory mammillary body was found at autopsy. However, no other patient has exhibited this finding.

Neoplasms. Malignancies are rarely described. The most unusual malignancy recorded to date has been carcinoma of the breast in an 11-year-old girl. Endometrial carcinoma (18) and maxillary osteosarcoma (4) have also been recorded. Instances of sarcoma arising in areas of fibrous dysplasia have been secondary to radiation therapy (35). Other neoplasms have been observed in patients with isolated polyostotic fibrous dysplasia, but could conceivably occur as components of McCune-Albright syndrome. Multiple intramuscular myxomas have been noted in a number of such patients (22,27,29,41,67,75). This is known as *Mazabraud syndrome* and may be associated with osteogenic sarcoma (38,44). Reticuloendothelial hyperplasia with lymphoid and myeloid metaplasia has been described (59). Leukemia (23), osteoma of the skin (63), osteosarcoma (68), and meningioma (23) have also been noted.

Other findings. At autopsy, the thymus and spleen are frequently hyperplastic, but the significance of this finding is unknown (18).

Differential diagnosis. Fibrous dysplasia may occur without McCune-Albright syndrome. The overwhelming majority of cases are monostotic; polyostotic involvement occurs much less frequently and, of these, only 3% have McCune-Albright syndrome (11,18,25,35,71). Radiographically, bone lesions should be distinguished from those of hyperparathyroidism, histiocytosis X, multiple myeloma, Paget disease of bone, neurofibromatosis, and giant cell tumor. It is unfortunate that some authors have referred to cherubism, an autosomal dominant disorder, as "familial fibrous dysplasia of the jaws," a designation it does not merit. *Jaffe-Campanacci syndrome* consists of café-au-lait macules with nonossifying fibromas of long bones and giant cell granulomas of the jaws (50,66). Some have mental retardation and hypogonadism and/or cryptorchidism (12,36).

Cole et al (16) described a congenital disorder of bone with unusual facial appearance, bone fragility, hyperphosphatasemia, and hypophosphatemia—a condition they called panostotic fibrous dysplasia. Viljoen et al (70) described a patient with polyostotic fibrous dysplasia without skin or hormonal abnormalities, who showed extensive cranial hyperostosis. A five-generation family with a craniofacial fibrous dysplasia was reported by Reitzik and Lownie (54).

Skin pigmentation is also seen in *neurofibromatosis.* "Coast of California" contour is typical of neurofibromatosis and a markedly irregular outline ("Coast of Maine") usually occurs with McCune-Albright syndrome; exceptions have been noted (31). Giant pigment granules, characteristically seen in malpighian cells or melanocytes in neurofibromatosis, are very rare in McCune-Albright syndrome (7,25). Precocious puberty occurs in the adrenogenital syndrome, with ovarian granulosa cell tumor, and occasionally in *Peutz-Jeghers syndrome.*

Laboratory aids. Radiographic studies are useful for fibrous dysplastic lesions, advanced bone age, and for occasional findings such as rickets, osteomalacia, or osteoporosis. Serum alkaline phosphatase is elevated in about 50% (53). Appropriate endocrine investigations should be carried out.

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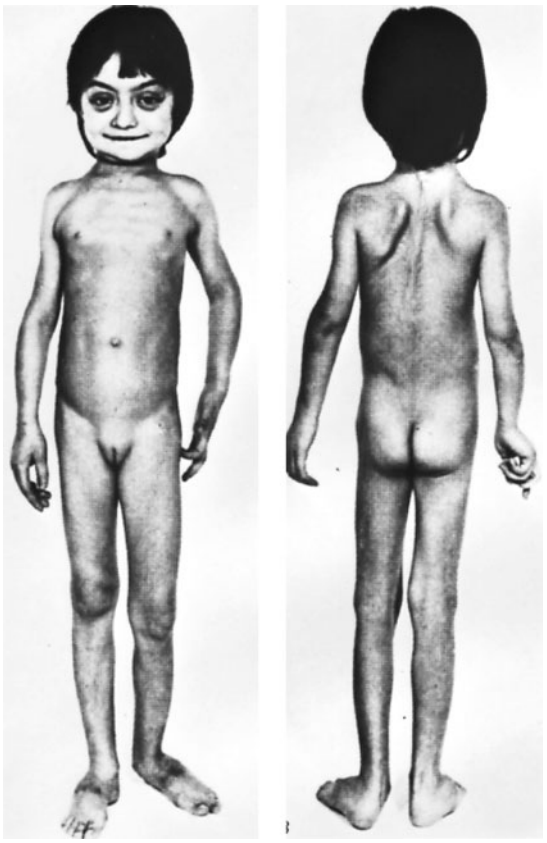

Fig. 9–36. *Melnick-Needles syndrome.* Dysplastic habitus, foot dysplasia. (From N Moelter and A Walther, Monatsschr Kinderheilkd 123:178, 1975.)

Melnick-Needles syndrome (osteodysplasty)

In 1966, Melnick and Needles (32) described a syndrome characterized by generalized bone dysplasia and abnormal facies (Figs. 9–36 to 9–38). About 50 cases have been reported to date (3,4,7,8,10,12,20, 23,24,26,27,29–31,34,35,37,39,42,45–47,51–53). In all but five examples, the patients were females, with about one-half the cases representing new mutations. In only five kindreds was there transmission from one generation to another (10,15,26,32,35,48) although the symptoms in the boy reported by Neou et al (35) were so mild as to make the diagnosis doubtful. Male patients, originally reported to be affected by Melnick and Needles (32), on follow-up were found to be normal (15). Several males born to normal parents had the same degree of expression as that of affected females (13,18,22,23,33,45,47,53); and five affected females had male stillborn infants with a distinct embryopathy (9,23,44,51,54) characterized by exophthalmos, omphalocele and/or malrotation of the gut, and skeletal anomalies (thin calvaria with stellate ossification pattern, cervical lordosis, cervicothoracic kyphosis, thoracolumbar lordosis, thin irregular ribs, curved long bones with sheathing, and hypoplasia or absence of thumbs and halluces (Fig. 9–39). Less certain example are those of Deleporte et al (6) and Gardner et al (14). Several cases (2,41,49) cannot be accepted as examples of Melnick-Needles syndrome on either clinical or radiographic grounds or due to inadequate documentation. Others (40) clearly have frontometaphyseal dysplasia. A disorder first reported by ter Haar et al (20,43), although having somewhat similar clinical but far less severe radiographic features, is a separate entity with autosomal recessive inheritance. The condition reported in twins by Kozlowski et al (21) as being a possible new syndrome, was probably reported later by Adés et al (1) as examples of Shprintzen-Goldberg syndrome, and may, in fact, have Melnick-Needles syndrome.

Gorlin and Knier (15) indicated that Melnick-Needles syndrome has X-linked dominant inheritance lethal in the male. Verloes et al (50) have opined that *frontometaphyseal dysplasia, otopalatodigital syndromes* I *and* II, and *Melnick-Needles syndrome* were but variants of the same disorder.

The pathogenesis is unknown, but it is thought to be a connective tissue disorder. Svejcar (42) reported increased collagen content in affected bones, and dense collagenous tissue was found at the constrictions in the ribs, and abnormal fibrovascular sites within epiphyses (33,51).

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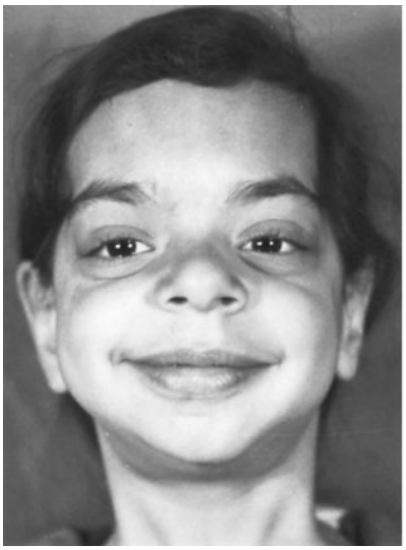
Fig. 9–37. *Melnick-Needles syndrome.* (A–D) Characteristic facial appearance showing exophthalmos, hypertelorism, outstanding nose, receding chin. (A courtesy of FH Stelling and P Meunier, Greenville, South Carolina. C,D from N Moelter and A Walter, Monatsschr Kinderheilkd 123:178, 1975.)



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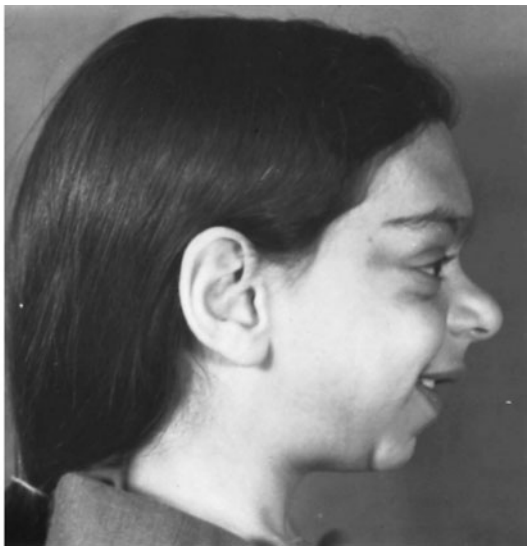

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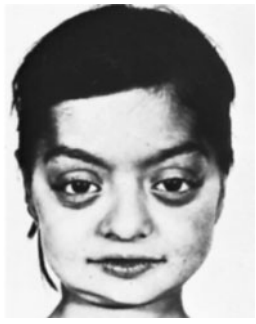

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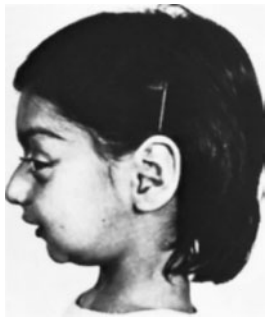

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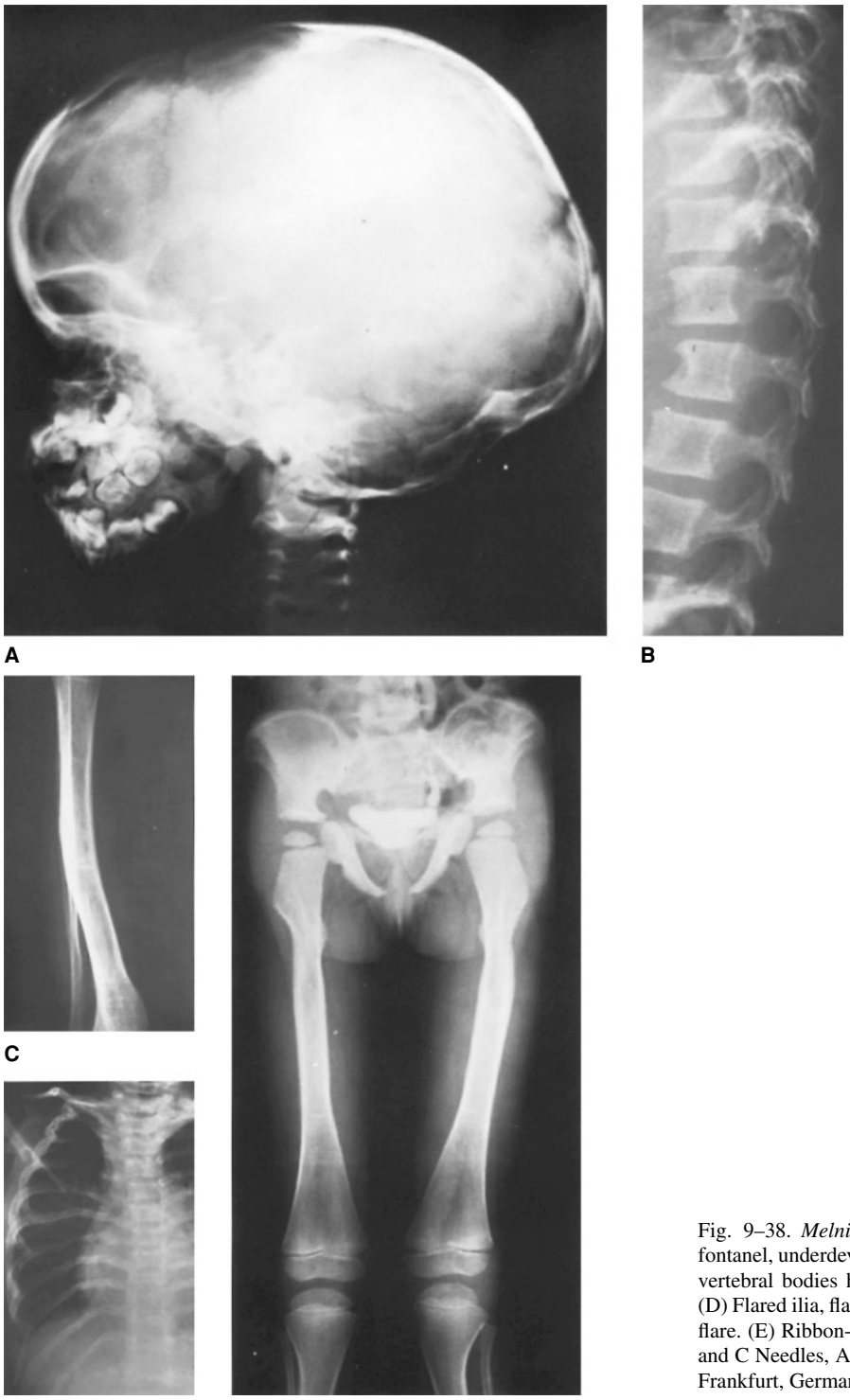

Fig. 9–38. *Melnick-Needles syndrome.* (A) Delayed closure of anterior fontanel, underdevelopment of paranasal sinuses. (B) Disproportionately tall vertebral bodies having anterior concavity. (C) S-shaped bowing of tibia. (D) Flared ilia, flat acetabula, tapered ischial bones, coxa valga, metaphyseal flare. (E) Ribbon-like ribs with cortical irregularities. (A,D from J Melnick and C Needles, Am J Roentgenol 97:39, 1966. B,C,E courtesy of B Leiber, Frankfurt, Germany.)

Early childhood is marked by recurrent respiratory and ear infections. Height and weight are usually below the 10th centile. The patients tend to remain thin. The breasts are very small and sexual hair is sparse (10,39). Mild developmental delay occurs (10,35).

Facies. The facies is characterized by high somewhat hirsute forehead, somewhat prominent supraorbital ridges, prominent eyes, full cheeks, large pinnae, and marked micrognathia (Fig. 9–37). Strabismus (8,33,36,52) and blue sclerae (3) have also been reported, and squamous cell carcinomas in another (32).

Skeletal alterations. The neck is long, the chest is narrow, and the upper arms and terminal digits are often short. There is valgus deformity at the elbows and extension is often diminished. Mild pectus excavatum has been noted in over 50% of the cases (10,20,33,52). About 35% exhibit delay in motor development and abnormal gait. Dorsal kyphosis and/or scoliosis are relatively common. Most patients exhibit genua valga, and about one-third have pes planus or valgus. Some have dislocated hips.

Radiographically, the calvaria often has digital markings. There is delayed closure of the anterior fontanel. The skull base and mastoid processes are sclerosed. There is mildly increased interorbital distance. The paranasal sinuses tend to remain underdeveloped. The mandible is small with scalloped rami and lack of coronoid processes (16,17,38). The mandibular bone is so thin that retromolar lucencies have been confused with cysts (10).

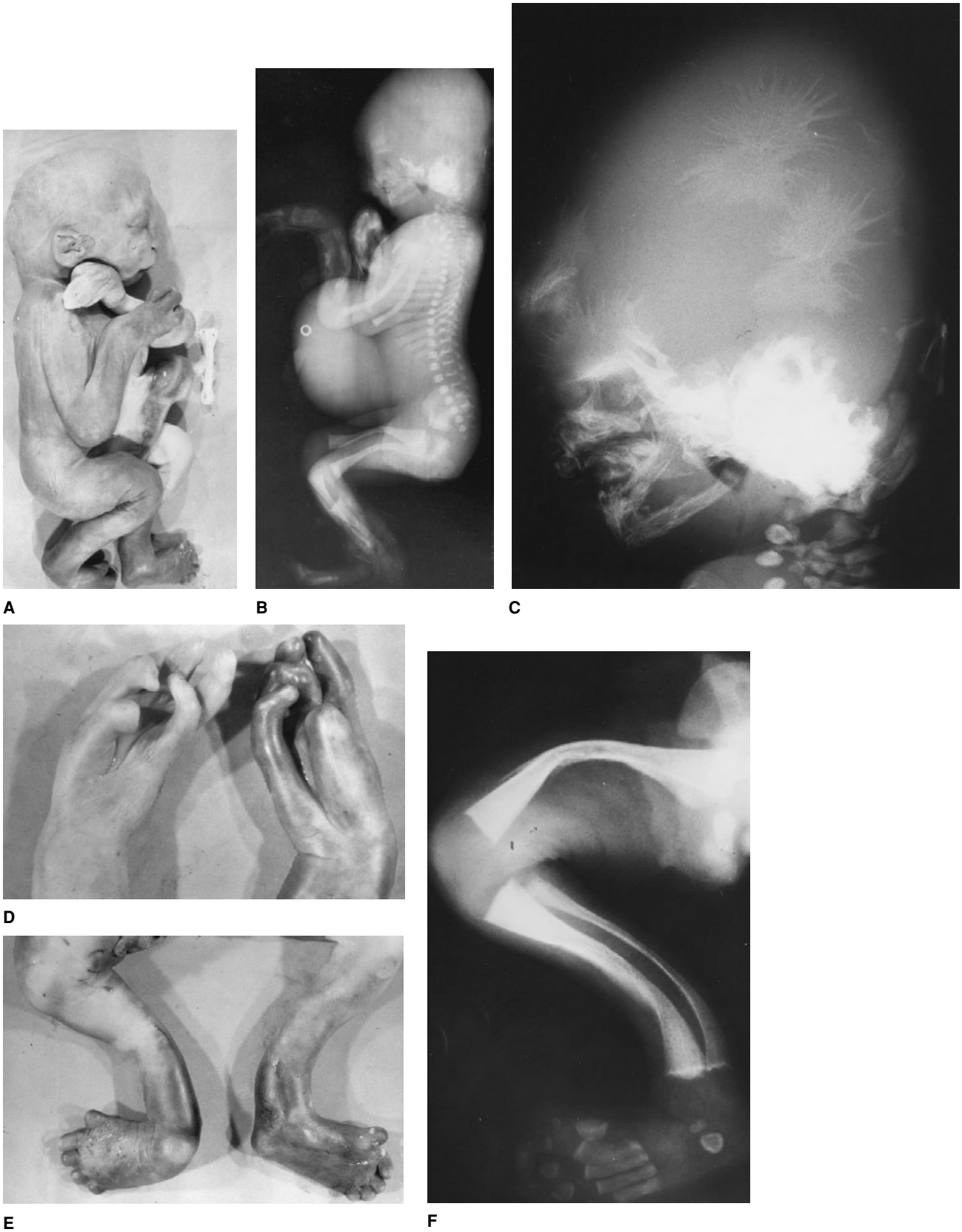

Fig. 9–39. *Melnick-Needles syndrome embryopthy.* (A–C) Male stillborn, mother affected. Note exophthalmos, omphalocele, thin calvaria with stellate ossification pattern, cervical lordosis, cervicothoracic kyphosis, thoracolumbar lordosis, and thin irregular ribs. (D–F) Curved long bones with sheathing, hypoplasia or absence of thumbs and halluces. (A courtesy of M Barr, Ann Arbor, Michigan. B,C, from G Theander and O Ekberg, Acta Radiol Diagn 22:369, 1981.)

All vertebral bodies are unusually tall, especially those of the axis, atlas, and occipital condyles (Fig. 9–38B). The thoracic vertebrae exhibit an anterior concavity with double beaking. Decreased disc space has been found in the lumbar area. The clavicles have cortical irregularity with flaring. Sternal ossification is delayed. The scapulae are hypoplastic.

Most striking are the changes in long bones. Bowing of the radius and tibia produces an S-shaped appearance. The metaphyses at the proximal and distal ends of the humerus, fibula, and tibia are flared. The terminal phalanges are short and thick, especially those of the thumbs. Cone-shaped epiphyses are found in the middle phalanx of the abbreviated fifth fingers and in the terminal phalanx of the thumbs (12,26,32,45). Coxa valga is marked. The iliac bones are flared at the crest and constricted in the supraacetabular area, whereas the ischial bones are tapered. The ribs are ribbon-like, with cortical irregularity (Fig. 9–38).

Other findings. Ureterovesicular obstruction has been documented in several cases (3,8,10,20,32,45) that were reviewed by Lamontagne (26). Fryns et al (13) reported hyperlaxity in affected males, and Krüger et al (24) noted mitral and tricuspidal valve prolapse. Pulmonary hypertension (20), tetralogy of Fallot (9), and noncompaction of the ventricular myocardium (52) have been found.

Oral manifestations. Micrognathia and marked malocclusion are constant features. Some have delayed tooth eruption (13).

Differential diagnosis. The radiographic features are so distinctive as to differentiate this syndrome from all other disorders in which there is delayed closure of the anterior fontanel. The *serpentine fibula-polycystic kidney syndrome,* characterized by overly long curved fibulas but without several of the skeletal abnormalities of Melnick-Needles syndrome, was reported by Dereymaeker et al (7, Case 1), Exner (11), and Majewski et al (28). However, it seems likely that this is the same disorder.

Melnick-Needles syndrome needs to be separated from *Hajdu-Cheney syndrome, frontometaphyseal dysplasia,* and *otopalatodigital syndrome*. A suggestion has been made that the latter entity is allelic to Melnick-Needles syndrome (37). Billette de Villemeur et al (5) described an entity first reported by Bowen, characterized by congenital glaucoma, exophthalmos, facial anomalies, and cardiac malformations, that superficially may resemble the lethal form of the entity in males. Radiographs were normal, however, and autosomal recessive inheritance was suggested.

Laboratory findings. Prenatal diagnosis has been carried out by ultrasonography (25).

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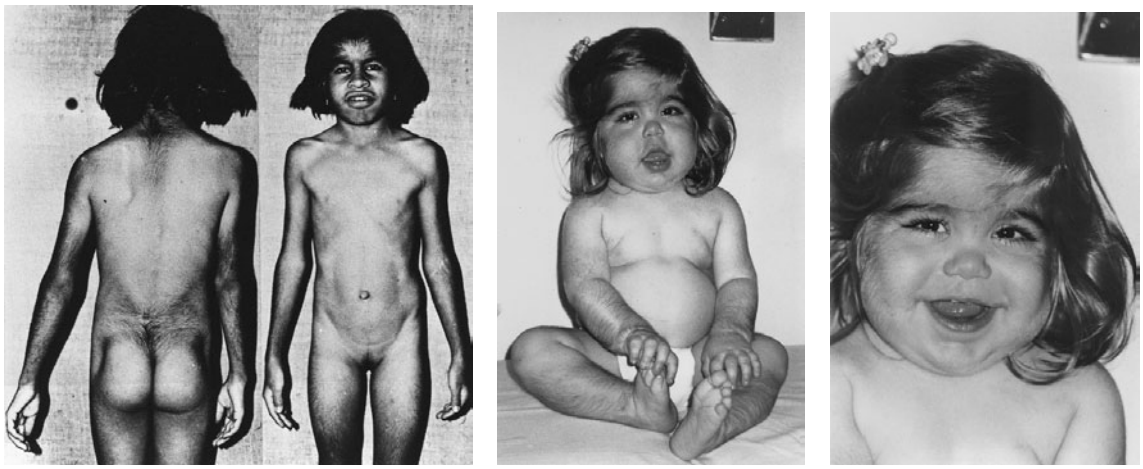

A B C D

Fig. 9–40. *Osteochondrodysplasia with hypertrichosis.* (A,B) Coarse facial features, abundant facial and body hair. (C) Hypertrichosis of arms and legs. (D) Hypertrichosis. Scalp hair extends onto forehead and cheeks. Note synophrys, bilateral epicanthic folds. Small nose with flattened nasal bridge. (A,B from JM Cantú et al, Hum Genet 60:36, 1982. C,D from SP Robertson et al, Am J Med Genet 85:395, 1999.)

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Osteochondrodysplasia with hypertrichosis (Cantú syndrome)

Cantú et al (2) described two sibs and two unrelated patients with congenital generalized hypertrichosis, coarse facies, cardiomegaly, and mild generalized skeletal dysplasia, including osteoporosis and delayed bone age. The same group of authors described four other unrelated patients and follow-up of one of the original patients (3). Nevin et al (5) described a single case, Rosser et al (7), three unrelated cases, and Robertson et al (6), a case. Parental consanguinity was present once (7), and affected sibs were described (2), pointing to a possible autosomal recessive inheritance. However, some cases (especially Case 3 from the Rosser report) resemble the entity described by Irvine et al (4), which was considered different because of the absence of skeletal anomalies, and which has autosomal dominant inheritance. Dominant inheritance was noted by Lazalde et al (4a). The occurrence of idiopathic cardiac effusions both in one of the original patients (3), in the patient of Nevin et al (5), and in one of the patients described by Irvine et al (4) form another point of overlap. Baumeister et al (1) provides guidelines for management of hypertrichosis.

Hypertrichosis is congenital, and changes from lanugo to terminal hair. It continues to grow. Only palms, soles, and mucosae are spared. Facial features (Fig. 9–40) include prominent forehead, epicanthal folds, long curly eyelashes, anteverted nostrils, long philtrum, and thick lips. Some patients have gingival hypertrophy (7) or macrocephaly (3,5). Birth weight can be elevated. Some have a short neck and narrow thorax. Cardiac problems were serious pericardial effusions necessitating surgery (3,5), congenital hypertrophy of left ventricle (2), patent ductus arteriosus (7), and idiopathic intermittent cardiac failure (7). One patient had primary lymphedema (3). Mentation has been normal or mildly delayed.

Radiologically, most patients had wide metaphyses, a delayed bone age, and generalized osteopenia. Other radiologic symptoms are wide ribs, platyspondyly, hypoplastic ischiopubic rami, coxa valga, and long bones with Erlenmeyer flask shape (Fig. 9–41). Megaepiphyses have also been noted (2a).

References [Osteochondrodysplasia with hypertrichosis (Cantú syndrome)]

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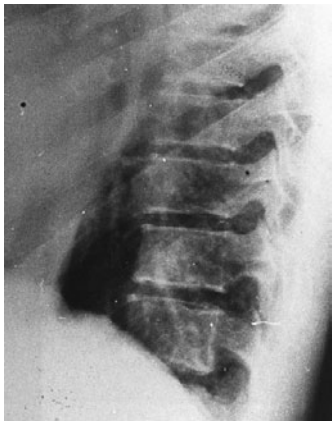
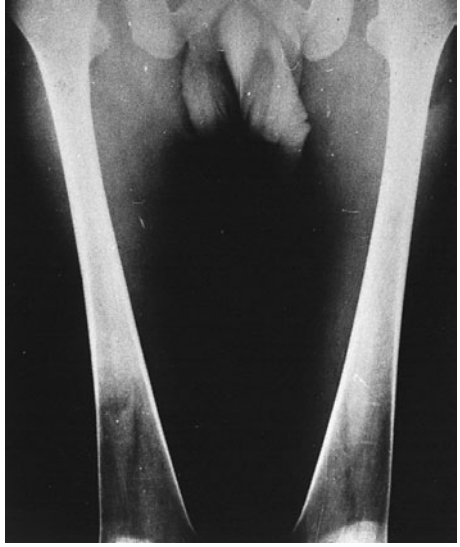
Pachydermoperiostosis [Touraine-Solente-Golé syndrome, primary (idiopathic) hypertrophic osteoarthropathy]

Pachydermoperiostosis is characterized by coarsening of facial features with thickening and furrowing of the face, forehead, and scalp, and clubbing of the digits with periosteal new bone formation (Fig. 9–42 to 9–44). Touraine et al (54), in 1935, first recognized pachydermoperiostosis as a distinct clinical entity, although examples were noted as early as 1868 by Friedreich (16). Other early cases are those of Unna (55) and Grönberg (18). An excellent review is that of Thappa et al (50a).

Most reports have been isolated cases of the condition. However, kindred have been reported in which the disorder appears to be autosomal dominant with variable expressivity (26,27,29,35–37,41,44,56,58), but only 12%–15% of the affected are females (36,44). Anticipation has been suggested (36). The disorder usually appears in the second decade of life (5,15,19,22,23,25,32,36,38,40,43,45,46,53). The cause of pachydermoperiostosis remains uncertain. It has been found that there are high concentrations of nuclear steroid receptors and very low concentrations

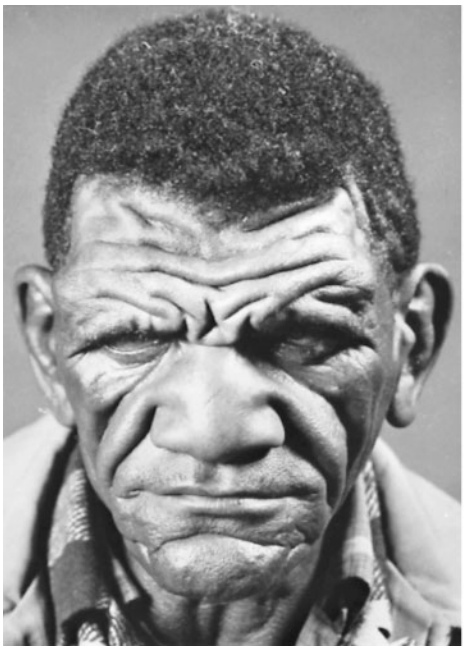


A



B

Fig. 9–41. *Osteochondrodysplasia with hypertrichosis*. (A) Platyspondyly, irregular surfaces. (B) Erlenmeyer flask femora. (From JM Cantú et al, Hum Genet 60:36, 1982.)



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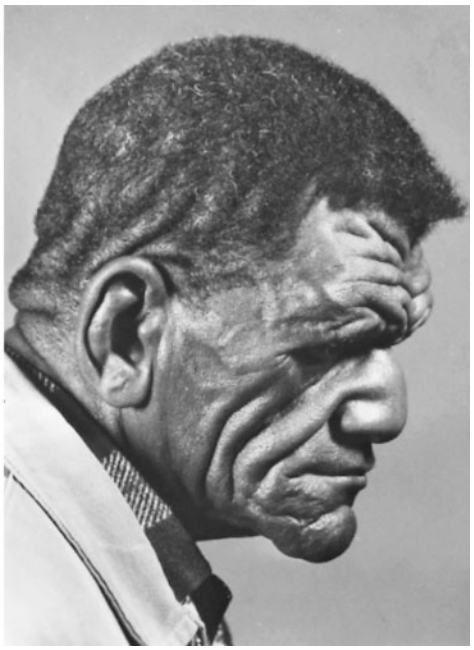

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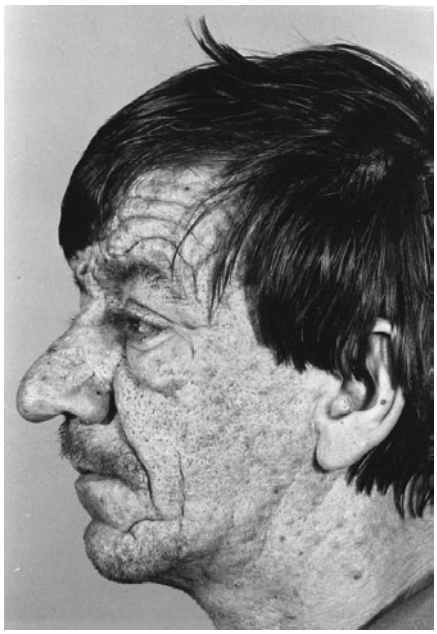
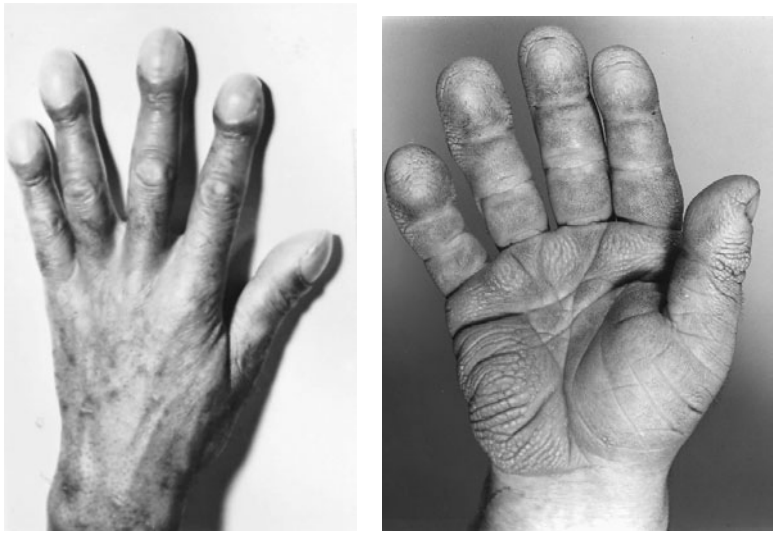


C

Fig. 9–42. *Pachydermoperiostosis.* (A,B) Coarse features, cutis gyrata. (C) Oily thickened skin with large sebaceous pores. No history of acne. (A,B courtesy of HW Kloepfer, New Orleans, Louisiana. C courtesy of A Oikarinen, Oulu, Finland.)



A B

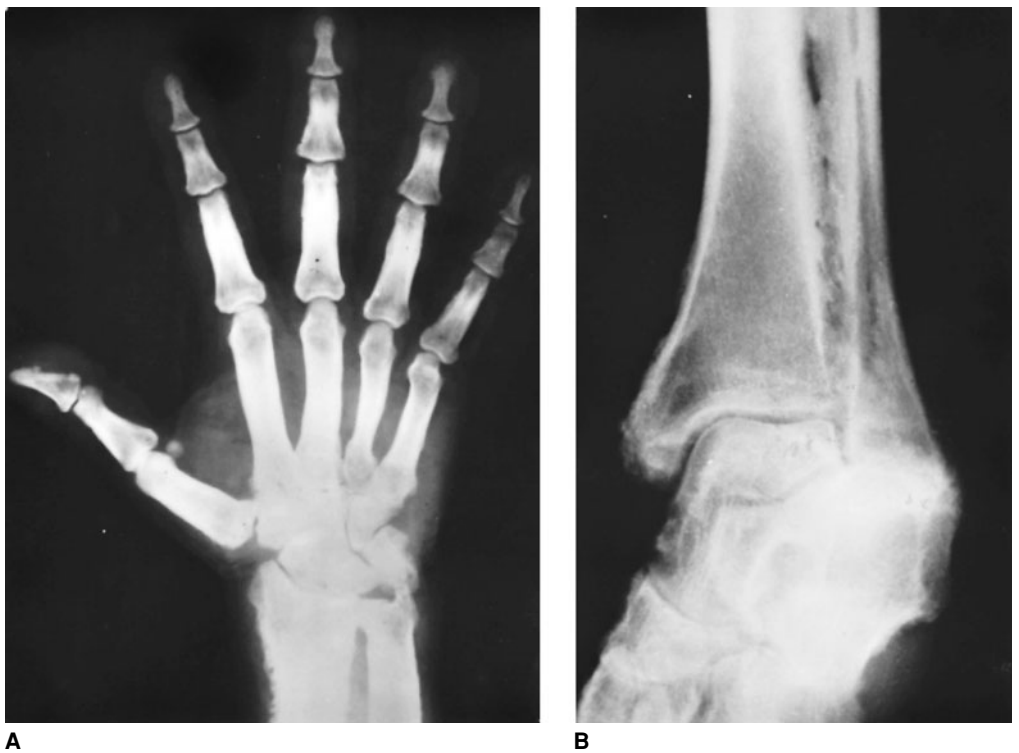
Fig. 9–43. *Pachydermoperiostosis.* (A,B) Clubbing of terminal phalanges and redundancy of skin of palms and fingers. (A courtesy of A Susmano, Chicago, Illinois. B courtesy of A Oikarinen, Oulu, Finland.)

of epidermal growth factor receptors (3) suggesting an increased tissue sensitivity to circulating sex hormones and enhanced production of transforming growth factor alpha. Silveira et al (47) discussed the possible role of vascular endothelial growth factor. The role of the increased peripheral blood flow (13,41) and platelet activation (11) remains uncertain. Connective tissue studies (39) showed accumulation of acidic mucopolysaccharides and some fibrillar material in the dermis. Matucci-Cerinic et al (36) and Jansen et al (27) provide useful reviews.

Facies, skin, and skin appendages. Thickening of the skin occurs over the face, forehead, scalp, hands, and feet. The face is drawn into thick folds, producing creasing or furrowing that causes the patient to look worried or angry, as well as prematurely aged (5,14,20,28,34,37,43,57). The nasolabial folds become deep (Fig. 9–42A,B). Thickening of the scalp tends to produce a corrugated surface or cutis verticis gyrata (18,55), although groups of patients without this characteristic have been described (19,36,52).

The skin has been reported to be greasy or oily (5,18,23,38, 46,50). The dilated sebaceous pores are filled with plugs of sebum that can be easily expressed (18) (Fig. 9–42C). Acne may be marked (25). Pseudoptosis, caused by thickening of the eyelids, may be so severe as to impair vision (5,19,28,50). Skin biopsy shows sebaceous gland hyperplasia, thickening of the stratum corneum, and perivascular round-cell infiltrates (18,36,41,57). The nails may be thick and curved (40). Hyperhidrosis of the hands and feet (1,19,20,23,25,36) is common. Multiple basal cell carcinomas were found in one case (52) and squamous cell carcinomas in another (31).

Fig. 9–44. *Pachydermoperiostosis.* (A) Note thickening and increased density of proximal phalanges and metacarpals, and periosteal thickening of radius. (B) Marked periosteal proliferation along entire length of tibia and fibula. (A from G Pietruschka et al, Klin Monatsbl Augenheilkd 154:525, 1969. B courtesy of A Susmano, Chicago, Illinois.)



A B

Skeletal alterations. Bone changes affect primarily the long tubular bones, metacarpals, metatarsals, and proximal phalanges (18,20, 25,30,36,37,52,58) (Figs. 9–43 and 9–44). Enlargement may be painful (3,6,25,29,30,36). The ends of the fingers and toes become thickened during the second decade of life (18,20) and may become very bulbous (16,19,36,46,52,58) (Fig. 9–43). This clubbing is produced by soft-tissue hyperplasia, which stops abruptly at the distal interphalangeal joints. A diffuse irregular periosteal ossification increases the circumference of the affected bones and results in loss of normal tubulation of long bones. Acroosteolysis in the hands and feet has been described (3,19,36). Bone marrow failure due to massive endosteal hyperostosis has occurred (36).

Joint effusions of the knees (20,25,30,38) and ossification of ligaments and tendons (19) lead to ankylosis of joints (19). The clavicles, patellas, and pubis may also be affected, but the carpal and tarsal bones, sella turcica, and articular surfaces are spared. The skull is usually not affected, but the posterior half of the calvarium has been described as thickened (46). Some patients have pretibial edema (3) as in thyroid disorders. Enlargement of the wrists and knees has been noted (6,19,20).

Hypertrophic gastritis (57) and gastric ulcers (36) occur more frequently than in the general population, and also Crohn's disease has been found within a family (8).

Differential diagnosis. All clinical aspects of pachydermoperiostosis have been described in secondary (pulmonary) hypertrophic osteoarthropathy (21). Patients with pulmonary hypertrophic osteoarthropathy lack a family history of the disorder but have a primary neoplasm, usually bronchogenic carcinoma. There appears to be increased blood flow in pulmonary osteoarthropathy (17), in contrast to reduced flow in pachydermoperiostosis (13,27,41).

In acromegaly, there is enlargement of the hands and feet, and thickening of the skin, particularly of the face (47,48,57). The mandible, nose, sella turcica, supraorbital ridges, and tongue are also enlarged, findings not seen in pachydermoperiostosis.

Thyroid acropathy may follow medical or surgical treatment of hyperthyroidism. As in pachydermoperiostosis, the distal parts of the limbs may be come enlarged, and clubbing of the fingers and toes may occur (12). There may be subperiosteal new bone formation in the hands. Severe exophthalmos and pretibial myxedema may be present, together with high levels of long-acting thyroid stimulator in the serum of such patients.

Simple hereditary clubbing (acropathy) has been described (10). Rimoin (41) has suggested that hereditary acropathy may be an incomplete form of pachydermoperiostosis.

Rosenthal and Kloepfer (42) and Harbison and Nice (22) described a combination of cutis verticis gyrata, corneal leukoma, marked supraorbital ridging, and enlarged frontal and sphenoid sinuses as an autosomal dominant syndrome in a large kindred; the cranium was thickened in some patients, but no periosteal reaction was seen along the shafts of long bones.

Members of the kindred reported by Boylen and Blackard (4) as pachydermoperiostosis had hyperthyroidism. They had coarse prominent facial features, frontal bossing, furrowing of the skin over the forehead, and large hands. Corneal leukomas were also found. The proband had no significant clubbing of the hands, but other members of the family exhibited this characteristic. There were no periosteal changes in the long bones, but radiographs of the proband's hands showed several cystic lesions. Inheritance was autosomal dominant. *Beare-Stevenson cutis gyrata syndrome* (2) should also be excluded.

A patient reported by Vogl and Goldfischer (58) had oily and thickened facial skin, deep folds on the forehead, deep nasolabial folds, and clubbing of fingers and toes. Onset of these changes was noted by the patient at about age 40. No evidence of periosteal proliferation was found. Familial idiopathic osteoarthropathy of childhood (7,9) is an autosomal recessive disorder characterized by eczema, clubbing of fingers, large hands and feet, thick arms and legs due to periosteal new bone formation, and persistent anterior fontanel. Onset has been reported during the second year of life.

The patient reported by Herbert and Fessel (24) had large, unusually shaped extremities since birth, which increased in thickness during adolescence, periosteal new bone formation affecting the distal ends of some of the long bones and clubbing of all fingers and toes, thickening of the skin of the lower legs, and acroosteolysis of the distal phalanges of the fingers and toes; there was no hyperhidrosis or cutis verticis gyrata, and facial features were normal.

Leibowitz and Kalk (33) reported a patient with coarsening of facial features beginning at puberty, cutis verticis gyrata, acneiform eruption on the face, unilateral ptosis, and prominent nasolabial folds; there was no clubbing or periostosis. The patient had depressed urinary excretion of 17-hydroxy- and corticosteroids, depressed response to thyrotropin-releasing hormone, and aminoaciduria.

Sirinavin et al (49) reported a 12-year-old girl, born to a consanguineous couple, with clubbing of fingers and toes since 7 months of age, hyperhidrosis of hands and feet, slightly tender and swollen distal phalanges, dystrophic nails, thickening of soft tissues of knees and ankles, generalized osteoposis, joint effusion in knees, and acroosteolysis. Although other skeletal abnormalities were present, subperiosteal ossification was not found.

Thomas (51) described a 22-year-old male with marked clubbing of fingers and toes of unknown onset and mild periosteal thickening of the tibias and forearms; the remainder of the physical examination was unremarkable. His father had similar hand and foot abnormalities.

References [Pachydermoperiostosis (Touraine-Solente-Golé syndrome, primary [idiopathic] hypertrophic osteoarthropathy)]

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Pycnodysostosis

Maroteaux and Lamy (32) and Andrén et al (2), in 1962, defined pycnodysostosis (the Greek word *pyknos* meaning "thick, stocky") as a syndrome consisting of short stature, osteopetrosis, abbreviated terminal phalanges, cranial anomalies, such as persistence of fontanels and failure of closure of cranial sutures, and hypoplasia of the mandibular angle.

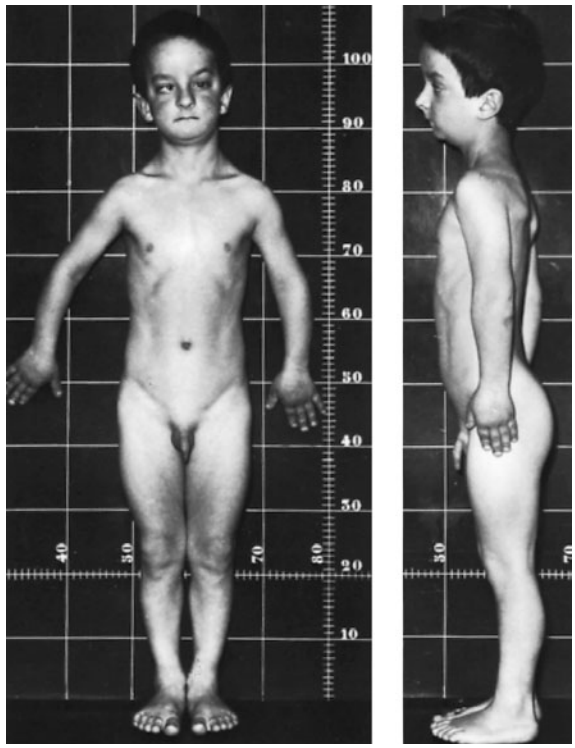


Fig. 9–45. *Pycnodysostosis.* (A,B) Eight-year-old boy with short stature, exophthalmos, and small mandible. (From A Giedion and M Zachmann, Helv Paediatr Acta 21:412, 1966.)

Several cases of the syndrome were published as examples of other disorders, chiefly osteopetrosis (1,40) and cleidocranial dysplasia (37,523). The first documented case is that of Montanari (37) in 1923. About 125 cases have been reported (26,41,48).

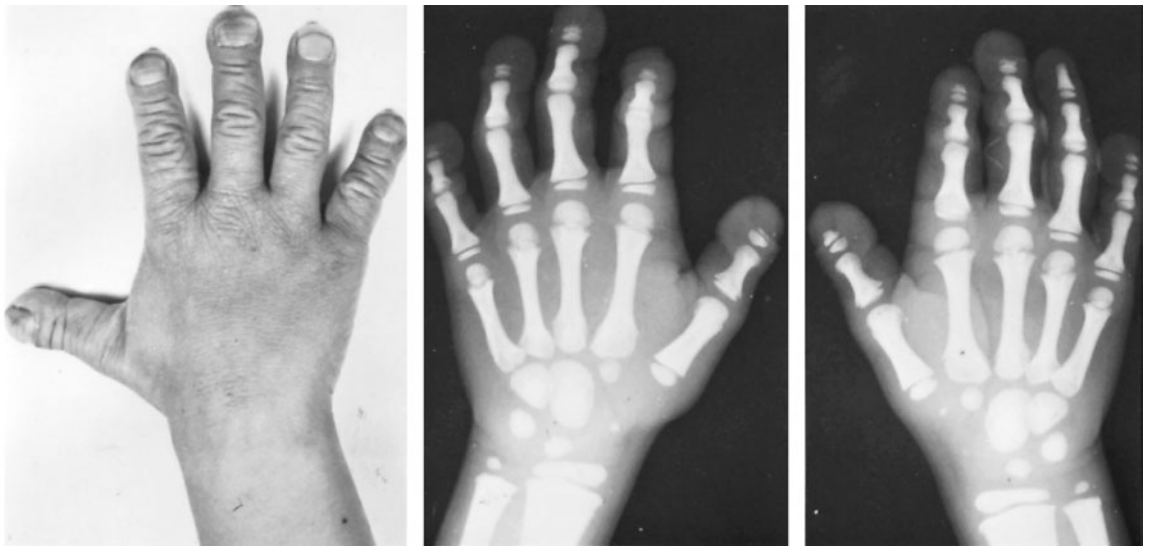
Affected sibs have been noted in many instances (1,12,30,35,37, 40,41,43,47,49,52,53). The syndrome has also been seen in identical twins (2). Parental consanguinity has been noted in more than 30% (44,48). Autosomal recessive inheritance is indicated. The disorder is more common in Japanese (38). Through a pooling strategy (41) and homozygosity mapping (18,19), the gene was located at chromosome 1q21. Gelb et al (20) found mutations in the cysteine protease gene cathepsin K. This is a lysosomal protease with high expression in osteoclasts, which secretes the enzyme for bone matrix degradation. Hence, pycnodysostosis is a lysosomal disorder caused by defective tissue-specific expression of cathepsin K (20,21a,22a).

A patient with pycnodysostosis due to paternal uniparental disomy of the 1q21 region has been described (21). It has been suggested that Toulouse-Lautrec had the syndrome (22,33), but a detailed study of pertinent data has shed doubts on this suggestion (17). The patient reported by Roth (42) does not have pycnodysostosis.

Mental development is normal, although exceptions have been described (5,26).

Facies. The head appears large because of occipital bulging. A large beaked nose with mild exophthalmos, deep nasolabial skin folds, and micrognathia are characteristic (Fig. 9–45). The micrognathia, together with the relatively long soft palate, can be severe enough to cause chronic respiratory airway obstruction (16). Several patients have developed sensorineural deafness (15,35). Mocan et al (36) described a hemangioma of the skull.

Skeletal alterations. Because of shortness of the extremities, adult height is reduced to 135–160 cm. Soliman et al (46) and Darcan et al (10) described defective growth hormone levels and improved growth after growth hormone supplementation. The trunk is not shortened but often exhibits marked pectus excavatum. The terminal phalanges are



A B C

Fig. 9–46. *Pycnodysostosis*. (A–C) Terminal digits of fingers reduced and widened. Nails often overlap ends of fingers. Note increased bone density, acroosteolysis of terminal phalanges, also pointed terminal phalanx. (From SE Shuler, Arch Dis Child 38:620, 1963.)

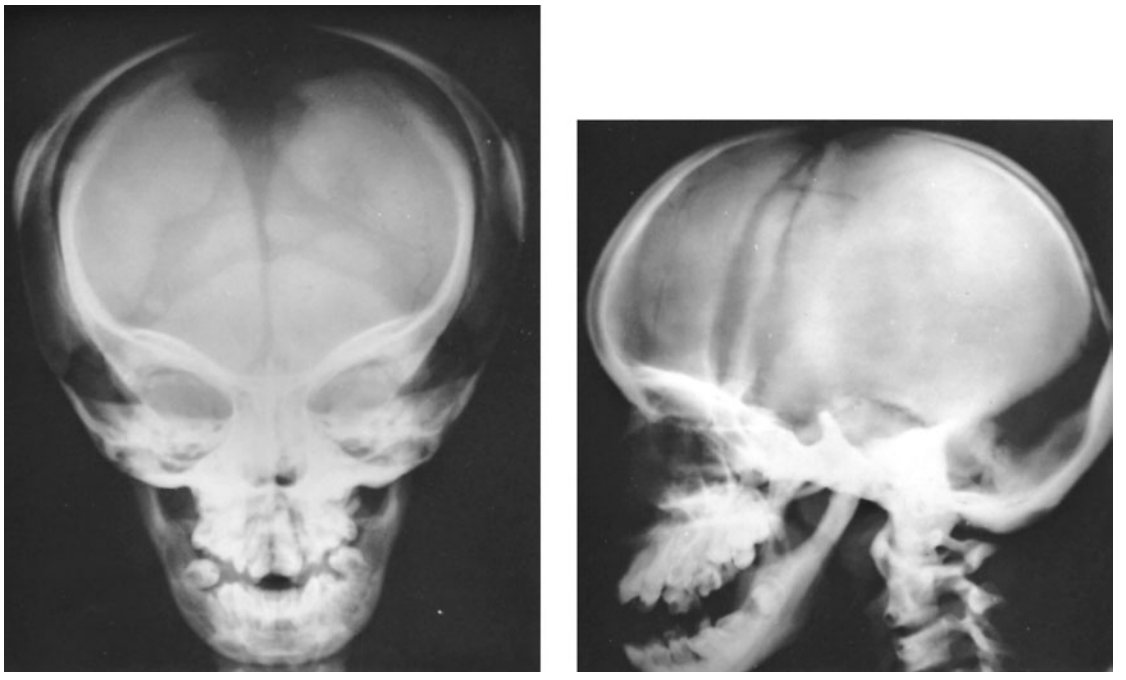
underdeveloped and widened and often present a drumstick appearance (Fig. 9–46 A–C). The nails may be thin and hypoplastic.

The acromial end of the clavicle is usually somewhat hypoplastic (2,45,48,52). Bilateral genua valga is frequent. Partial disappearance of the hyoid bone has been reported (51). In one report, indifference to bone-related pain was noted (12).

On radiographic examination, the skull is dolichocephalic with frontal and occipital bossing (1,20,49). Most cranial sutures and fontanels are open, especially the parietooccipital. The bones of the calvaria are thin, dense, and without diploic markings. Wormian bones are commonly observed (2,12,15,43,44,47). Craniosynostosis has been reported rarely (6). The frontal sinuses are consistently absent, and other paranasal sinuses are hypoplastic or missing. The mastoid air cells are often not pneumatized (2,43,44,52) (Fig. 9–47).

There is increased radiopacity of all bones, but especially of the long bones, spine, and cranial base. Through densitometry, Karkabi et al (24) found the increased bone density to be mainly in the trabecular bone and not in the cortical bone. Spondylolysis of cervical vertebra has been described (9,12,48). Bone fragility is increased, over 70% having multiple fractures during their lifetime (5,35,50). The terminal phalanges of the fingers and toes exhibit fragmentation of the heads with preservation of the bases, osteolysis of the unguiculate portions, or narrowing of the ends

Fig. 9–47. *Pycnodysostosis.* Radiographs. (A,B) Absence of fusion of sutures and closure of fontanels. Increased bone density and absence of mandibular angle. (From SE Shuler, Arch Dis Child 38:620, 1963.)



A B

of otherwise normal terminal phalanges (4,25). Brachymesophalangy of the fifth fingers, less often of the index finger, is a common finding. The fourth metatarsal is occasionally abbreviated (48).

Microscopic studies of the involved bones (45,47,49) have shown reduction in osteoclastic and osteoblastic activity, with reduced rates of bone formation and resorption. The bone has been found to be markedly sclerotic. Electron microscopic studies have demonstrated that osteoclasts have diminished or even inactive secretory functions (34).

Eyes. The eyes may be somewhat exophthalmic (1,48,49,52) with blue sclerae (53).

Oral manifestations. Obtuse mandibular angle is a constant feature. Facial bones are often underdeveloped, with relative mandibular prognathism (2,38,52,54). Oral and dental anomalies include premature or delayed eruption (1,13,14,21,48,54), ectopic teeth (14), enamel hypoplasia (15,40,49), malposed teeth (7,13,35,48,49), grooved palate (35,38,48,49), and sometimes cleft palate (15). The soft palate tends to be long (38,55). Lacey et al (28) described a patient with short and blunted tooth roots and multiple congenitally missing permanent tooth germs. Several patients developed osteomyelitis of the mandible after tooth extractions (23,35,43), which may be related to the impaired monocyte killing activity (24).

Differential diagnosis. Acquired acroosteolysis may occur in workers synthesizing polyvinyl chloride (31) and in a host of other disorders: psoriasis, various collagen disorders, thermal injury, hyperparathyroidism, and in guitar players (11). Lamy and Maroteaux (29) described isolated autosomal dominant acroosteolysis. Differential diagnosis includes *osteopetrosis, Hajdu-Cheney syndrome*, and *mandibuloacral dysplasia*.

Hajdu-Cheney syndrome is associated with progressive reduced height, kyphosis, bathrocephaly, basilar impression, numerous wormian bones, absence of frontal sinuses, and fusion of the spinous processes of the cervical vertebrae. The terminal phalanges are shortened and often exhibit tenderness, pain, and paresthesia. The alveolar process often is markedly atrophic, but the mandibular angle is not missing as in pycnodysostosis. It has autosomal dominant inheritance.

Stanescu osteosclerosis syndrome, a rare form of craniofacial dysostosis, inherited as an autosomal dominant trait, is characterized by small skull, thin cranial bone, depressions over the frontoparietal and occipitoparietal sutures, poorly developed mandible with obtuse angle, exophthalmos, and very short limbs with massive thick cortices.

Mandibuloacral dysplasia resembles pycnodysostosis in delayed closure of skull sutures, wormian bones, and hypoplasia of terminal phalanges, but there is no increase in bone density or aplasia of the mandibular angle. Instead there is antegonial mandibular notching, stiff joints, and cutaneous atrophy.

Laboratory aids. Reduced serum alkaline phosphatase has been found in a few cases (49,53). Cabrejas et al (8) described increased intestinal calcium absorption and diminished exchangeable calcium pool turnover as well as diminished bone accretion rate. Hepatosplenomegaly, thrombocytopenia, and iron deficiency anemia also have been found (4,5,27,30,34,39). Monocyte function tests showed normal phagocytic activity and impaired killing activity (24).

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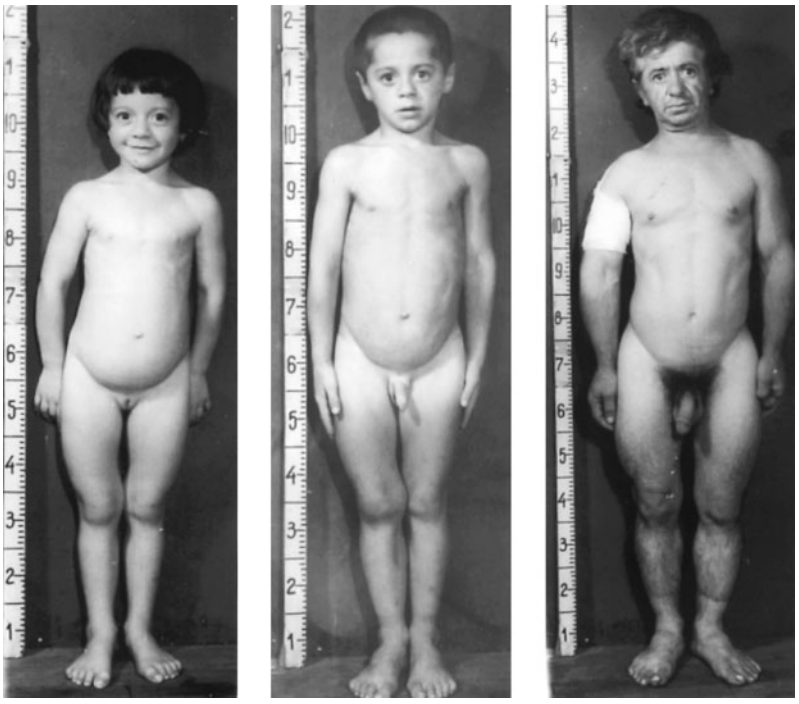

A B C

Fig. 9–48. *Osteosclerosis syndrome, Stanescu type.* (A–C) Short stature, brachycephaly, ocular proptosis. (From C Maximilian et al, J Genet Hum 29:129, 1981.)

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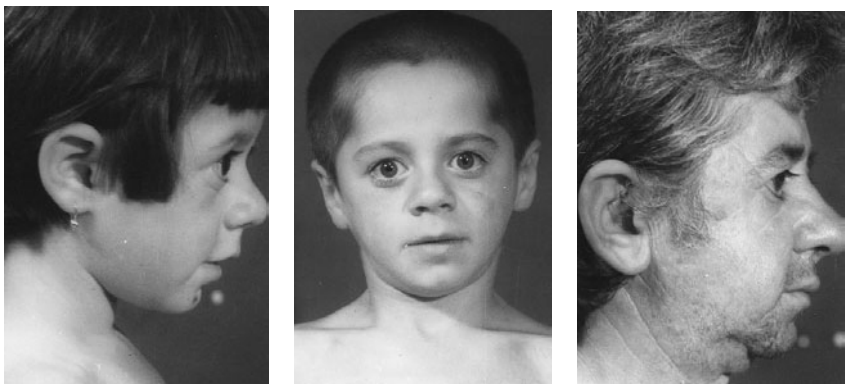
Osteosclerosis syndrome, Stanescu type

Osteosclerosis, Stanescu type, is characterized by short stature, hypoplastic midface, prognathism, long thorax, lack of pneumatization of frontal and sphenoidal bones, and dense cortices of long bones (Figs. 9–48 to 9–50). In the family first reported by Stanescu et al (5) and later by Maximilian et al (4), 14 individuals were affected. Dipierri and Guzman (1) described an affected mother and daughter, and Horovitz et al (3) expanded the phenotype in describing a mother and son and 11 other possibly affected family members, which allowed inclusion of the sporadic case reported by Hall (2) despite lack of brachydactyly and severe involvement of the spine and thorax.

Horovitz et al (3) provided a good review. Generally, patients have short stature due to shortened limbs. They may have prominent forehead, ocular hypertelorism, and exophthalmos. The malar bones are usually hypoplastic. The nasal base can be wide, and the nares prominent. The palate is shallow; the teeth are abnormally implanted and show increased caries due to insufficient enamel formation. The jaw may be relatively large.

Kyphosis can be expressed, the thorax gives a long impression, and the fingers are short. Radiologically, sinus development is deficient, the frontoparietal and occipitoparietal sutures are depressed, and the mandible small, but with an open angle that causes prognathism. The cortex of the long bones is thick, the marrow space is small. The first sacral vertebra



A B C

Fig. 9–49. *Osteosclerosis syndrome, Stanescu type.* (A–C) Note brachycephalic skull in B, mild midface deficiency with ocular proptosis and micrognathia in A and C. (From C Maximilian et al, J Genet Hum 29:129, 1981.)

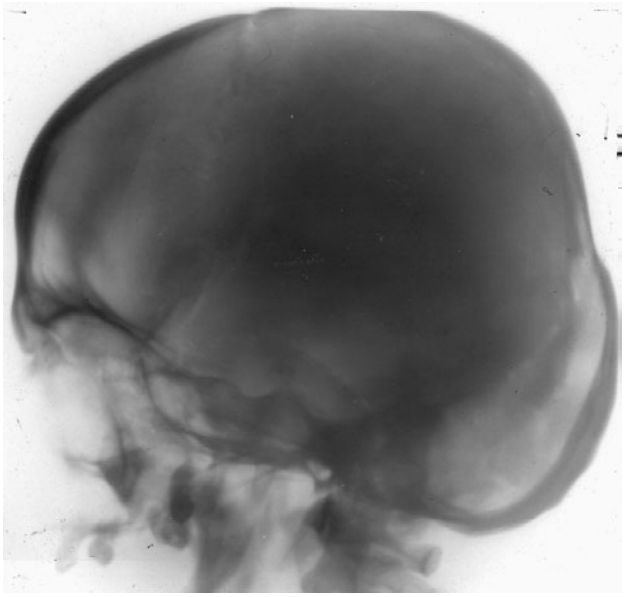


Fig. 9–50. *Osteosclerosis syndrome, Stanescu type.* Dense cranium, shallow sella, and obtuse mandibular angle. (From V Stanescu et al, Rev Fr Endocrinol Clin 4:219, 1963.)

may be lumbarized. Several patients had exostoses (4), wormian bones (3,5), and calcification of falx (3).

Inheritance is autosomal dominant.

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Stickler syndrome (hereditary arthroophthalmopathy)

Stickler and Pugh and Stickler et al (45,46), in 1967–68, described the classic form, now called *Stickler syndrome type 1* and constituting about 75% of cases. It is characterized by flat midface, cleft palate, high myopia with retinal detachment and cataracts, hearing loss, arthropathy with generally mild spondyloepiphyseal dysplasia, and either diminished height or Marfan-like build in some cases. The binary combination of eye changes and cleft palate was described both earlier (10,19) and later by a large number of authors (8,9,11,13,17,18). We believe that Walden syndrome (51) is the same as Stickler syndrome. Excellent reviews are those of Temple (47) and Snead and Yates (39).

Stickler syndrome type 2, representing the other 25%, is characterized by midface hypoplasia, anteverted nares, small mandible, sensorineural (40%) or mixed (30%) hearing loss, and joint pain (50%). Height is not reduced. There is mild myopia (5,14,27,41). Phenotypically, Stickler syndrome type 2 is similar to *Marshall syndrome* (35), the latter probably having in-frame deletion near the 3′ end of the gene.

Inheritance for both types is autosomal dominant with considerable variable expression, especially interfamilial but also intrafamilial (57). About 70% of cases of Stickler syndrome are due to mutations in the COL2A1 gene (Type 1 Stickler syndrome) that maps to 12q13.11–q13.2 (1,2,5,6,12,14,21,30,32,40,50,52,54,55). Virtually all mutations involve premature stop codons (1,32,55) predicting a truncated protein. An unusual exception is the family reported by Ballo et al (3).

Table 9–4. Stickler syndrome and related syndromes[a]

	Stickler syndrome		OSMED[b]	
	Type 1	Type 2	Heterozygous	Homozygous
Findings				
Midface hypoplasia	+	+	(+)	++
Hearing loss	+	+	+	+
Ocular changes	+	+	−	−
Small stature	−	−	−	+
Vertebral dysplasia	+	+	+	+
Long bones slender	+	?	−	−
Enlarged epiphyses	−	?	+	++
Flattened epiphyses	+	?	−	−
Mutated gene	COL2A1	COL11A1	COL11A2	COL11A2
Chromosome	12q13.11	1p21	6p21	6p21
Inheritance	AD	AD	AD	AR

[a] From T Pihlajamaa et al, Am J Med Genet 80:115, 1998.
[b] Heterozygous OSMED: non-ocular "Stickler" syndrome or Weissenbacher-Zweymüller phenotype; homozygous OSMED: Insley-Astley syndrome.

Type XI collagen, a heterotrimer composed of α1(XI), α2 (XI), and α1 (II) chains copolymerizes with Type II collagen and probably regulates fibril thickness. Mutations of the COL11A1 gene that maps to 1p21 lead to Type 2 Stickler syndrome and/or Marshall syndrome (15,31, 36–39).

Non-ocular "Stickler" syndromes were mapped at 6p21 near the COL11A2 gene (7). These have been collectively called OSMED (otospondylo-megepiphyseal dysplasia), a condition that may be dominant (heterozygous; also called Weissenbacher-Zweymüller phenotype) or recessive (homozygous; also called Insley-Astley syndrome). The symptoms resemble Stickler syndrome, but midface hypoplasia is more expressed, and patients are small, have large epiphyses, and lack eye involvement (Table 9–4). It is caused by mutations in the COL11A2 gene on chromosome 6p21 (31,38,48,49). The original patient of Weissenbacher and Zweymüller (53) has been found to have a dominant heterozygous COL11A2 mutation (28). There is still further genetic heterogeneity (27,50,52,54).

Facies. The craniofacial spectrum ranges from an essentially normal face (15%–25%) to midfacial flattening due to short maxilla, prominent eyes, epicanthic folds, depressed nasal bridge, anteverted nares, long philtrum, and small chin (Fig. 9–51A–C). The facies becomes less distinctive with age. Cleft palate, submucous cleft palate, bifid uvula, or abnormal palatal mobility has been reported in 20% of type 1 cases, less often in type 2 cases (16) (Fig. 9–51D). About 30% of infants with Robin sequence have Stickler syndrome (22,33).

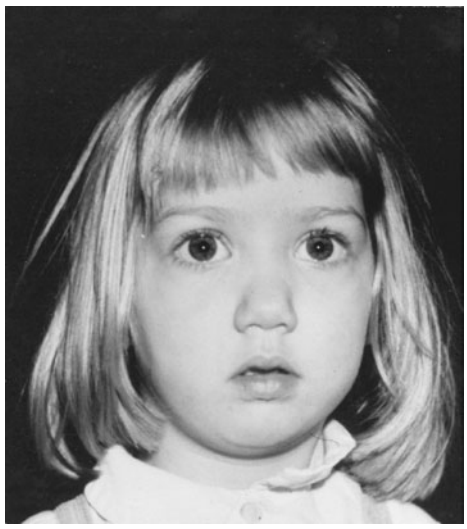
Eye. In type 1, myopia, 8–18 diopters, is found in 75%–80% of patients, usually earlier than 6 years of age. It is possibly congenital and stable. Before the twentieth year, paravascular pigmented lattice degeneration or retinal detachment is observed in 70%, often bilaterally. If untreated, this leads to blindness. Associated eye findings are astigmatism (60%), wedge- and fleck-type curved cortical cataracts (45%), strabismus (30%), and open-angle glaucoma (10%). Detachment occurs in 60%. Eye findings have been extensively discussed (4,6,20,25,34,56).

In Type 2 families, one sees severe early-onset myopia and retinal degeneration, but the vitreous changes are not membranous as in type 1 (31,40,54). There are sparse and irregularly thickened (beaded) bundles of fibers throughout the vitreous cavity. Detachment occurs in less than 50% (39).

Ears. Progressive sensorineural high-tone hearing loss has been noted in 60% of type 1 patients (17,26,29,42,45,47,57). In type 2, sensorineural loss occurs in 90%. Conductive hearing loss has rarely been noted (43,47).

A

B



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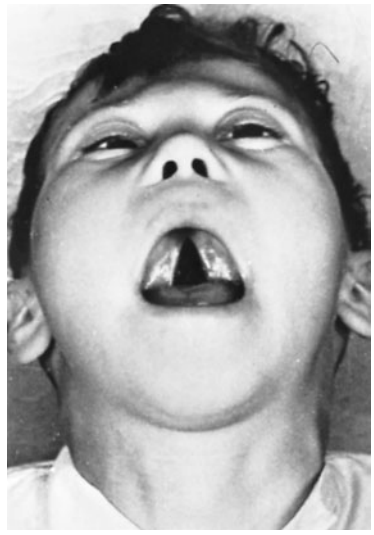

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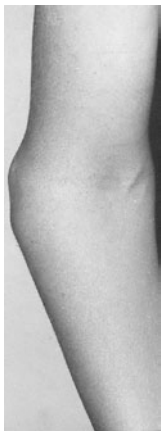

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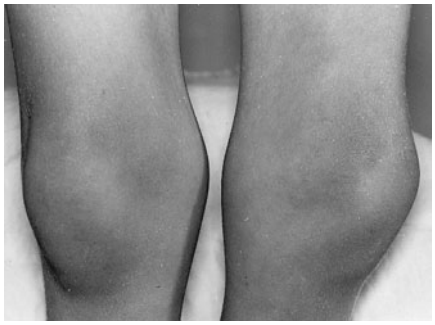

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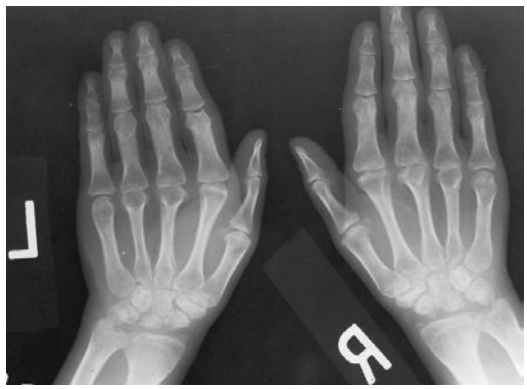

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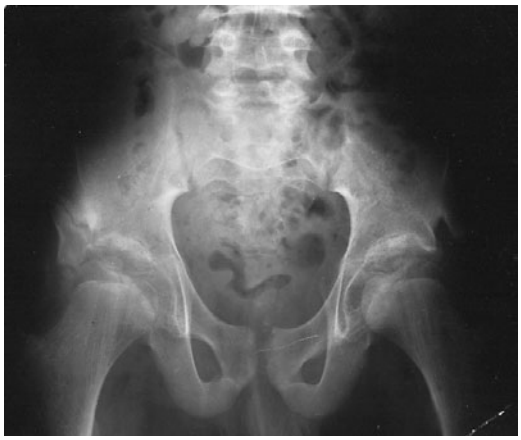

H

Fig. 9–51. *Stickler syndrome.* (A,B) Some patients have body habitus resembling Marfan syndrome. (C) Round face with midface hypoplasia. (D) Cleft palate. (E,F) Enlargement of elbows and kness. (G,H) Flattening of the ends of metacarpals and radii, and degenerative changes at hip. (A,B from GB Stickler and DG Pugh, Mayo Clin Proc 42:495, 1967. C from J Hall, Birth Defects 10(8):157, 1974.)

Musculoskeletal findings. Some patients have Marfanoid body habitus (Fig. 9–51A,B), but at least 25% are below the 3rd centile in height. In childhood, joint hypermobility is common (23) but decreases with age. The joints may be enlarged, often hyperextensible (35%) and sometimes painful and warm with use, becoming stiff with rest (Fig. 9–51E–G). Talipes equinovarus may occur (17).

In infancy, there is rhizomelic shortening of limbs, metaphyseal widening, and vertebral coronal clefts. During childhood, mild spondyloepiphyseal dysplasia (multiple epiphyseal ossification disturbances, moderate flattening of vertebral bodies) and diminution of the width of the shaft of tubular bones are noted. Scoliosis has been evident in 10%. The pelvic bones are hypoplastic, the femoral necks being poorly modeled and plump (Fig. 9–51H). There is progressive early joint degeneration in 30%, beginning in the third or fourth decades (23). The skeletal features observed radiographically and the clinical joint involvement are not always present in Stickler syndrome (17,29,43). Short cranial base and hypoplastic midface have been borne out by cephalometric study (33).

Other findings. Mitral valve prolapse has been found in almost 50% in some studies (24) but not in others (39).

Differential diagnosis. All patients with *Robin sequence*, especially with an autosomal dominant history, should be examined periodically for severe myopia to prevent ocular complications of Stickler syndrome. Other disorders with some degree of overlap include *Kniest dysplasia, SED congenita, Wagner syndrome, Marshall syndrome*, and SPONASTRIME *dysplasia*. SPONASTRIME dysplasia exhibits midfacial hypoplasia but does not manifest myopia, generalized epiphyseal dysplasia, or sensorineural hearing loss. The so-called Weissenbacher-Zweymüller syndrome is not, in fact, a syndrome but a phenotype common to Kniest syndrome, OSMED, and Stickler syndrome. *Knobloch syndrome*, a recessive disorder, is characterized by severe myopia and exencephaloceles, most often in the occipital area.

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Short stature, low nasal bridge, cleft palate, and sensorineural hearing loss (OSMED, megepiphyseal dysplasia, non-ocular Stickler syndrome)

Several authors (1–7,9,11,14) have described a syndrome characterized by midface hypoplasia, generalized epiphyseal dysplasia, and sensorineural hearing loss. Giedion et al (3) and Gorlin et al (4) used the terms *oto-spondylo-megaepiphyseal dysplasia (OSMED)* and *megepiphyseal dwarfism*, respectively, to apply to this disorder. The same syndrome was described by Insley and Astley (5) and Nance and Sweeney (11). About 20 cases have been reported. We are uncertain about the diagnosis of two cases (8,13).

Both homozygous and heterozygous forms have been described. Autosomal recessive inheritance is indicated by multiple affected sibs and parental consanguinity (5,10,14,16). Homozygosity for a missense mutation in the COL11A2 gene on 6p21.3 has been demonstrated (9a,16,17). The original patient with *Weissenbacher-Zweymüller syndrome* has been shown to have heterozygous OSMED (nonocular Stickler) syndrome (2,13,17) (Table 9–4).

Feeding difficulties are noted during the neonatal period, and infancy is characterized by enteritis and respiratory problems (bronchitis, pneumonia, etc.) that recur throughout life.

Stature is significantly reduced in most cases.

The nose is very small with anteverted nostrils and the nasal bridge is severely depressed (Fig. 9–52A–D). High myopia is not seen because the mutated α2 (XI) chain is not expressed in the vitreous (15). The midface is hypoplastic and the mandible small. Cleft palate has been observed in about 65%. Moderate to severe nonprogressive sensorineural or rarely mixed hearing loss has been documented in most cases.

The limbs are short. The hands are short with stubby fingers. The metacarpophalangeal joints are enlarged and have reduced mobility, and the fifth metacarpals are often shortened. In later life, the joints become enlarged and painful, and there is progressive lumbar lordosis. Radiographically, at birth, the leg bones are relatively short and broad (dumbbell form) with mild metaphyseal flaring and absent to small capital femoral epiphyses. The epiphyses are enlarged (Fig. 9–52E–G). Coronal clefts of the spine are seen in infancy. During childhood, platyspondyly with anterior wedging becomes evident with squared iliac wings. Wide flat epiphyses, metaphyseal flaring, mild vertebral dysplasia, large fused carpal bones (50%), and short metacarpals are seen in adults. The tarsal bones are large in 50%. Osteoarthritis is manifest in early adulthood.

Histologic study of cartilage shows severe osteoarthritis. Ultrastructurally, collagen fibrils are increased in diameter and exhibit aggregation (16). This reflects the size-limiting function of type XI collagen.

The homozygous recessive syndrome should be distinguished from types 1 and 2 *Stickler syndrome* and from the dominantly inherited nonocular form of Stickler syndrome due to a COL11A2 splice site mutation (2,17). Both OSMED and Stickler syndrome exhibit midface hypoplasia, epiphyseal dysplasia, and hearing loss that are more marked in OSMED. Myopia and vitreoretinal degeneration are not seen in OSMED. This can be explained by the absence of the α2-chain of type XI collagen in the human vitreous.

References [Short stature, low nasal bridge, cleft palate, and sensorineural hearing loss (OSMED, megepiphyseal dysplasia, non-ocular Stickler syndrome)]

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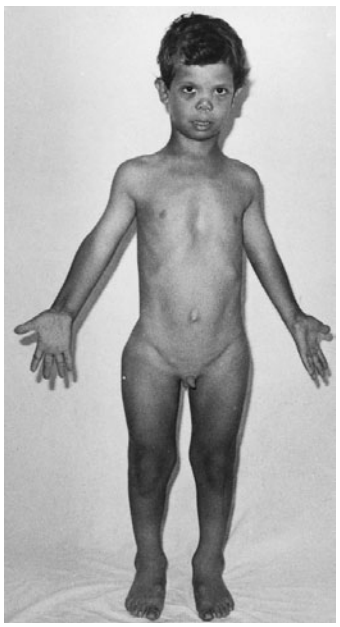
Weissenbacher-Zweymüller phenotype

The Weissenbacher-Zweymüller phenotype, a congenital neonatal rhizomelic dwarfism with metaphyseal widening of long bones and vertebral coronal clefts, first described in 1964 (10), has been considered to be the neonatal form of Stickler syndrome (4,8,11), but may also be seen in *OSMED* and in *Kniest syndrome*. Chemke et al (1), in 1992, presented a critical analysis of reported cases and demonstrated autosomal recessive inheritance. This is supported by two affected sibs in an inbred kindred. We believe that they had OSMED. Pihlajamaa et al (6) demonstrated that the original patient had heterozygous OSMED caused by a mutation in COL11A2 (Table 9–4).

There is short length at birth. The limbs are abbreviated. The face is flat, the nose small. The mandible is hypoplastic and the palate cleft (Robin sequence). There may be nasal root depression and mild sensorineural hearing loss (1–3,5,8,9). There is no eye involvement.

The long bones exhibit rhizomelic shortness with widened metaphyses, especially the distal femur. Further, there is a characteristic coronal clefting of lumbar vertebrae. These changes disappear with time, and there is catch-up growth after 3 years of age (1–3,5).

The identical twins reported by Ramer et al (7) with occipital encephalocele and meningocele and hearing loss, respectively, are difficult to classify. The children described by Kelly et al (4) and Winter et al (11) appear to have *Stickler syndrome*.



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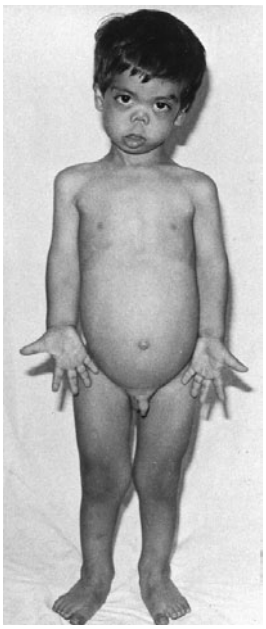

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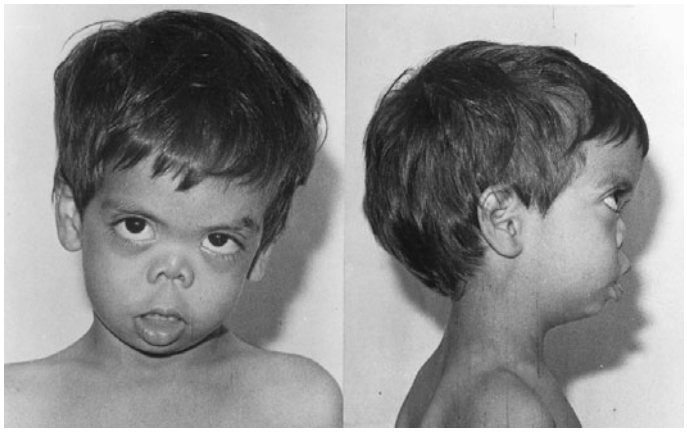

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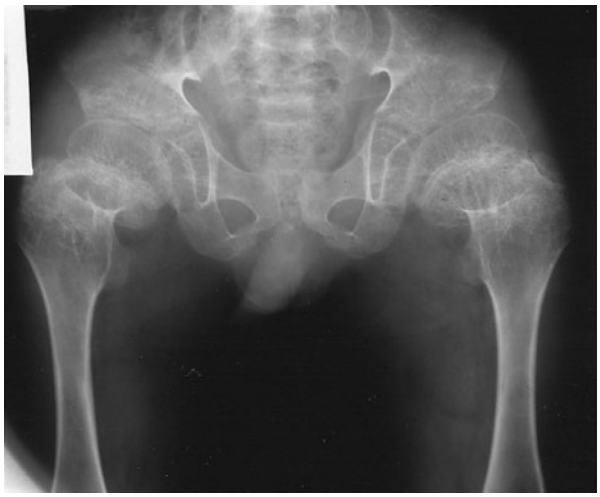

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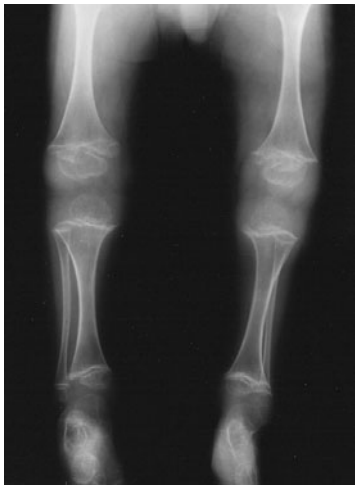

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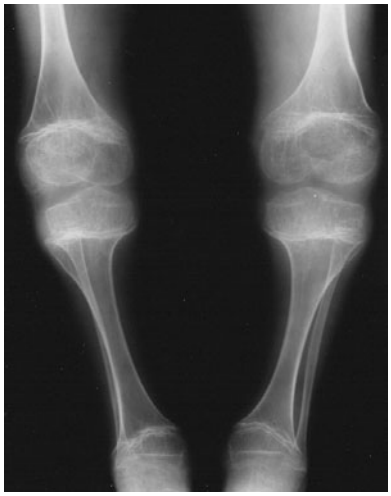
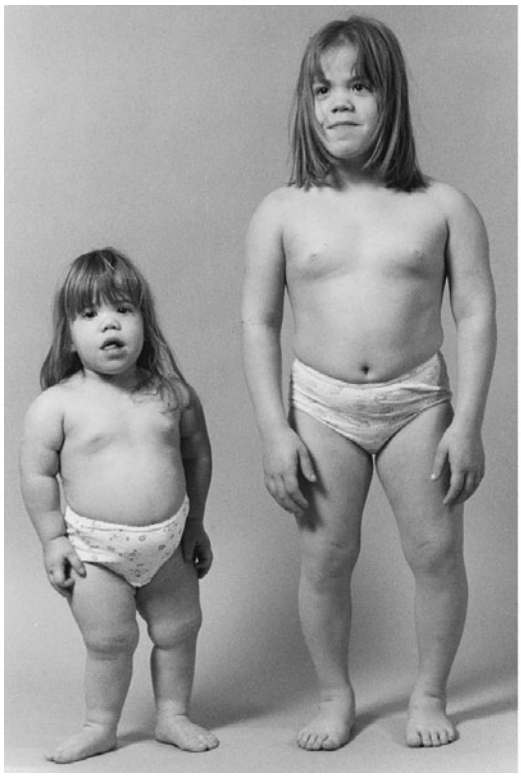


G

Fig. 9–52. *Short stature, low nasal bridge, cleft palate, and sensorineural hearing loss (OSMED) syndrome*. (A–D) Two affected brothers with close-up of younger showing hypoplastic nose and midface. (D–F) Grossly enlarged epiphyses of long bones. (A–D courtesy of C Salinas, Charleston, South Carolina.)



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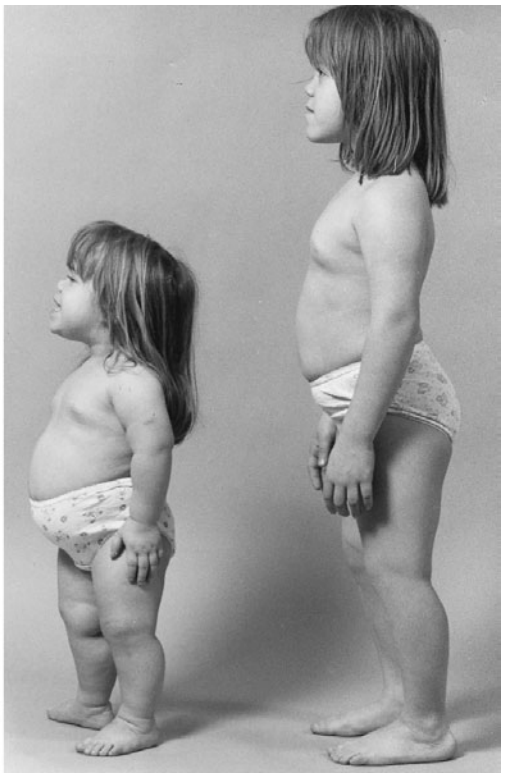

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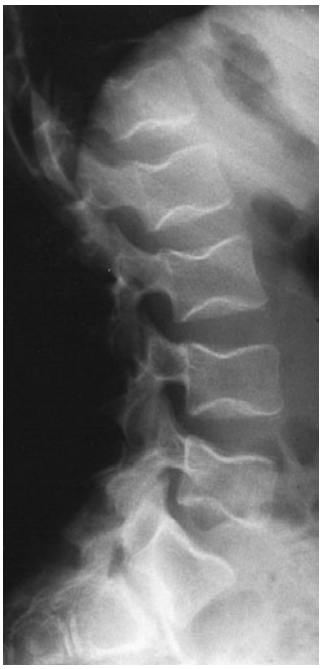

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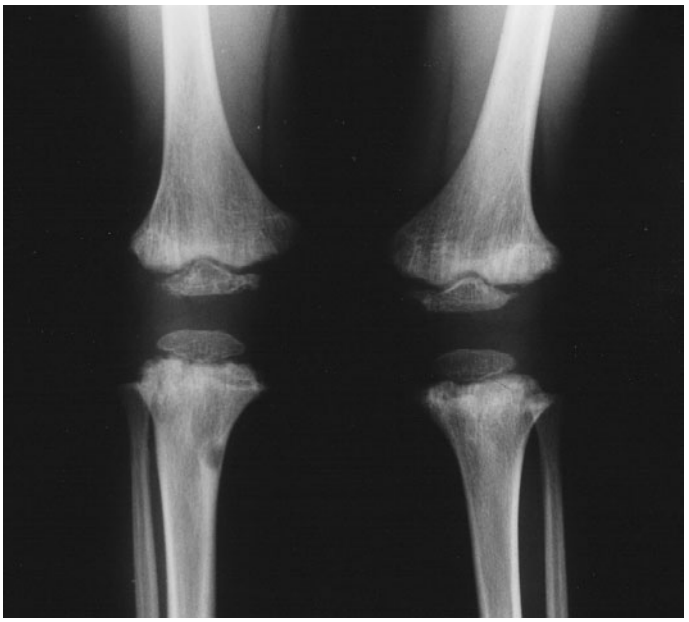

D

Fig. 9–53. *SPONASTRIME dysplasia*. (A,B) Midface hypoplasia and angular deformity of legs. (C) Increased lumbar lordosis, deformity of vertebral bodies with thickened concave end plates. (D) Mildly striated metaphyses. (A,B,D from L Langer et al, Am J Med Genet 63:20, 1996. C from S Fanconi et al, Helv Paediatr Acta 38:267, 1983.)

References (Weissenbacher-Zweymüller phenotype)

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10. Weissenbacher G, Zweymüller E: Gleichzeitiges Vorkommen eines Syndroms von Pierre Robin und einer fetalen Chondro-dysplasie. Monatsschr Kinderheilkd 112:315–317, 1964.

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SPONASTRIME dysplasia

Fanconi et al (4) and other authors (2,3a,3,5–10) have described a condition that resembles Stickler syndrome, but appears to have autosomal recessive inheritance because of occurrence in sibs and parental consanguinity (Fig. 9–53). Several authors named the entity SPONASTRIME dysplasia because of the *SPO*ndylar-*NA*sal anomalies and *STRI*ated *ME*taphyses, although the term was not thought very useful (6).

The disorder should be differentiated from *otospondylomegaepiphyseal dysplasia* (*OSMED*) (Table 9–4), in which the epiphyses are large and the joints are more markedly restricted in mobility, especially in the hands, and which is caused by mutations in the COL112A gene on chromosome 6p21. Differentiation of the *Weissenbach-Zweymüller* phenotype can be difficult (20).

Verloes et al (10) suggested division of SPONASTRIME dysplasia into two types, one with normal intelligence and normocephaly (4–8), and one with severe mental impairment, microcephaly, and a somewhat different facial appearance (2,10). Although splitting into two groups seems justified, the use of the terminology SPONASTRIME dysplasia for the patients of Camera et al (2,3) and Verloes et al (10) has been rightfully disputed (6).

Feeding difficulties have been noted during the neonatal period, and infancy has been characterized by recurrent infectious respiratory problems and enteritis. Developmental milestones are normal. The limbs are short. Prenatal and postnatal growth are below the 5th centile (−3.4 to −4.6 SD). The tallest adult male was 154 cm, the tallest female 145 cm (6). The elbows and metacarpophalangeal joints may have somewhat reduced mobility, but usually joints are hypermobile. Progressive kyphoscoliosis and lumbar lordosis have been noted. The abdomen is prominent.

The head appears large. The forehead is prominent, and the midface is hypoplastic. The nose is very small with anteverted nostrils and the nasal bridge is severely depressed (Fig. 9–53). Epicanthic folds are prominent. Intelligence is normal. Two patients had avascular necrosis of the hip, and one a subglottic stenosis and tracheomalacia (6).

Radiographically, the long bones, especially of the legs, are relatively short and broad with mild metaphyseal flaring and dense longitudinal metaphyseal striations around elbows and knees, especially after the fifth year. Metacarpals are short. Kyphoscoliosis and lumbar hyperlordosis are evident with defects of the upper anterior angles of the vertebral bodies at the thoracolumbar junction. Vertical striation of long bones can be present, too. Langer et al (6) carefully described the change in lumbar vertebral characteristics with time.

One patient had biochemically a growth hormone deficiency, but supplementation did not result in catch-up growth (6). Two other sibs had chemical hypothyroidism, again without change in growth pattern after treatment (6).

The EVE syndrome, an acronym for *E*piphyseal, *V*ertebral, and *E*ar dysplasia, is somewhat similar to SPONASTRIME dysplasia (1). It, too, is autosomal recessive. Another condition, *CODAS syndrome*, appears to be sporadic.

References (SPONASTRIME dysplasia)

1. Amiel J et al: Epiphyseal, vertebral, and ear (EVE) dysplasia: A new syndrome? J Med Genet 36:561–564, 1999.

2. Camera G et al: Sponastrime dysplasia: Report on two siblings with mental retardation. Pediatr Radiol 23:611–614, 1993.

3. Camera G et al: Sponastrime dysplasia: Report on a male patient. Pediatr Radiol 24:322–324, 1994.

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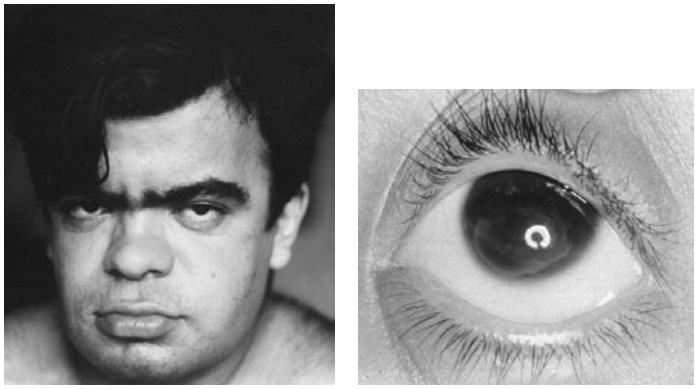

A B

Fig. 9–54. *Winchester syndrome*. (A) Coarse facies. (B) Peripheral corneal opacity. (From DW Hollister et al, J Pediatr 84:701, 1974.)

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7. Langer LO Jr et al: Sponastrime dysplasia: Diagnostic criteria based on five new and six previously published cases. Pediatr Radiol 27:409–414, 1997.

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9. Nishimura G et al: Another observation of Langer-type sponastrime dysplasia variant. Am J Med Genet 80:288–290, 1998.

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Winchester syndrome

Winchester et al (13), in 1969, reported two sibs from Puerto Rico with a connective tissue disorder of short stature, joint contractures with claw hands, peripheral corneal opacities, osteoporosis, carpal-tarsal osteolysis, stiff joints with severe rheumatoid-like joint destruction, skin lesions, and coarse facies (Figs. 9–54 to 9–57). Mentation was normal. Brown and Kuwabara (1) described the same sibs. Other patients have been recorded by several authors [2,3(Case 2),4–9,12]. Because of three sets of affected sibs and parental consanguinity (5,7,13), inheritance is autosomal recessive. Winchester et al (13) suggested their cases to have a mucopolysaccharidosis. Dunger et al (3) noted excessive collagen turnover in skin and gingival biopsies and identified an abnormal oligosaccharide in the urine of two patients of which the first one probably had infantile systemic hyalinosis (14). Repeat analysis did not confirm the findings (14). Hollister et al (5) suggested a collagen synthesis disturbance as they found focal areas of fibroblastic proliferation replacing normal collagen bundles in the skin. The condition is well reviewed by Winter (14).

Painful joints and limited mobility in the hands and sometimes wrists, knees, and spine arise in the first year of life or shortly thereafter. With time, clawing of the hands, and flexion contractures of other joints arise. Walking can be difficult. Height growth falls below the third centile. The face may be normal at birth, but later coarsens. There are prominent forehead, large and fleshy nose, and thick lips. Gingival enlargement is common. Most cases developed peripheral corneal opacities between the second and fifth year. Liver and spleen are not enlarged. The skin can be normal (1,13), or thickened, hyperpigmented and leathery (2,5,6), and may show patches of soft hair on limbs or trunk (3).

Radiologically, the main symptoms are generalized osteoporosis and progressive carpal and tarsal osteolysis. The long bones show widened metaphyses, somewhat irregular epiphyses, and a thin cortex. Destructive and erosive changes are clear on the articular margins of the metacarpals and metatarsals. Ankylosis may be present. The vertebral column can

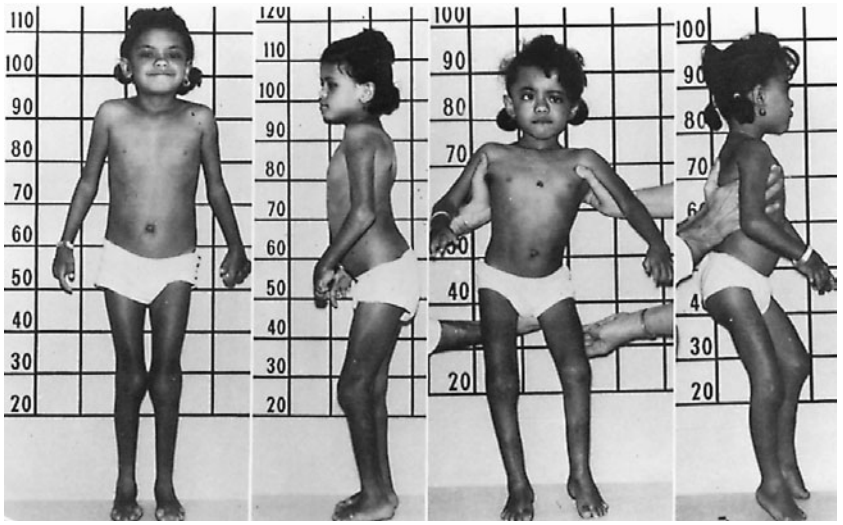
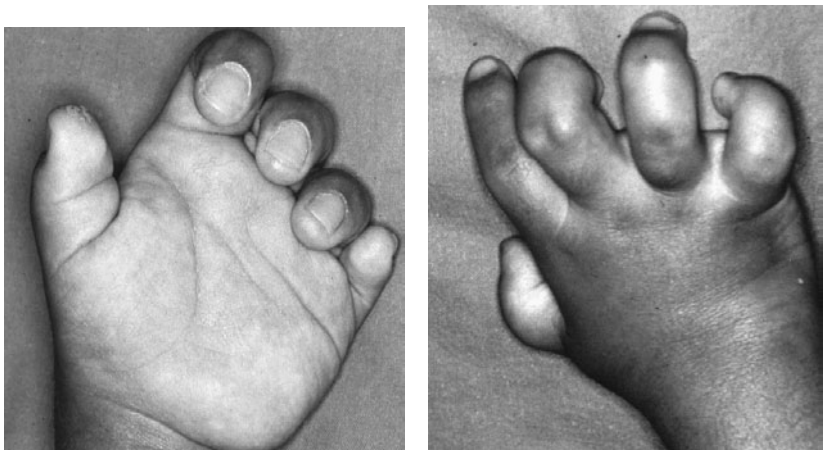


Fig. 9–55. *Winchester syndrome*. (A–D) Short stature and contractures in two sisters. (From DW Hollister et al, J Pediatr 84:701, 1974.)



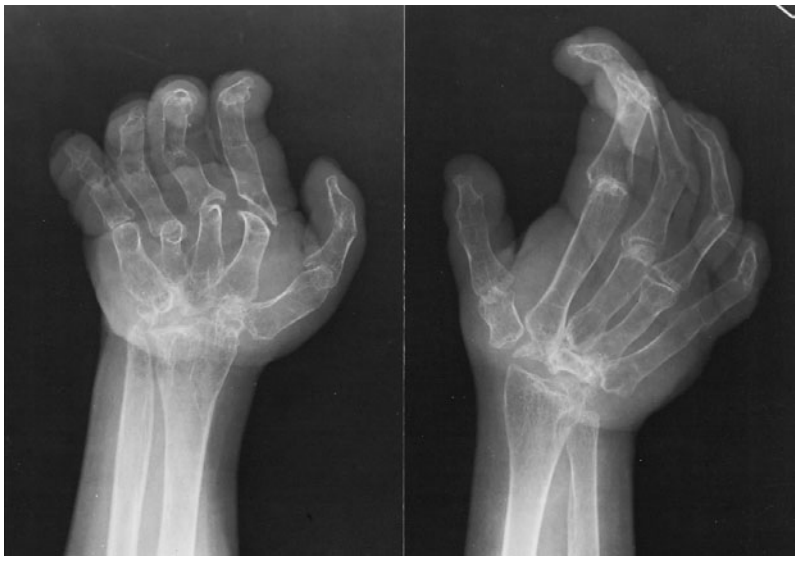
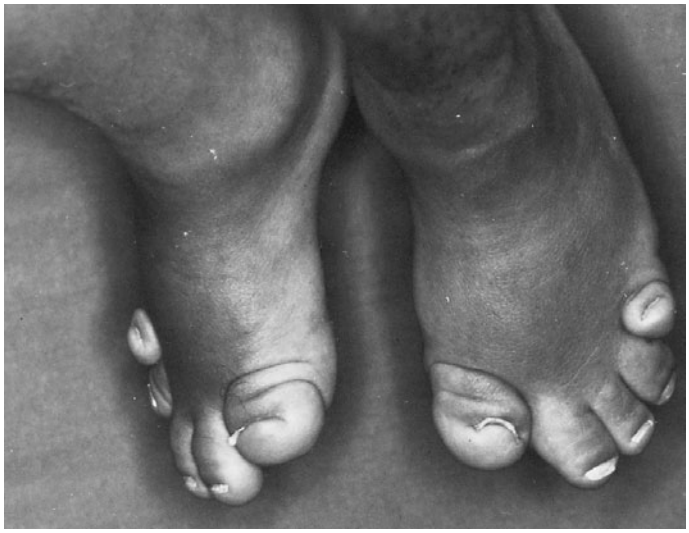


Fig. 9–56. *Winchester syndrome*. (A,B) Claw hands. (C) Osteoporosis, carpal osteolysis, and severe joint destruction. (From DW Hollister et al, J Pediatr 84:701, 1974.)



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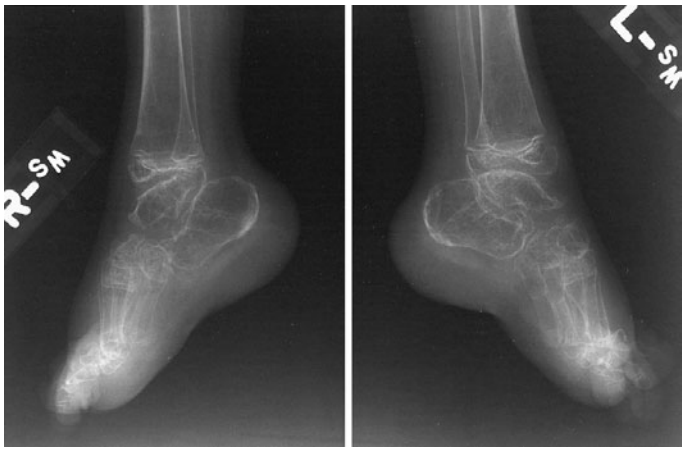

B

Fig. 9–57. *Winchester syndrome*. (A,B) Similar changes in feet. (From DW Hollister et al, J Pediatr 84:701, 1974.)

show compression of vertebral bodies, instability of first cervical vertebrae, and kyphoscoliosis.

Winchester syndrome resembles Farber disease and *Scheie disease*, and infantile systemic hyalinosis, and, in the first years, confusion with juvenile rheumatoid arthritis may arise. Torg et al (11) described three sibs with osteolytic changes of hands and feet, generalized osteoporosis, and skin symptoms (tender subcutaneous nodules, hyperpigmentation, erythema), which resembles Winchester syndrome strongly.

Shinohara et al (10) reported a single girl with generalized osteoporosis, osteolysis of hands and feet, corneal opacities, normal skin, and in addition pulmonary stenosis and nephropathy (proteinuria and focal glomerulosclerosis).

References (Winchester syndrome)

1. Brown SI, Kuwabara T: Peripheral corneal opacities and skeletal deformities: A newly recognized acid mucopolysaccharidosis simulating rheumatoid arthritis. Arch Ophthalmol 83:667–677, 1970.
2. Cohen AH et al: The skin in the Winchester syndrome: Histologic and ultrastructural studies. Arch Dermatol 111:230–236, 1975.
3. Dunger DB et al: Two cases of Winchester syndrome with increased urinary oligosaccharide excretion. Eur J Pediatr 146:615–619, 1987.
4. Gheysens E, Durero S: Le syndrome de Winchester: deux cas familiaux. Thèse Docteur Médicine, Nice, 1984.
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9. Prapanpoch S et al: Winchester syndrome. A case report and literature review. Oral Surg 74:671–677, 1992.
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12. Vouzellaud B: Le syndrome de Winchester: Contribution à partir trois cas familiaux. M.D. Thèse, Université Claude Bernard, June 23, 1988.
13. Winchester P et al: A new acid mucopolysaccharidosis with skeletal deformities simulating rheumatoid arthritis. Am J Roentgenol 106:121–128, 1969.
14. Winter RM: Winchester syndrome. J Med Genet 26:772–775, 1989.

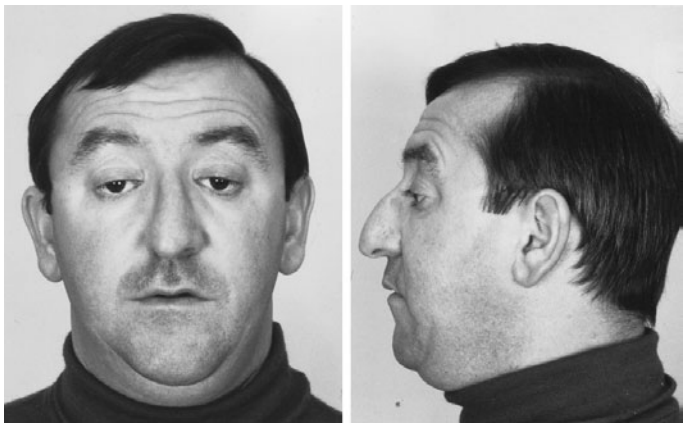
Mesomelic short stature, acral synostosis, unusual facies, umbilical anomalies, and agenesis of soft palate (Verloes-David syndrome)

Verloes and David (3) described a father and two children with mesomelic shortness of stature with severe alterations in the ankle, knee, and elbow. Other possible examples are those of Leroy et al (1) and Pfeiffer et al (2).

The facies was unusual with downslanting palpebral fissures, hypertelorism, ptosis, beaked nose, microretrognathia, and agenesis of the soft palate (Fig. 9–58A,B).

Skeletal anomalies included brachymetacarpy and brachymetatarsy of rays 3–5, partial fusion of proximal row of carpal bones, tarsometatarsal

Fig. 9–58. *Mesomelic short stature, acral synostosis, unusual facies, umbilical anomalies, and agenesis of soft palate*. (A,B) Downslanting palpebral fissures, hypertelorism, ptosis, beaked nose, small lower jaw. (C) Short fingers 3–5 due to brachymetacarpy; note clinodactyly of fifth fingers. (From A Verloes and A David, Am J Med Genet 55:205, 1995.)



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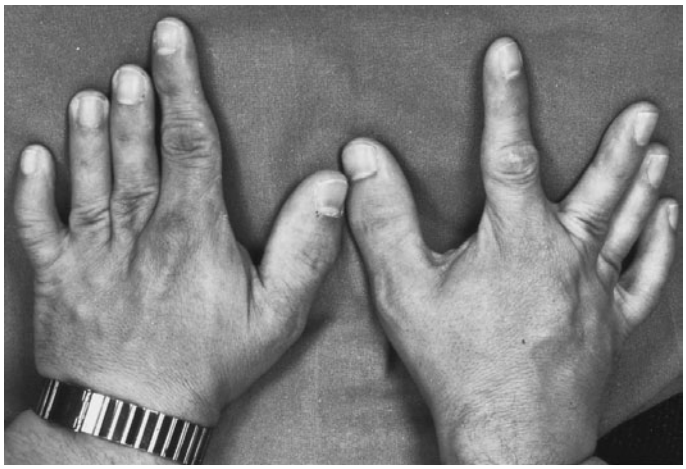

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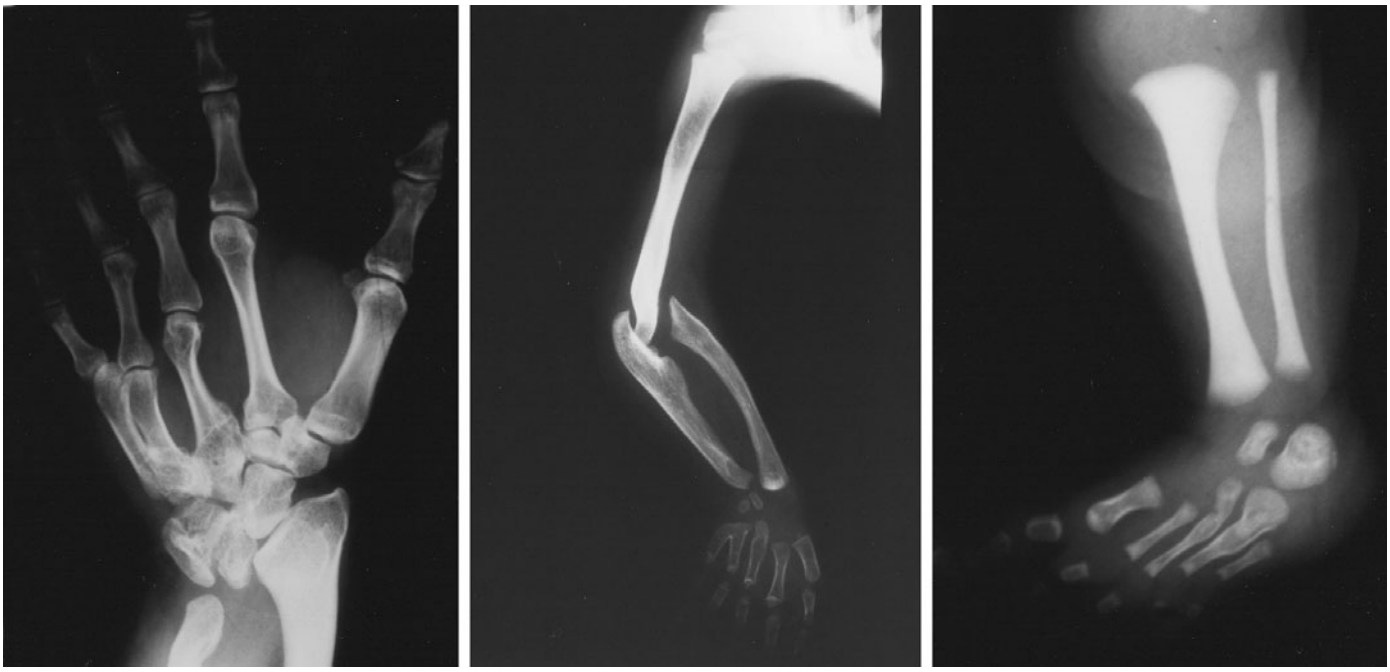

A B C

Fig. 9–59. *Mesomelic short stature, acral synostosis, unusual facies, umbilical anomalies, and agenesis of soft palate*. (A) Brachymetacarpalia, carpometacarpal synostoses, carpal coalition, bizarre bone relationship in wrist. (B) Early ossification of metacarpals, multiple synostoses at birth. (C) Distal leg at birth showing advanced ossification and early synostosis. (From A Verloes and A David, Am J Med Genet 55:205, 1995.)

fusion, and deformation of the radius and ulna somewhat resembling Langer-type mesomelic dysplasia (Figs. 9–58C and 9–59).

The umbilical cord near the body is covered with skin.

Inheritance is autosomal dominant.

References [Mesomelic short stature, acral synostosis, unusual facies, umbilical anomalies, and agenesis of soft palate (Verloes-David syndrome)]

1. Leroy JG et al: Dysmorphic facies, heart defect, hydronephrosis, bilateral club hand, and club foot due to acromesomelic dysostosis: Second edition of Verloes-David syndrome? XXI David W. Smith Workshop on Malformations and Morphogenesis, La Jolla, California, August 2–5, 2000.

2. Pfeiffer RA et al: Specific acromesomelia with facial and renal anomalies: A new syndrome. Clin Dysmorphol 4:38–43, 1995.

3. Verloes A, David A: Dominant mesomelic shortness of stature with acral synostoses, umbilical anomalies, and soft palate agenesis. Am J Med Genet 55:205–212, 1995.

Metaphyseal acroscyphodysplasia

The combination of alopecia and a metaphyseal bone dysplasia has been reported by Bellini and Bardare (1) in 1966 (Fig. 9–60A). Other cases were subsequently noted (2–6).

Height is reduced, largely due to abbreviation of the lower limbs (1,4). The metaphyses are widely splayed and the epiphyses are extremely wedge-shaped, especially at the knees. Cone-shaped epiphyses involve both long and short bones. Bone maturation is accelerated. The posterior clinoid processes are elongated. The vertebral bodies are biconcave, and the odontoid is hypoplastic (Fig. 9–60B–D).

There was absence of hair, eyebrows, and eyelashes in two reports (1,5).

Miscellaneous findings include hypospadias and cryptorchidism (1,5) and bilateral vesicoureteral reflux (1), craniosynostosis (4), and mental retardation (2,3).

Inheritance is autosomal recessive.

A similar bone dysplasia but with more severe brachydactyly and without alopecia was delineated by Verloes et al (7).

References (Metaphyseal acroscyphodysplasia)

1. Bellini F, Bardare M: Su un caso di disostosi pereferica. Minerva Pediat 18:106–110, 1966.

2. Bellini F et al: Wedge-shaped epiphyses of the knees in two siblings: A new recessive rare dysplasia? Helv Paediatr Acta 39:365–372, 1984.

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5. Jequier S et al: Metaphyseal chondrodysplasia with ectodermal dysplasia. Skeletal Radiol 7:107–112, 1981.

6. Kozlowski K et al: Dutch variant of Bellini metaphyseal dysplasia. Report of two siblings. Australas Radiol 39:282–286, 1995.

7. Verloes A et al: Metaphyseal acroscyphodysplasia. Clin Genet 39:362–369, 1991.

Micromelic dysplasia with dislocated radius

Four patients (2 sets of sibs), the children of an inbred Arabic Muslim kindred, presented at birth with severe short-limbed dwarfism. Borochowitz et al (1) suggests that, in addition to these children, patients 4 and 5 of Maroteaux et al (2), alleged to have omodysplasia, really had this same constellation of anomalies.

The humeri were short with distal deficiency and a twisted appearance, lateral eversion of the humeral condyle, and dislocated radial head. The proximal radii and ulnae were widely separated. The femora were short with distal deficiency.

The face was round with a median frontal port wine stain. The nose was short with a depressed bridge. The philtrum was protruded with a prominent vermilion.

Viljoen et al (3) reported a similar patient.

References (Micromelic dysplasia with dislocated radius)

1. Borochowitz Z et al: Familial congenital micromelic dysplasia with dislocation of radius and distinct face: A new dysplasia syndrome. Am J Med Genet 39:91–96, 1991.

2. Maroteaux P et al: Omodysplasia. Am J Med Genet 32:371–375, 1989.

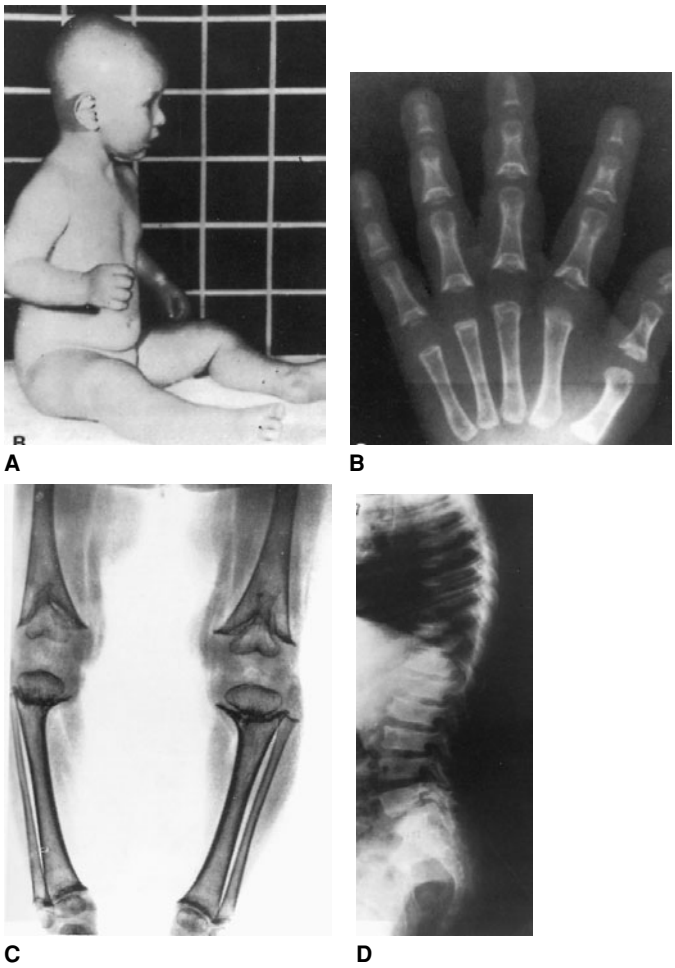

Fig. 9–60. *Metaphyseal acroscyphodysplasia.* (A) Note alopecia. (B) Cone-shaped epiphyses of proximal and middle phalanges. (C) Widely splayed metaphyses with wedge-shaped epiphyses, especially at knees. (D) Platyspondyly. (From F Bellini and M Bardare, Minerva Pediatr 18:106, 1966.)

3. Viljoen D et al: Familial rhizomelic dysplasia: Phenotypic variation or heterogeneity. Am J Med Genet 26:941–947, 1987.

Oto-facio-osseous-gonadal syndrome

da-Silva (1), in 1997, described two male sibs and possibly a female sib, the product of a consanguineous union, with short stature, brachycephaly with prominent forehead, flat midface, downslanting palpebral fissures, low nasal root, hypoplastic alae and round nasal tip, prominent low-set pinnae, sensorineural hearing loss, narrow thorax, genu valgum, inguinal hernia, and cryptorchidism.

Radiographs showed wormian bones, fusion of carpal bones, and delayed bone age.

There was some resemblance to *otopalatodigital syndrome.*

Reference (Oto-facio-osseous-gonadal syndrome)

1. da-Silva EO et al: Oto-facio-osseous-gonadal syndrome: A new form of syndromic deafness. Clin Genet 52:51–55, 1997.

Pointer syndrome

Mahbubul Huq et al (1) described a complex syndrome of facial anomalies, skeletal abnormalities, and camptodactyly. The term "Pointer" is derived from the camptodactyly involving all except the index fingers that point. There are neonatal respiratory problems and feeding problems owing to absent or poor suck. The face is characterized by microretrognathia, a box-shaped nasal bridge with prominent nasal tip and anteverted nares, hypertelorism, downslanting palpebral fissures, hypoplastic and low-appearing supraorbital ridges, and microretrognathia. Camptodactyly of the 2nd, 3rd, and 4th fingers with pointing appearance of index fingers is already present at birth. There is progressive bowing of the limbs, especially the legs, and pathologic fractures.

Radiologic findings include camptodactyly with phalangeal dislocations, lateral and anterior bowing of the tibiae, metaphyseal widening of long bones, rounded vertebral bodies, generalized osteoporosis, and mild shortness of long bones with pathologic fractures as noted above.

An affected brother and sister, the offspring of first cousins once removed, suggests that autosomal recessive inheritance is involved.

Reference (Pointer syndrome)

1. Mahbubul Huq AHM et al: The Pointer syndrome: A new syndrome with skeletal abnormalities, camptodactyly, facial anomalies and feeding difficulties. Am J Med Genet 68:225–230, 1997.

Schimke immuno-osseous dysplasia

Initially believing that he was dealing with a mucopolysaccharidurıa, Schimke et al (13), in 1971, first described the combination of short stature due to spondyloepiphyseal dysplasia, progressive renal failure, episodic lymphopenia with recurrent infections, cerebral ischemia, and unusual facies. Additional examples were provided by Schimke et al (14) and others (1–5,7–12,15–17). About 25 cases have been reported to date. Hashimoto et al (6) reported a similar condition with late onset.

Intrauterine growth retardation has been noted in about 50%. Postnatal growth is disproportionate with short neck and trunk, exaggerated lumbar lordosis, and protruding abdomen in almost all patients (Fig. 9–61A,B).

Facial changes, seen in 80%, include low broad nasal bridge with bulbous tip and elongation of philtrum (Fig. 9–61C). Corneal opacities have been seen in 25%. The neck, as noted above, is almost always short. About 35% have microdontia. Dentinogenesis imperfecta has been noted but needs confirmation (2a).

Skeletal alterations include lordosis with flattened and anteriorly rounded vertebral bodies, small capital femoral epiphyses with lateral subluxation, and slanted acetabular roofs. The pelvis is hypoplastic (Fig. 9–61D,E).

Intellectual and/or motor delay is found in 20% (1,1a,17).

Focal glomerular sclerosis and nephrotic syndrome with proteinuria and progressive renal failure is an almost constant feature. About 95% exhibit hypertension. Hypercholesterolemia is probably also seen in most cases. About 50% exhibit transient ischemic attacks leading occasionally to infarction (1,1a). Autoimmune enteropathy has also been noted (7). TSH is elevated in 50% (1a).

Hematologic changes include episodic leukopenia/lymphopenia (90%), neutropenia and thrombocytopenia (40%), anemia (65%), and defective cellular immunity (absent mitogenic response). About 50% have recurrent infections. Abnormal immunoglobulin levels have been seen in 60%.

Multiple lentigines of the skin have been seen in 80%. The hair may be fine or thin in 65% (1,15).

Affected sibs were reported by Spranger et al (16), Lama et al (8), and Boerkoel et al (1). Inheritance appears to be autosomal recessive.

While various combinations may be found in a number of disorders, the phenotype of this syndrome appears distinctive.

Elevated TSH has been noted in 50% (1).

References (Schimke immuno-osseous dysplasia)

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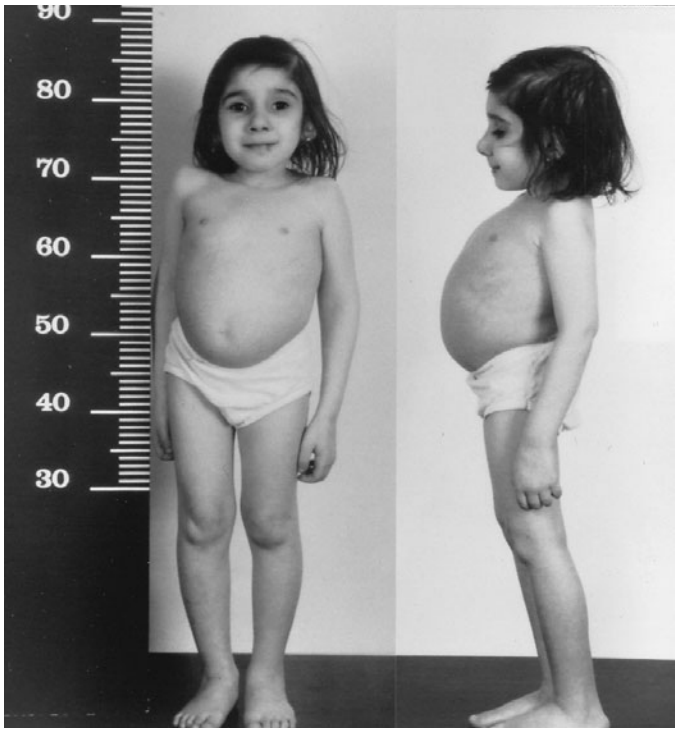

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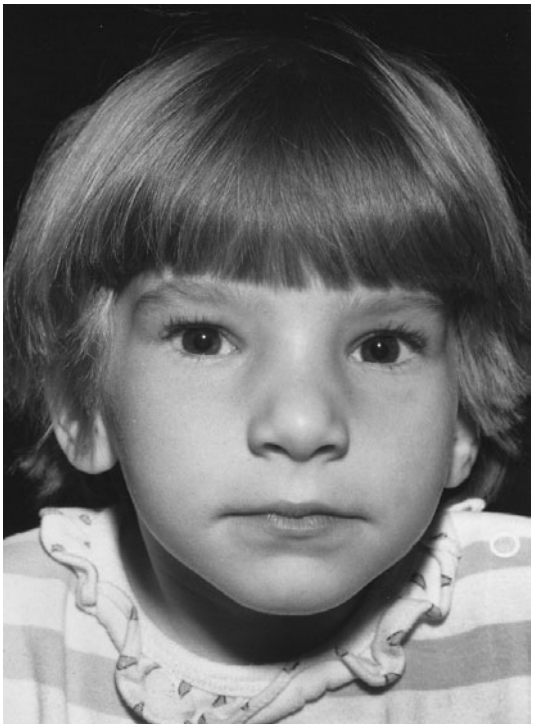

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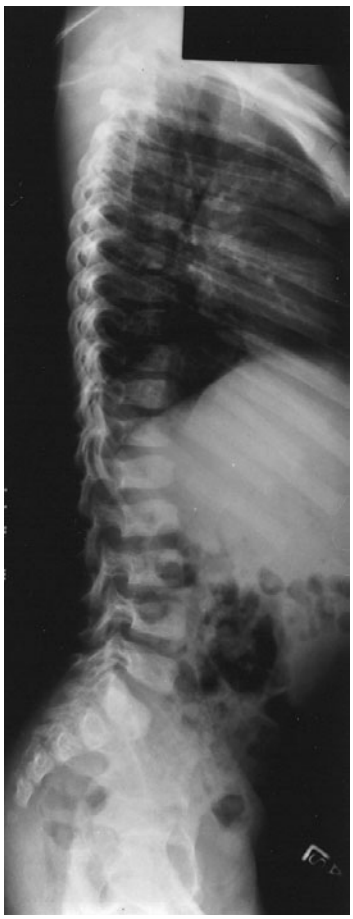

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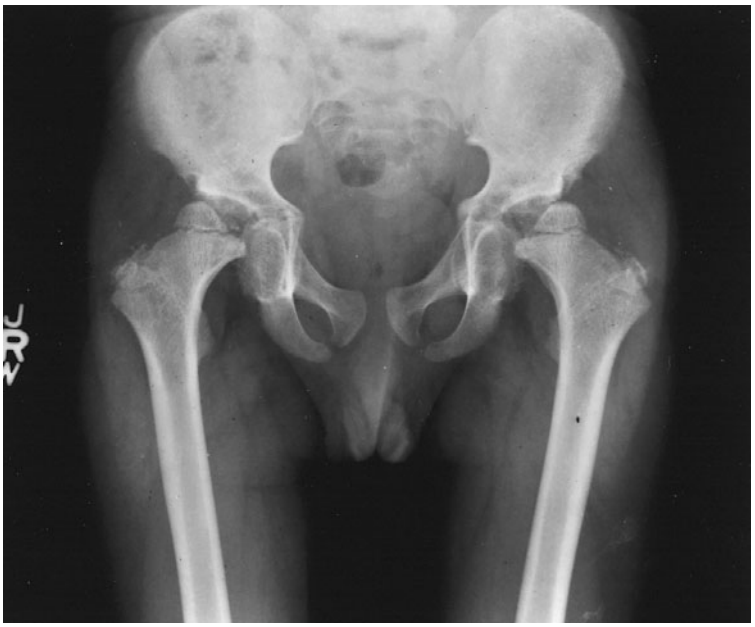

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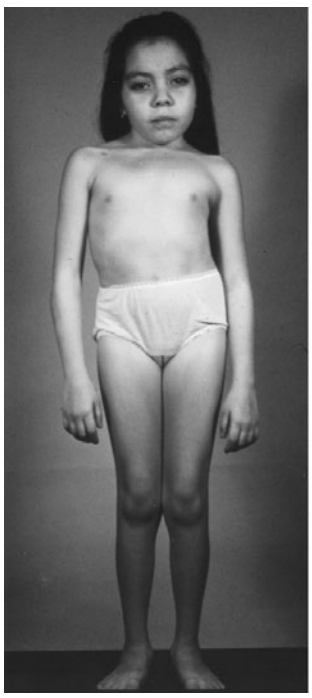
Fig. 9–61. *Schimke immuno-osseous dysplasia*. (A,B) Disproportionate stature with short neck and trunk and protruding abdomen. Also note herpetic lesion of lower lip due to immunodeficienty. (C) Upslanting palpebral fissures, broad nasal bridge, bulbous nasal tip. (D) Flattened and anteriorly rounded vertebral bodies. (E) Small capital femoral epiphyses with lateral subluxation and slanted acetabular roofs. (A,B) courtesy of C Boerkoel and R Weksberg, Toronto, Ontario. C from MD Ludman et al, Am J Med Genet 47:793, 1993.)



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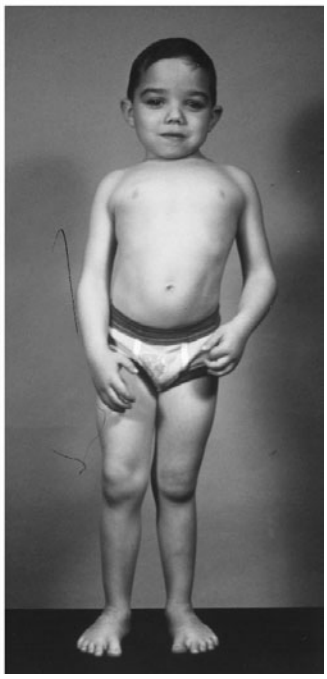

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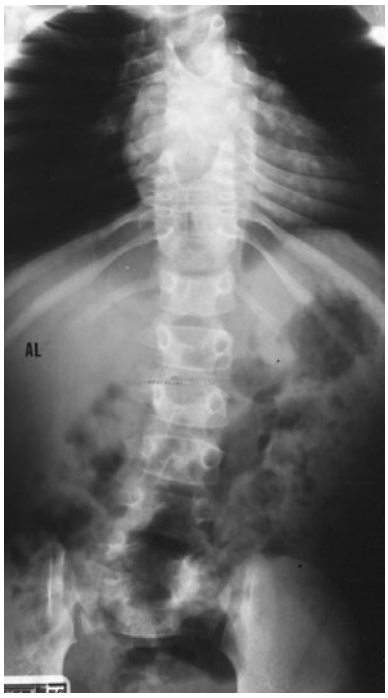

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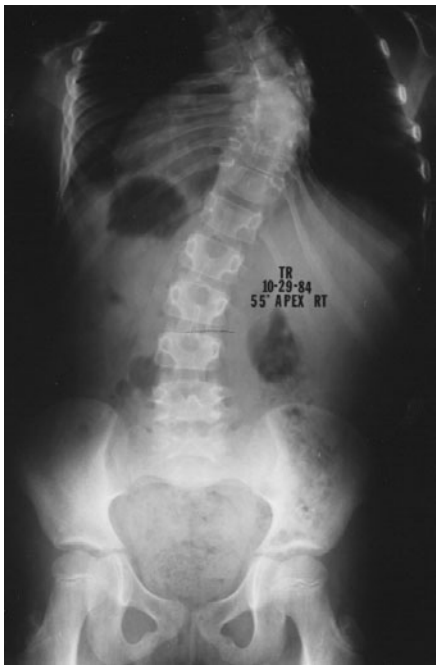

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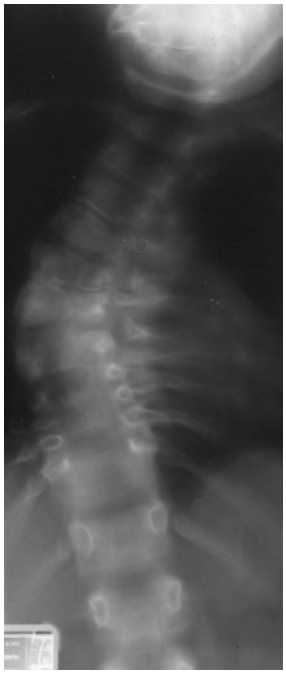

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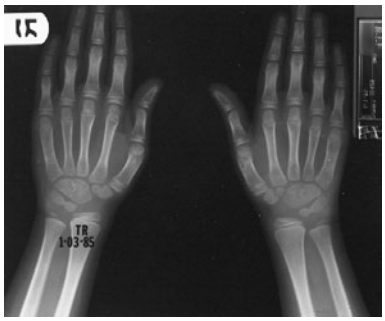

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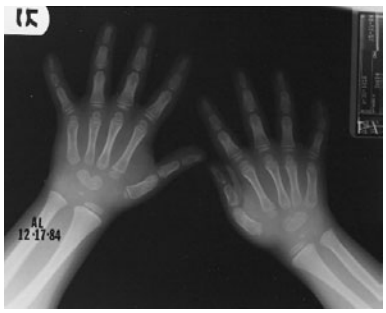
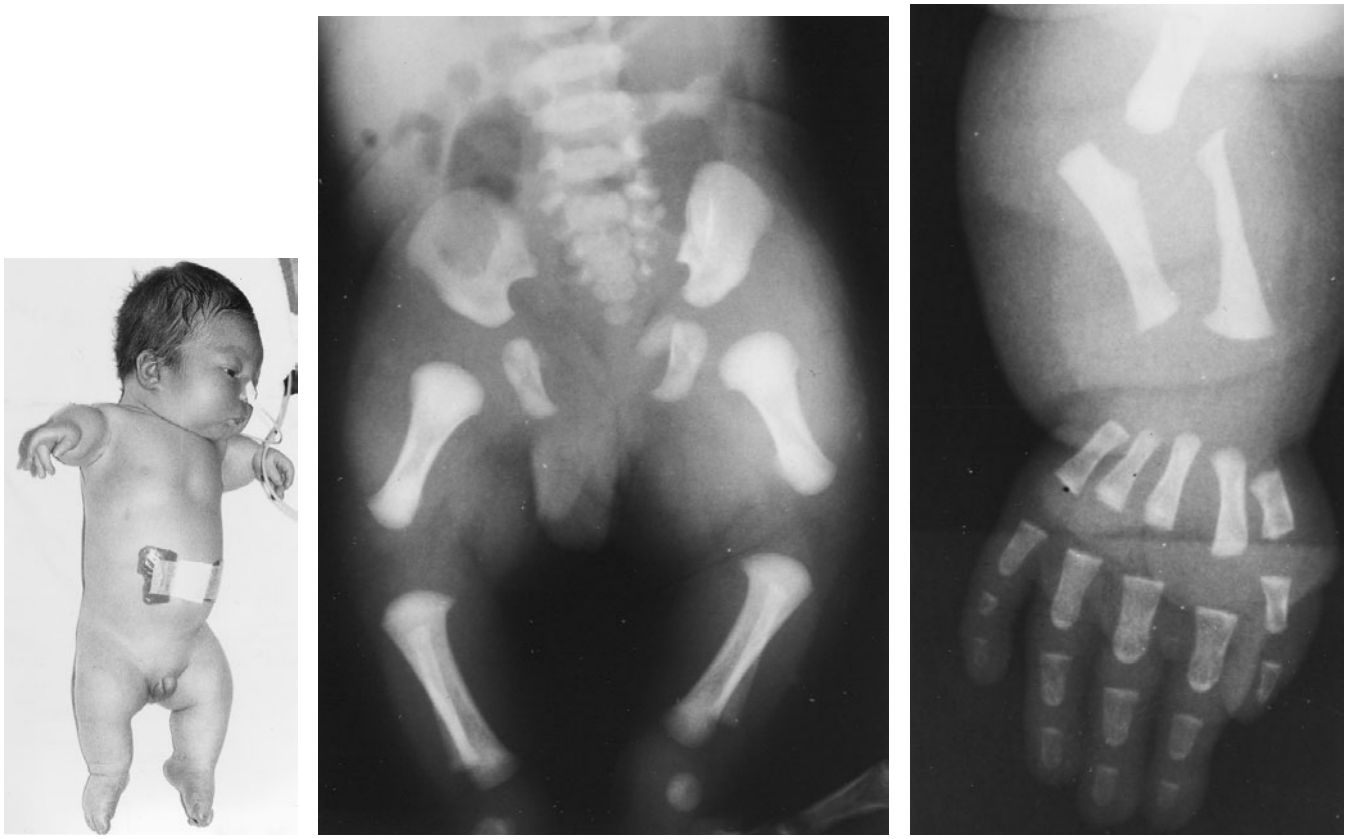


G

Fig. 9–62. *Spondylocarpotarsal synostosis syndrome*. (A,B) Patients exhibit scoliosis, short trunk, short neck, flat feet. (C) Note wedge-shaped vertebral bodies with narrowed discs between them and unilateral unsegmented bar. (D) Scoliosis. (E) Frontal tomogram showing asymmetric laminar and facet fusion with a bar. (F,G) Radiographs showing carpal synostosis to varying degrees. (A,B from LO Langer, Jr et al, Am J Med Genet 51:1, 1994.)



A B C

Fig. 9–63. *Unusual facies, short limbs, and congenital heart disease*. (A) Rhizomelic shortening of upper limbs more severe than of lower limbs, micrognathia, short neck, talipes equinus. (B,C) Shortened and thickened long bones. Femora and humeri especially shortened. (From M Barrow and JS Fitzsimmons, Am J Med Genet 18:431, 1984.)

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Spondylocarpotarsal synostosis syndrome

Spondylocarpotarsal synostosis syndrome was probably first described in 1975 by Langer and Moe (5), who reported a type of congenital scoliosis in sibs. At least 18 cases have been reported (1–4,6–10). Langer et al (6) suggested the name *spondylocarpotarsal synostosis syndrome (with or without unilateral unsegmented bar).*

Inheritance is clearly autosomal recessive (1,2,5,6).

Height is usually at the third centile. The trunk is disproportionately short (5). Scoliosis, usually recognized before the age of 6, increases in severity in time, often resulting in restricted vital capacity (Fig. 9–62A,B). The spine shows asymmetric segmentation, i.e., multiple symmetrical block vertebrae. There may be subluxation of C_2 on C_3 (7). Other abnormalities in the thoracic spine include small vertebral bodies slightly smaller on the concave side of the curve. The discs between them are narrowed. There is often a unilateral unsegmented bar on the concave side of the curve. Most of the ribs in the region of the bar are fused to the vertebral bodies (Fig. 9–62C–E). Lordosis is also common.

In addition to scoliosis, the carpal bones are abnormally formed; the first multangular is often abnormally shaped. There may be two bones in place of the second multangular, and there is fusion of the capitate-hamate and lunate-triquetrum. The navicular may be smaller than normal (Fig. 9–62F,G). The fifth fingers may have clinodactyly. The feet show calcaneonavicular synostosis, and often there is pes planus. Often there is limitation of pronation and supination at the elbows (6).

Cleft palate and sensorineural or mixed hearing loss are variable manifestations (2,6). Cataracts, rarefication of retinal pigmentations, and narrowing of retinal vessels have also been noted (8).

References (Spondylocarpotarsal synostosis syndrome)

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Unusual facies, rhizomelic bone dysplasia with club-like femora (omodysplasia)

The term *omodysplasia* was coined by Maroteaux et al (7) in 1989. It consists of rhizomelic shortening, especially of the upper limbs. Two of their patients (Cases 4 and 5) have *omodysplasia.* An earlier example is that of Barrow and Fitzsimmons (2). Several other examples have been documented (1–6,8,9).

Facial anomalies include posterior sloping of forehead, frontal and/or glabellar and facial hemangiomata, epicanthic folds, narrow palpebral fissures, small nose, depressed nasal bridge, broad nasal base, long philtrum, thin vermilion, micrognathia, and short neck (Fig. 9–63A). Small pterygia may be present in the axillary and popliteal regions.

Extension and flexion at the knees and elbows are limited. Skeletal changes involve short humeri with defective growth at distal ends, proximal hypoplasia of radius, distal hypoplasia of ulna, hypoplastic everted condyle, upper radioulnar diastasis, anterior dislocation of radial head, and ulnar subluxation. The femora have a clubbed shape proximally (Fig. 9–63B,C).

Some examples of congenital heart anomalies have been found (2,7). Undescended testes have been noted (2,5).

Inheritance is autosomal recessive (1,3,4,8,9).

Differential diagnosis would include *atelosteogenesis III.*

References [Unusual facies, rhizomelic bone dysplasia with club-like femora (omodysplasia)]

1. Al Gazali LI, Abou Al-Asaad F: Autosomal recessive omodysplasia. Clin Dysmorphol 4:52–56, 1995.
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Chapter 10
Proportionate Short Stature Syndromes

Aarskog syndrome (facial-digital-genital syndrome)

Credit is usually given to Aarskog (1) for describing the disorder in 1970. However, earlier reports had been made (4,28,57). The condition is characterized by unusual facies, short stature, abnormalities of hands and feet, and genital anomalies. In most families, inheritance is compatible with an X-linked recessive pattern, female heterozygotes frequently exhibiting minor stigmata (43). Bawle et al (9) and Tyrkus et al (52) reported women with full expression of the syndrome, each of whom had an affected son. Porteous et al (43) localized the gene to Xp11.21, which was later confirmed (46) and called FGD1 (44). Pasteris et al (40), using positional cloning methods, identified a mutation in a gene that showed strong homology to RAS-like RHO/RAC guanine nucleotide exchange factors. The Rho family plays important roles in the regulation of actin cytoskeleton organization and cell growth. Mutations probably result in a disturbance of signal transduction and, hence, developmental growth anomalies (58). A mouse model has become available (41).

Several pedigrees demonstrating male-to-male transmission have been reported (14,25,29,55,57). Genetic heterogeneity is likely. About 150 male cases have been published. Several reviews (3,43,51) and surveys (20,43) are available. A summary of the major clinical features can be found in Table 10–1.

Facies. The forehead is broad with prominent ridging of the metopic suture (10,12,16), and the face is usually round. There is a widows' peak in approximately 70% (10,12,16,17,22,24,43,51). Scalp defects (22) and macrocephaly may be encountered (34). The corneal diameter may be enlarged (3,32). Hypertelorism in 90%, ptosis of upper eyelids in 50% (12,23,28), and short, broad, stubby nose with anteverted nostrils in 70% characterize the face. Various other eye anomalies include tortuosity of retinal vessels (42), strabismus (32), and ophthalmoplegia (23,28,36,48). The philtrum is usually long (16,17,22,25). A variety of malformations of the external ear has been described, most commonly thickened or fleshy earlobes (3,43,51). The maxilla is often hypoplastic (25,36,48). A linear curved depression below the lower lip is common (10,12,33) (Fig. 10–1).

Musculoskeletal system. Although birth size has been normal in most reports, growth retardation usually becomes evident during the first few years of life. Most patients are below the 3rd centile in height, and many patients exhibit prolonged pubertal growth spurt, although adults rarely exceed 160 cm (25). Hands and feet are short as are the fifth fingers (16,53), and there is mild soft tissue webbing between the fingers in over 70% (6,12,25,28,30,43,51). Hyperextension of the proximal interphalangeal joints and flexion of the distal interphalangeal joints are found in 80% (10,20,23–25,39,48) (Fig. 10–2). In approximately 80%, there is fifth finger clinodactyly (25,43,51). The feet are small, broad, and flat with splayed bulbous toes (12,30,35). Occasionally, there is metatarsus adductus (10,23,31,47). In approximately 45%, pectus excavatum is noted (43). Inguinal hernia has been seen in over 60% (25,30,43). The umbilicus is prominent with a protruding buttonlike central area surrounded by a deep ovoid depression (11,19,24,52).

Radiographically, striking changes are generally limited to the cervical spine and hands (10,34,48). Spina bifida occulta or cervical vertebral defects have been found in over 50% (24). Scott (see 46) described hypoplasia of the first cervical vertebra with an unfused posterior arch; on extension, the vertebra entered the foramen magnum. Odontoid hypoplasia has also been described (7). With flexion, there was subluxation of the first and second cervical vertebrae. Spinal cord compression at C1–C2 has required occipito-cervical fusion (47). RJ Gorlin has observed a patient with fusion of the second and third cervical vertebrae. Supernumerary ribs have been noted (16). The terminal phalanges of the fingers and the middle phalanx of the fifth finger are hypoplastic in over 80% (25,43,51). Camptodactyly is rare (37). Hanley et al (28) noted osteochondritis dissecans. Bone age is often retarded (25).

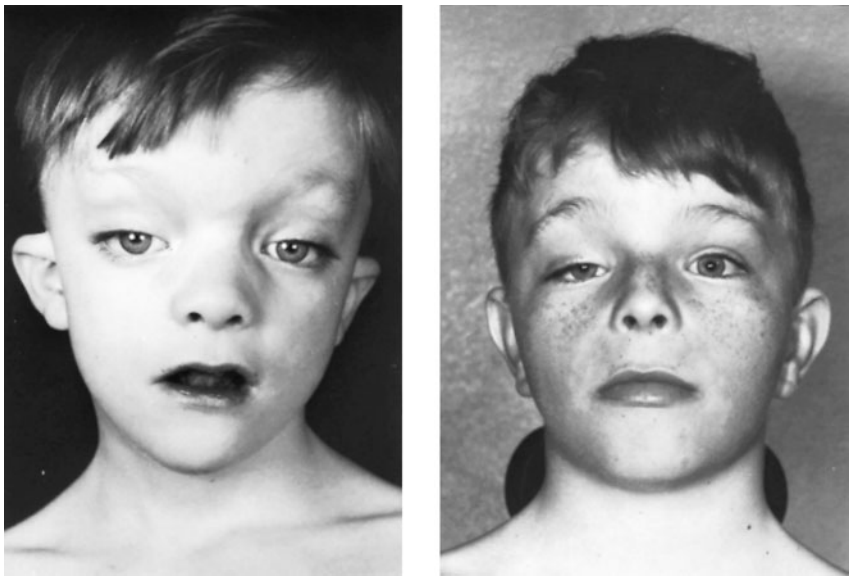
Genital anomalies. The scrotum appears bifid, with the scrotal fold extended ventrally around the base of the penis, somewhat resembling a shawl about the neck (Fig. 10–3). Presumably this genital anomaly results from failure of caudal shift of the fused labioscrotal folds. With age, shawl scrotum disappears (20,43). Commonly, one or both testes are undescended (25). Hypospadias (16) and macroorchidism (20) are rare findings. No characteristic genital anomaly is described in girls, although one female was noted to have clitoral hypertrophy (35).

Other findings. Bilateral single palmar creases (8,12,25,30) and a single crease in the fifth fingers are frequent (10,12,30,46,56); distally displaced axial triradii have also been noted (11,25,30,39). Most patients are of normal or low normal intelligence (17), but mild to moderate mental retardation has been reported (20,22,34,36,48). Growth hormone was deficient in two patients (3,33), but normal in several others (1,22,39,46). Lymphedema (37), dolichomegasigmoid (21), cardiac defects including pulmonary stenosis, aortic coarctation, aortic stenosis, and atrial and ventricular septal defects (1,18,54), and anomalous cerebral venous drainage (54) have been described.

Table 10–1. *Aarskog syndrome*—clinical features in 130 male patients

Clinical feature	%
Craniofacial	
Widow's peak	70
Hypertelorism	90
Ptosis	52
Downward slanted palpebral fissures	55
Short nose	70
Wide philtrum	85
Maxillary hypoplasia	85
Crease below lower lip	82
Abnormal auricles	80
Skeletal	
Short stature	85
Short/broad hands	82
Clinodactyly fifth finger	80
Mild interdigital webbing	70
Joint laxity	70
Broad feet, bulbous toes	70
Genital	
Shawl scrotum	80
Cryptorchidism	65

Adapted from MEM Porteous and DR Goudie, J Med Genet 28:44, 1991; and AS Teebi et al, Am J Med Genet 46:501, 1993.



A B

Fig. 10–1. *Aarskog syndrome*. (A) Facies is characterized by broad forehead, hypertelorism, bilateral ptosis of upper eyelids, and low-set ears. (B) Similar facies in patient from a different family. Note unilateral ptosis. [From CI Scott Jr, Birth Defects 7(6):240, 1971.]

Oral manifestations. Enamel hypoplasia and a "col" deformity of the anterior mandible have also been noted in one patient (36). Halse et al (27), in examining 10 patients in three families, found delayed dental eruption in 3 of 4 patients aged 7–11. Congenitally missing teeth and short roots were found in the family originally reported by Aarskog (1,2), and Dayal et al (13) described taurodontism. Upper central incisors were found to be large in adults (20). Cleft lip and palate have been described in a few affected males (15,26,30,35,48,56); a carrier female (30) had cleft lip.

Differential diagnosis. *Noonan syndrome* and *LEOPARD syndrome* share features with this disorder such as short stature, hypertelorism, ptosis of upper eyelids, and hypogonadism. Seaver and Cassidy (45) reported a mother and son who had features of Aarskog and Noonan syndrome. *Robinow syndrome* also resembles the Aarskog syndrome, as does *pseudohypoparathyroidism*.

Teebi et al (49,50) reported a newly recognized autosomal recessive disorder, the *facio-digito-genital syndrome*, with some similarities to Aarskog syndrome, including short stature, hypertelorism, short stubby nose, anteverted nostrils, ear anomalies, small broad hands, and shawl scrotum. However, the eyes did not downslant nor was there ptosis. The hair was sometimes coarse, dry, and hypopigmented. Sixteen patients, both male and female, are known, all born to consanguineous parents. Naguib (38) reported 3 sibs with an Aarskog-like entity, consisting of large upward slanted palpebral fissures, telecanthi, ptosis, proptosis, hypospadias, shawl scrotum, and polysyndactyly. The parents were first cousins.

Fig. 10–2. *Aarskog syndrome*. The hands are short and wide with frequent webbing of the fingers, hypermobility, and subluxation of the proximal interphalangeal joints. (Courtesy of P Berman, Montreal, Canada.)

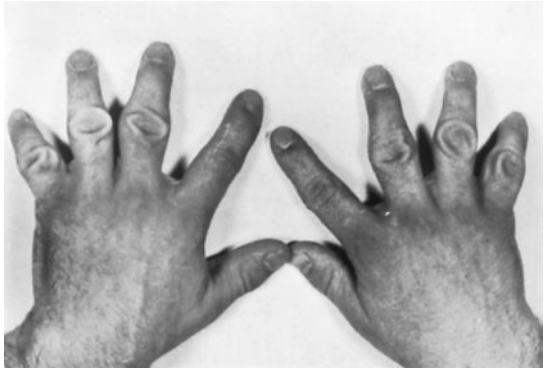


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Fig. 10–3. *Aarskog syndrome*. Abnormal penoscrotal configuration due to scrotal folds joining ventrally over the base of the penis. Note left inguinal hernia. [From CI Scott Jr, Birth Defects 7(6):240, 1971.]

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Bloom syndrome

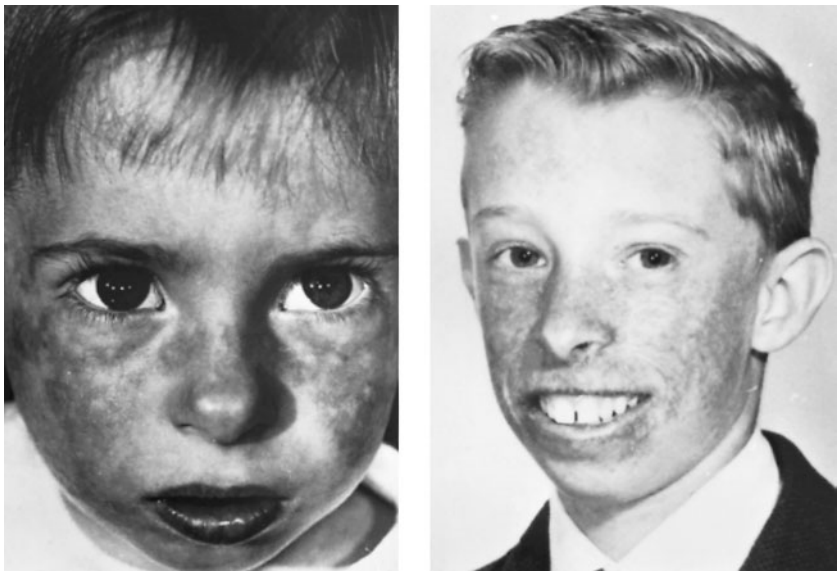
Bloom syndrome consists of intrauterine growth retardation, sunlight sensitivity leading to telangiectatic erythema (Figs. 10–4 and 10–5), a tendency to chromosomal breakage with dicentrics, tetraradial figures, and high frequency of sister chromatid exchanges (Figs. 10–6 and 10–7), immunologic deficiency, hypogonadism and infertility in males, and an increased risk of neoplasia. The condition was first recognized by Bloom (5–7), a genetically oriented dermatologist, in 1954. Another case was reported by Torre and Cramer (56) as a case of discoid lupus erythematosis with primordial dwarfism. German (18) first recognized chromosomal breakage and emphasized the predilection for neoplasia. The Bloom Syndrome Registry currently has 168 patients on record (22,25,26,54).

The reader is referred to the following sources for detailed coverage: extensive reviews (13,18,19,21,44,58), neoplastic aspects (8,9,22), tumor surveillance (21,25,26,28), chromosomal breakage and sister chromatid exchange (3,10,13,20–24,27,30,38,51), immunologic deficiency (50,58,61), endocrine aspects (1,34,37,42,58), dermatologic aspects (18), growth (18,58), and genetic aspects (14,29,32).

Genetics. The syndrome has autosomal recessive inheritance. Both sexes are affected, although a slight female deficit remains unexplained. Heterozygous carriers are normal, the only unusual finding to date being a tendency for low levels of blood immunoglobulins. The gene occurs with high frequency among Ashkenazi Jews who orginated from Eastern Europe and in non-Jews of Spanish ancestry (16). More than 1 in 120 is a heterozygous carrier among Israeli Ashkenazi (28). In 1998, 52 of the 168 registered persons were of Askenazi descent (54). The gene probably expanded to high frequency through the founder effect and random genetic drift in a relatively isolated population. German et al (29) suggested genetic heterogeneity.

Parental consanguinity is not increased in affected Jewish families. The gene does occur with very low frequency in other populations and, in contrast, parental consanguinity in non-Jewish families is very high (28,41,44), for example, in the Japanese population (23).

A maternal uniparental disomy for chromosome 15 was reported to be associated with the syndrome (64). Bloom syndrome was later mapped at 15q26.1 (53). The gene product was shown to have homologies with Rec Q helicase, one of the DNA helicases that can unwind DNA in



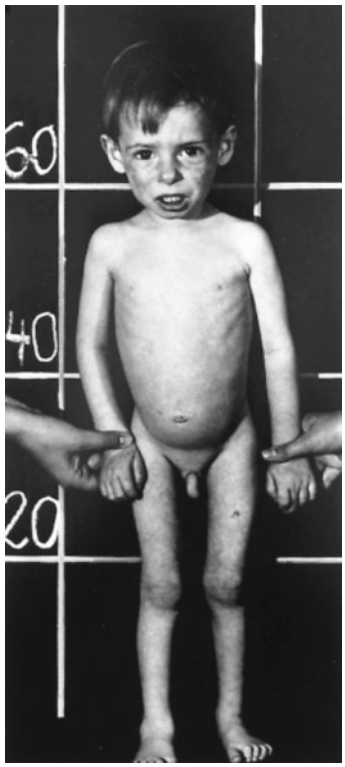
A B

Fig. 10–4. *Bloom syndrome*. (A) Telangiectatic erythema of face. (B) Extensive facial telangiectasia in 14-year-old male. (From J German, Am J Hum Genet 21:196, 1969.)

the 3′ to 5′ direction along the bound strand (14,15,45). Unrestrained recombination probably leads to disturbed cell death (17) The helicase gene is closely linked to the proto-oncogenes (FES) (21). A rapid method to detect the 6 base pair deletion–base pair insertion that is commonly found in Ashkenazi Jews has been developed (54).

Cytogenetics. Chromosomal breakage and sister chromatid exchanges are characteristic (24). The unusually high rate of approximately 60–120 sister chromatid exchanges per cell, representing a 5- to 10-fold increase, is pathognomonic (3,10,13). Chromosome changes in leukemic clones are nonrandom (52). No increased chromosomal breakage has been detected in heterozygous carriers (38). Phenotypic dysmorphism occurs in patients with cells that are normal and cells that have a 10-fold increase in sister chromatid exchanges (27,58). Retarded DNA chain growth has also been documented, possibly resulting from a slow rate of replication fork movement. It has further been suggested that mitotic activity is low in fibroblast cultures (31). Vijayalaxmi et al (60) indicated that approximately eight times the normal number of 6-thioguanine-resistant lymphocytes were detected in blood, the basis for the increase being unknown, with genomic instability from chromosomal aberrations as one possible explanation. Willis and Lindahl (63) and Chan et al (12) reported DNA ligase I deficiency in lymphoid cells.

Fig. 10–5. *Bloom syndrome*. Four-year-old boy far below third percentile in height, with telangiectatic erythema of face. (From J Keutel et al, Z Kinderheilkd 101:165, 1967.)



Growth. Growth deficiency of prenatal onset is a prominent clinical feature, birth weight rarely exceeding 2300 g at term. Mean birth length is 44 cm. Final height attainment rarely exceeds 145 cm in males and 130 cm females (18,36). Body habitus is normal except for its fragile appearance. Affected infants and children eat much less than normal and subcutaneous fat is sparse during infancy and childhood, although vigor and strength are generally normal. There is disproportionate microcephaly, accentuated by delicacy and narrowness of the face. The head is dolichocephalic. Some patients have prominent nose and ears, with slightly receding mandible (Figs. 10–4 and 10–5) (7,9,33,36,39,55).

Performance. Intelligence is usually normal, although mild mental deficiency has been observed in some patients (8,18,19,36,55). Psychological problems are common and may result from short stature and unsightly facial lesions; interference with school progress may occur and simulate low intelligence. A squeaky, high-pitched strident voice is characteristic and occurs in both sexes (7,33,36).

Skin. Light sensitivity is noticed early in infancy and leads to development of telangiectatic erythema, which may appear anytime between early infancy and 2 years of age. Erythema involves light-exposed areas of the face; superficially it resembles lupus erythematosus because of the butterfly distribution across the nose. Severe lesions also may occur on the lower eyelids, lips, ears, and neck. A chronic fissure or ulcer of the lower lip is a bothersome complication and chronic cheilitis is a prominent feature. The eyelashes may be lost. The forearms and dorsa of the hands may become involved, but rarely does the erythema extend to the trunk. Exposure to sunlight may cause bullae and vesicles. Milia may be seen in scarred areas (5,7,8,33,39,49,55). German (18) noted that skin lesions appeared to be less severe in females than in males. Heavily pigmented individuals, such as Mexicans (48) and Japanese (2,35), exhibit less telangiectasia and sun sensitivity than lightly pigmented individuals.

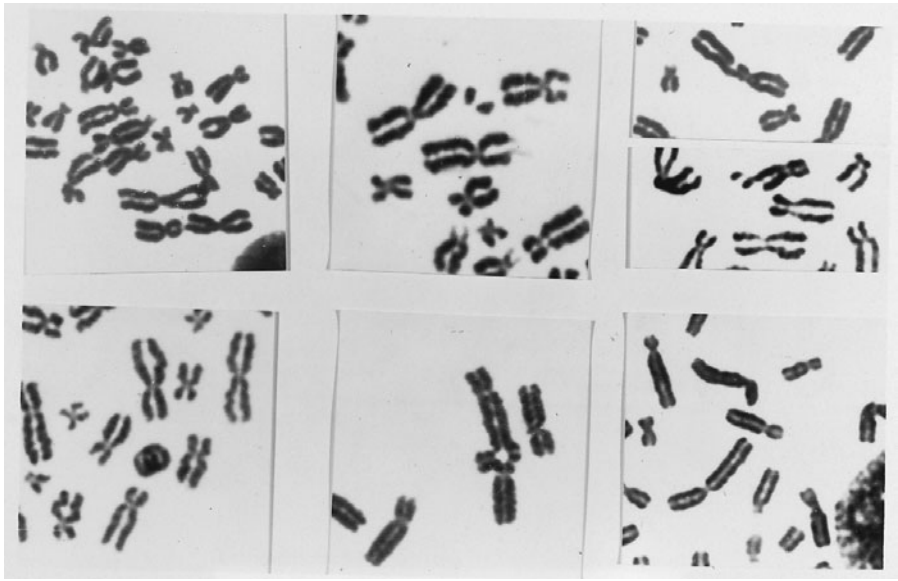


Fig. 10–6. *Bloom syndrome*. Various chromosome changes including dicentrics, acentric fragments, ring, breaks, and tetraradial figure. (Courtesy of J German, New York, New York.)

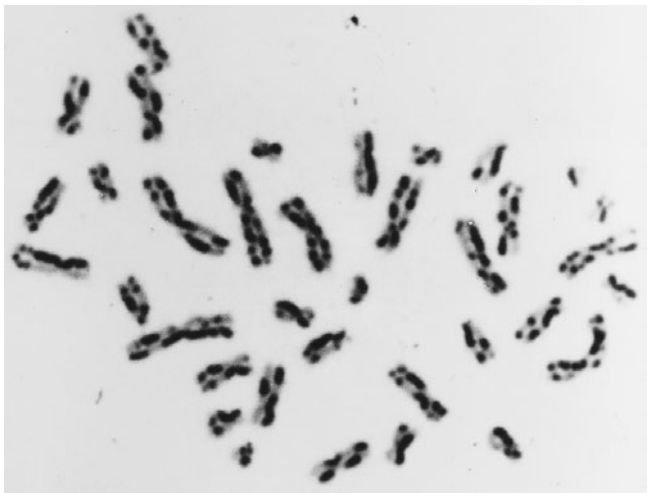
Hyperpigmented areas, irregular in outline and shape and varying from one to many centimeters in greatest dimension, are found mainly on the trunk, but also on various parts of the extremities. The spots are café-au-lait in color, although in affected black patients they are dark brown, almost black. Less often observed are hypopigmented areas that are irregular in outline and smaller in size. In some instances, both hyper- and hypopigmented spots may be observed in the same patient. Keratosis follicularis is found in approximately 20%. Acanthosis nigricans was noted in one patient who developed diabetes mellitus during puberty (7,18).

Immunologic features. Decreased immunoglobulin levels are characteristic and manifest as reduced IgA, IgG, or IgM. Although the immunologic disturbance has variable expression, a specific deficiency is similar in affected members of the same family (18,33,36,39,50,59–61). A single complementation defines patients of diverse ethnic background (62).

Endocrine findings. Hypogonadism of moderate degree and infertility are characteristic of affected males. Involvement of the tubular elements of the testes explains the occurrence of sterility and, although the Leydig cells also appear to be affected, patients have normal secondary sexual characteristics except for testicular development. Testes are small to diminutive in size, and cryptorchidism is common. Adult males seem to have no sperm (19). Menstruation occurs in postpubertal females, but periods may be irregular and infrequent in some (18,34,58).

Normal growth hormone response has been observed following pituitary stimulation in two instances, although deficient release of growth hormone was documented in another patient (1,58). Growth velocity was noted to increase during administration of exogenous human growth hormone in one instance (58). Insulin-dependent diabetes appearing from ages 11–40 years has been reported (19,37,42).

Fig. 10–7. *Bloom syndrome*. Note markedly increased number of sister chromatid exchanges (partial mitosis). (Courtesy of J Cervenka, Minneapolis, Minnesota.)



Neoplasia. Commonly observed malignancies include leukemia, lymphoma, adenocarcinoma, and squamous cell carcinoma (4,8,9,20,21, 25,26,28,43,44,55) (Table 10–2). Wilms tumor has been recorded three times (11). Recently, a cerebellar medulloblastoma was described (46). The mean age of detection has been 24.8 years, the earliest occurring at 4 years of age and the latest at age 44. Four patients have each had two malignancies: adenocarcinoma of the sigmoid at age 37 and adenocarcinoma of the gastroesophageal junction at age 44 in one patient; adenocarcinoma of the sigmoid and squamous cell carcinoma of the esophagus, both detected at age 39, in another patient; disseminated lymphoma and squamous cell carcinoma of the epiglottis, both detected at age 30, in still another patient, and Hodgkin lymphoma, and subsequently leukemia at age 21 (25,26,28,44). Takemiya et al (55) described multiple tumors of the skin, lung, and colon.

There is an overall risk of at least 44% for developing a neoplasm ($n = 132$). This must be considered a minimal estimate because other malignancies will probably be detected in this same population with time.

Other findings. Conjunctivitis and telangiectasia of the conjunctival vessels may be observed (48). Colloid body–like spots in Bruch's membrane have been noted (40,55). A variety of low-frequency abnormalities have been recorded, including congenital heart defect, unequal leg lengths, absent toe, syndactyly, supernumerary digits, clinodactyly, hip dislocation, pes equinus, hypodontia, large protruding ears, single palmar crease, sacral dimple, and urethral or meatal narrowing (7,18,33,39,44).

Differential diagnosis. Bloom syndrome has been grouped with *ataxia telangiectasia, Cockayne syndrome, Rothmund-Thomson syndrome, Werner syndrome, dyskeratosis congenita*, Fanconi anemia, and *xeroderma pigmentosum* (18,39). Nearly all these disorders are characterized by growth retardation, increased neoplasia (both lymphoreticular and carcinomatous), immunologic deficiency, late-onset diabetes, and premature senility of the skin and conjunctiva.

Table 10–2. *Bloom syndrome*—the first 100 neoplasms recorded in the Bloom syndrome registry

Type of neoplasm	No. cases identified
Leukemia	
Acute lymphyocytic	7
Acute myelogenous	6
Other	9
Malignant lymphoma	
Non-Hodgkin	20
Hodgkin	2
Carcinoma	
Skin	8
Auditory canal, external	2
Tongue, posterior	4
Tonsil	1
Larynx, epiglottis	3
Esophagus, squamous cell carcinoma	4
Esophagus, adenocarcinoma	1
Stomach	2
Colon	13
Lung	1
Breast	7
Uterus	5
Metastatic, primary site unidentified	1
Other	
Wilms tumor	3
Medulloblastoma	1
Osteogenic sarcoma	2

Adapted from J German and NA Ellis, The Genetic Basis of Human Cancer (B Vogelstein, KW Kinzler, eds), McGraw-Hill, New York, 1998.

Sunlight sensitivity is also a feature of *Cockayne syndrome, Rothmund-Thomson syndrome, and xeroderma pigmentosum*. Pigmentary skin changes are seen in sun-exposed areas of patients with *ataxia telangiectasia, Werner syndrome, dyskeratosis congenita*, and Fanconi anemia. Increased chromosomal breaks have been reported in Fanconi anemia, *Cockayne syndrome, ataxia-telangiectasia,* and *dyskeratosis congenita* (18,39). However, they are unlike the changes found in Bloom syndrome (51), and in no other disorder investigated to date are sister chromatid exchanges as strikingly increased in frequency as in Bloom syndrome (30).

Laboratory aids. A characteristically increased number of chromosome breaks and sister chromatid exchanges is demonstrable in blood lymphocytes, freshly aspirated bone marrow cells, skin fibroblasts and long-term culture, and some lymphoblastoid cell lines (18,33,36,39,50,59,60). Serum IgA, IgG, and IgM are reduced and there is in vitro impaired response to pokeweed mitogen (59,61). Prenatal diagnosis may be possible using serial sonographic estimates of fetal size and growth rate to detect severe growth retardation (14), and should also be possible molecularly. Increased numbers of micronuclei are found in exfoliated cells in patients with Bloom syndrome (47).

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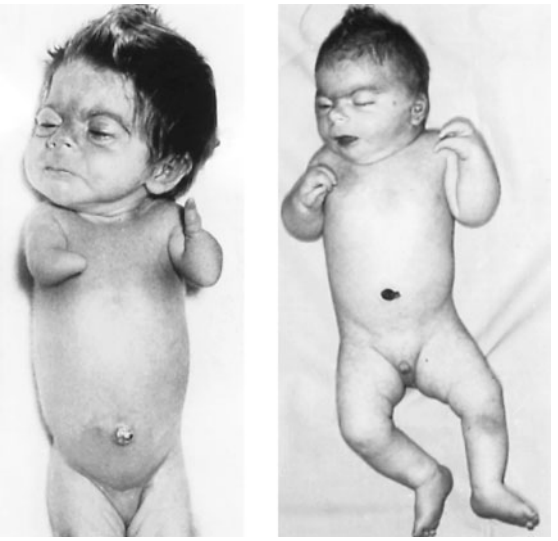
de Lange syndrome (Brachmann-de Lange syndrome)

The syndrome of primordial growth deficiency, severe mental retardation, anomalies of the extremities, and characteristic facial appearance (Figs. 10–8 to 10–13), was independently described by Brachmann (14) in 1916 and by de Lange (24) in 1933. The condition has been known as de Lange syndrome (1,4,9,11–13,27,30,38,60), de Lange Amsterdam dwarf syndrome (31), Cornelia de Lange syndrome (2,7,10,34,35,42, 43,51,53,54,55,59,71,74,85), Brachmann-de Lange syndrome, and typus degenerativus Amstelodamensis (24,80,93). The reader is referred to the following sources for special coverage: extensive surveys (13,39, 45,74), references (67), numerical taxonomy (73,92), epidemiology (9), history (23,66,67), chromosomal findings (9,16,97), genetic studies, familial cases, and twins (7,12,19,27,28,33,51,61,65,69,76,89), evolution of phenotype (42,71), phenotypic overriding of racial characteristics (40), radiographic findings (14,38,52), neurological, psychometric, and behavioral aspects (2,5,11,31,34,35,46,49,78,79,84), limb anomalies (70), cardiac defects (13,30,37,45,62,75,91), gastrointestinal abnormalities (17,53), dermatoglyphics (13,87), and pregnancy (28,64).

Over 400 cases are known (1,10,42,45). Epidemiologic estimates vary. Beck and coworkers (8,10) reported a population prevalence of 0.6/100,000 in Denmark. Opitz (67) suggested a birth prevalence of 1/10,000 in the United States.



A B

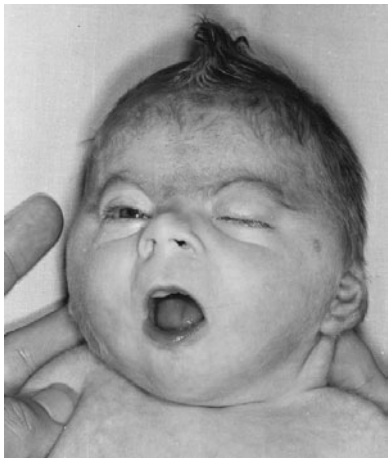
Fig. 10–8. *de Lange syndrome*. (A) Typical craniofacies and oligodactyly of upper limbs. Hirsutism of thighs. (B) Characteristic cranio-facial appearance with microcephaly, small hands and feet, small external genitalia. (A courtesy of RW Smithells, Leeds, England. B courtesy of M Silverman, Atlanta, Georgia.)

Most cases are sporadic. Affected sibs have been reported on a number of occasions (12,16,33,45,50,69,73). Several families with vertical transmission have been observed (3,7,20,22,28,45,50,55,61,76). Pregnancy in a woman with de Lange syndrome has been described; a clinically normal female infant was delivered (64). Instances of consanguinity (10,71,73), concordant monozygotic twins (65,67,94), discordant monozygotic twins (19), and discordant dizygotic twins (45,89) have also been noted. Chromosomal studies have been normal in most instances, although occasional, inconsistent chromosomal anomalies have been recorded (10,13, 16). Recurrence risk has been estimated to be 1.5% or less (45). The phenotypic overlap between de Lange syndrome and duplication 3q syndrome has been suggestive for a locus on 3q26.3 (27,40,54,57,97). Ireland et al (43) have described a genuine patient with a de novo translocation between 3q26.3 and 17q23.1. A patient with a partial duplication of 3q26 but without de Lange features has been reported (57). Searches for uniparental disomy in patients with de Lange syndrome have been negative (26,83). Multiple mitochondrial DNA deletions were found once (63).

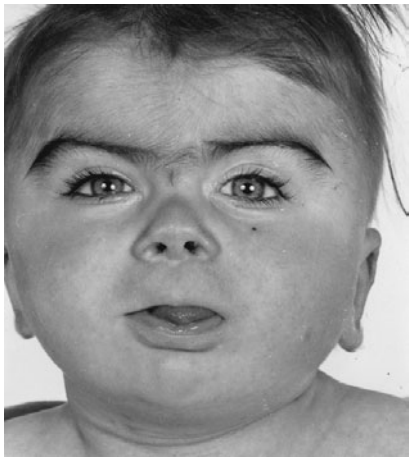
Clinical variability and diagnosis. Lower birth weights are correlated with more severe phenotypic features (39), including more severe upper limb anomalies and greater psychomotor retardation (35). A significant excess of females is also found in the lower-birth-weight group (5,39). Variability is marked. We believe that many with mild phenotypic changes are being missed (1,22,36,42,82).

Using the technique of numerical taxonomy, Preus and Rex (73) constructed a diagnostic index of 30 characters that could discriminate de Lange from non-de Lange syndrome in 99% of the cases, leaving a 1% zone of doubt. The possibility of mildly affected individuals with minimal mental deficiency or borderline IQ, normal head circumference, normal height, and/or normal limbs has been discussed by Opitz (67) and others (4,6,22,81,83,92). Findings in de Lange syndrome are summarized in Table 10–3.

Growth. Birth weight is 2500 g or less in approximately 70% in spite of normal duration of pregnancy (48). Postnatal growth retardation is severe in 96%, both height and weight usually remaining far below the third centile for age (48). Bone age is delayed, and, not uncommonly, the sequence of development of various centers of ossification may be disturbed (12). Recurrent respiratory infections and an early demise before 6 years of age are common (9,13).



A



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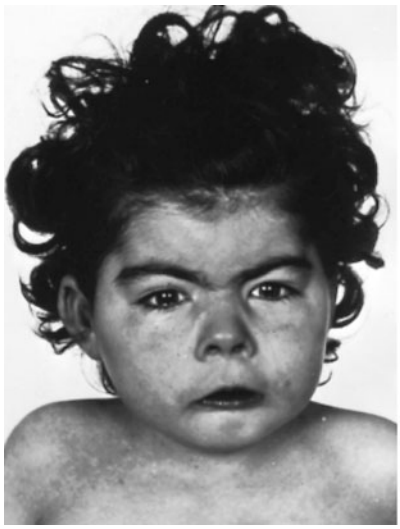

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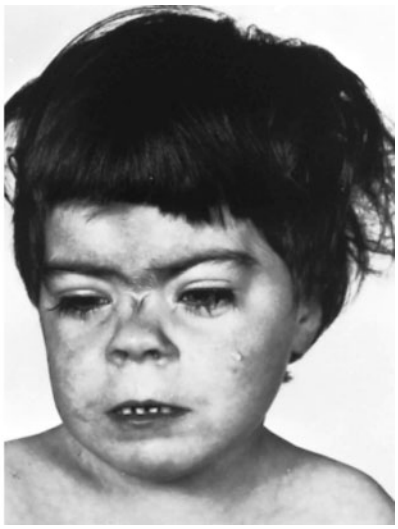
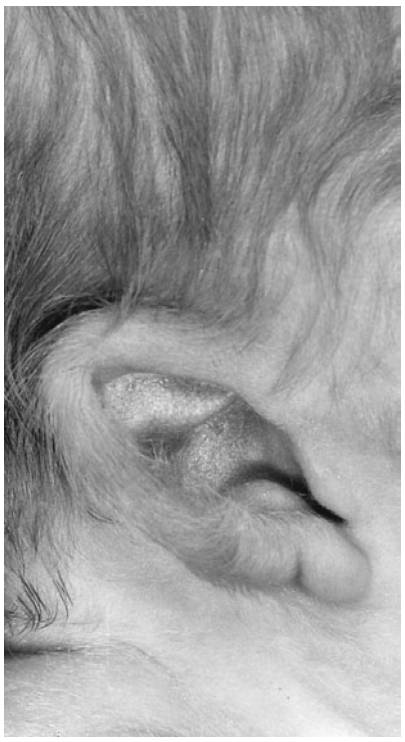


D

Fig. 10–9. *de Lange syndrome*. (A–D) Compare characteristic facies. Note microcephaly, low hairline, synophrys, small nose with anteverted nostrils, thin lips. (A,B courtesy of M Silverman, Atlanta, Georgia. C,D from B Schlesinger et al, Arch Dis Child 38:349, 1970.)



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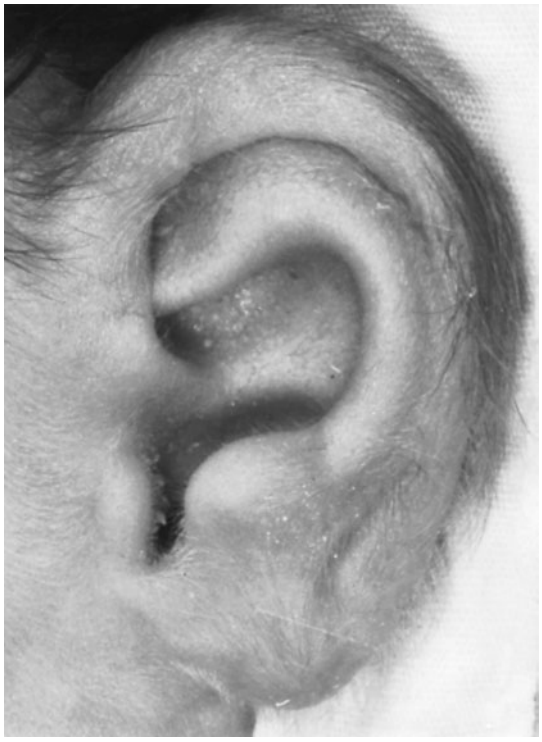


B

Fig. 10–10. *de Lange syndrome*. (A,B) Small malformed ears. Note hirsutism. (A courtesy of M Silverman, Atlanta, Georgia.)

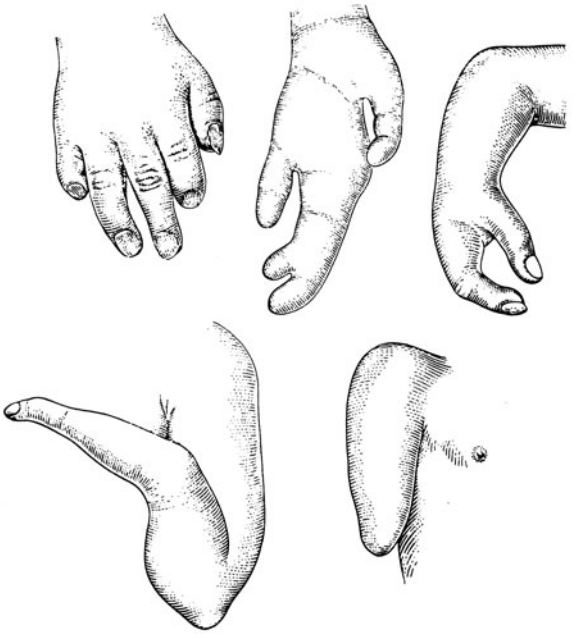
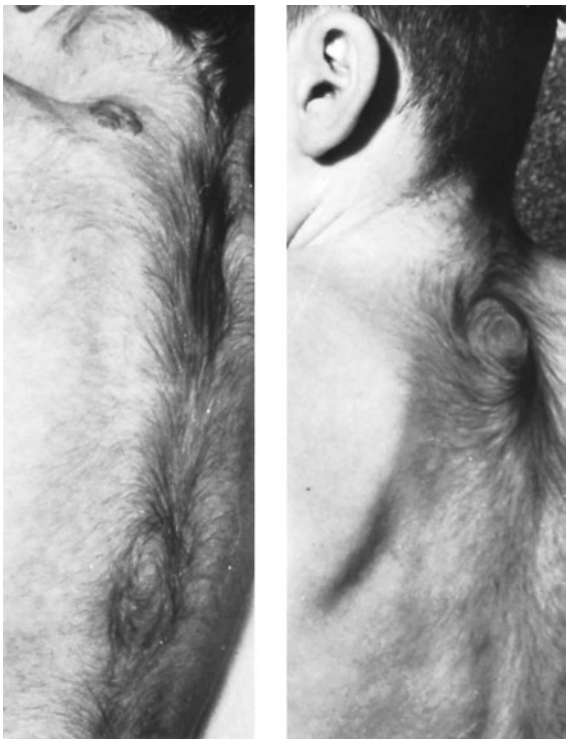


Fig. 10–11. *de Lange syndrome*. Examples of various types of malformed upper limbs found in de Lange syndrome. (From JM Berg et al, The de Lange Syndrome, Pergamon, Oxford, 1970.)



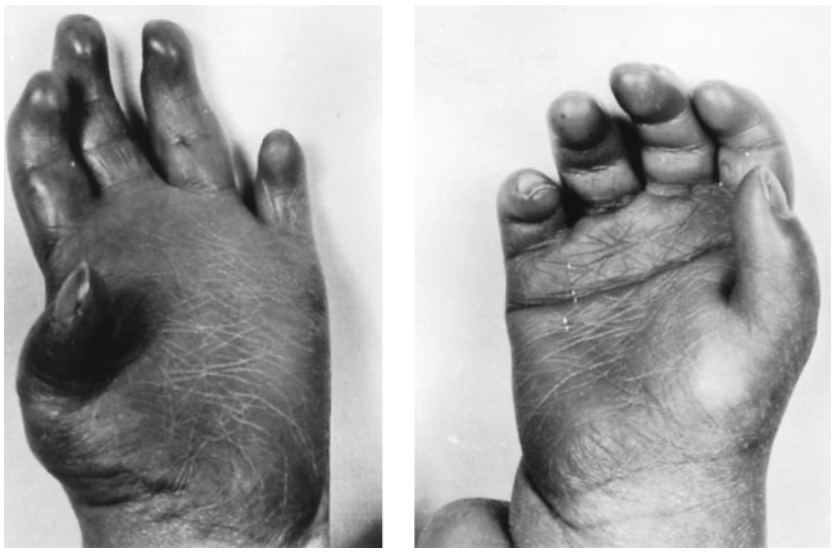
A B

Fig. 10–13. *de Lange syndrome*. (A,B) Hirsutism of back, with whorling. (From O Noe, Clin Pediatr 3:541, 1964.)

Central nervous system. Microbrachycephaly is usual, reported frequencies varying from 50% to 90% (8,13,16,48). Mental deficiency (75%–100%) (11,16), abnormal speech development (75%–100%) (16), behavioral problems (57%) (39,79), vermis hypoplasia (68), seizures (14%–20%) (5,39), hypertonia (less than 25%) (16), and, rarely, hypotonia (16) have been reported.

The cry is usually low pitched and growling (13). Patients frequently do not exhibit facial expression of emotion and commonly display stereotypic movements (13a). Vestibular stimulation or vigorous movement tends to elicit pleasurable responses (46,79). Younger patients are dysphonic, with a frequency below normal pitch register, and older subjects are hoarse (31). In the studies of Hawley et al (39), Sarimski (79), and Berney et al (13a), behavior problems included regurgitation, projectile vomiting, chewing and swallowing difficulties, lack of interest in food, and excessive screaming, biting, and hitting as well as frequent temper tantrums. Self-mutilation has been discussed by Shear et al (84). Andrasik et al (2) reported therapeutic strategies. Early intervention appears to play a major role in the level of developmental (49). Hearing loss occurs in 24% (39). IQ scores range from 4 to 101 (5,34,76,78,93); however 80% of the patients reported by Barr et al (5) were severely or profoundly retarded. Berney et al (13a) noted that 18% were borderline or mild while 43% were profoundly retarded.

Craniofacial features. Patients resemble one another to a remarkable degree (Fig. 10–9) and Huang et al (41) noted that the facial phenotype overrides racial characteristics. The typical facial appearance may not be evident during the first year of life (69), and Passarge et al (71),



A B

Fig. 10–12. *de Lange syndrome*. (A,B) Micromelia with proximally placed thumbs, small fifth fingers with single flexion crease, finger contractures, right single palmar crease, and lack of palmar creases on left. (From B Schlesinger et al, Arch Dis Child 38:349, 1970.)

Table 10–3. *de Lange syndrome*—clinical findings ($n = 310$)

Feature	%
Craniofacial	
Low posterior hairline	92
Ocular anomalies	57
Synophrys	99
Long eyelashes	99
Depressed nasal bridge	83
Anteverted nostrils	88
Prominent philtrum	94
Thin lips	94
Downturned angles of mouth	94
Widely spaced teeth	86
Highly arched palate	86
Micrognathia	84
Low-set ears	70
Limbs	
Limitation of extension at elbow	64
Oligodactyly/phocomelia of upper limb(s)	27
Small hands/feet with short digits	93
Proximally placed thumbs	72
Clinodactyly of 5th finger	74
Single palmar crease	51
Cutaneous syndactyly of toes 2-3	86
Skin	
Hirsutism	78
Cutis marmorata	60
Small nipples	55
Other	
Short neck	66
Cryptorchidism	73
Cardiac anomalies	14
Small umbilicus	53

Adapted from L Jackson et al, Am J Med Genet 47:940, 1993.

Ireland and Burn (42), and Allanson et al (1) have discussed and illustrated evolution of the facial phenotype with age.

The skull is microbrachycephalic. The temporal and scalp veins may be conspicuous. The eyebrows are confluent (synophrys), the eyelashes long and curly, and the hairline is low. Myopia, ptosis, and nystagmus are common (56). The nose is small with a flat nasal bridge. The nostrils are anteverted and the philtrum is long. A bluish hue is often observed about the eyes, nose, and mouth. The ears may be malformed, small, apparently low-set, and hirsute (13) (Fig. 10–10). The neck is short and thick. Craniometric studies are available (1,86).

Micrognathia is common and prominent mental spur may be seen (14). The lips are thin, with the corners of the mouth downturned. Cleft palate occurs in approximately 20% (12,13,27,30,60,69,74,93). Patients with cleft palate have a high chance of having hearing loss (45). Delayed tooth eruption and microdontia have been noted (12,60). Late eruption and widely spaced teeth were found in 93% of 64 patients reported by Hawley et al (39). A broad acellular zone with gracile fibers around blood vessels has been observed in the gingiva (77).

Limbs. Generally, the hands and feet are small. The fingers are often short and tapering, with clinodactylous fifth digits that have only a single flexion crease. The thumbs are proximally placed in approximately 70% and the thenar muscles are hypoplastic. Flexion contractures of the elbow are present in approximately 65%. Soft tissue syndactyly of the second and third toes is common. Approximately 25% exhibit severely malformed upper limbs, varying from oligodactyly to more severe phocomelia. Limb involvement may be unilateral or bilateral and, when bilateral, is not necessarily identical or even closely similar (Figs. 10–8, 10–11, and 10–12) (13,45,70).

Radiographically, the humerus, radius, and ulna are shortened. Hypoplasia and dorsal dislocation of the radial head are observed in 80%. Often the neck of the humerus is elongated. The semilunar notch of the ulna is shallow. In some cases, the forearm bones are absent. The first metacarpal and middle phalanx of the index and fifth fingers are often hypoplastic, as are the third, fourth, or fifth metatarsals (29). The acetabular angle is low, especially when the child is less than 1 year of age. Coxa valga is a constant feature. The sternum is short with a reduced number of ossification centers, and the ribs are rather thin (13,14,24,52). The available metacarpophalangeal profile analysis showed a characteristic pattern, especially in shortening of the first metacarpal and fourth middle phalanx (14,18,38).

Dermatoglyphic findings include hypoplastic ridge patterns, single palmar creases, and increased atd angle. There is also an increase in radial loops on the third and fourth fingertips (87) and c–d interdigital triradius (13).

Skin. Hirsutism is often generalized, with hair whorls over the shoulders, lower back, and extremities (Fig. 10–13). The nipples and umbilicus are frequently hypoplastic. Cutis marmorata is present in 60% (13,45,85). Pigmented nevi are relatively common.

Genitourinary system. The kidneys are often hypoplastic, dysplastic, or cystic (30). Cryptorchidism and/or hypospadias occur in 73% (45) to 94% (39). Females commonly have bicornuate or septate uterus and long narrow ovaries (93).

Gastrointestinal abnormalities. A variety of gastrointestinal abnormalities have been reported, including malrotation, annular pancreas, pyloric stenosis and/or duodenal obstruction, hiatus hernia, inguinal hernia, umbilical hernia, colon duplication, Meckel's diverticulum, and gastric ulcer perforation (17,39,53,96). Extensive reflux may lead to the Sandifer complex (88). A congenital diaphragmatic hernia has been described several times (20).

Cardiovascular system. Approximately 15%–20% of all patients have a congenital heart defect (13,37,45,62,91). Recorded defects have included VSD, ASD, tetralogy of Fallot, endocardial cushion defect, PDA, hypoplasia of leaflets of aortic valve, tricuspid stenosis, pulmonic stenosis, rudimentary left ventricle, anomalous venous drainage, overriding aorta, and ventricular fibroelastosis (31,62,69,91).

Other findings. A variety of miscellaneous anomalies have been discussed by Berg et al (13) and others (45,59,96). Endocrinological aspects have been discussed elsewhere (13,81). Laboratory studies have not revealed any consistent abnormalities (13). Melegh et al (63) reported mitochondrial DNA deletions, and Froster and Gortner (32) described thrombocytopenia.

Differential diagnosis. There is considerable phenotypic overlap with *dup(3q) syndrome* that we feel is nevertheless distinct. Clinical features of *fetal alcohol syndrome, Coffin-Siris syndrome*, and *KBG syndrome* may occasionally be confused with de Lange syndrome. The case described by Ponder et al (72) had *Peters plus syndrome*. Children with *Gorlin-Chaudhry-Moss syndrome* can exhibit facial resemblance to de Lange syndrome. Stratton et al (90) described a patient with pre- and postnatal growth retardation, bilateral severe upper limb defects including ulnar agenesis, ASD, VSD, and facial dysmorphisms distinctive from de Lange syndrome. It should also be noted that de Lange (25), in 1934, described another syndrome with congenital muscular hypertrophy, hypertonia, and developmental retardation. This condition, too, has sometimes been called de Lange syndrome, but it has nothing to do with the syndrome discussed here.

Laboratory aids. Pregnancy-associated plasma protein A has been suggested as a marker in prenatal diagnosis (95). Prenatal diagnosis by sonography, using especially the ulnar limb defects and diaphragmatic hernia as parameters, has been accomplished (47,58).

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Dubowitz syndrome

In 1965, Dubowitz (5) reported sibs with intrauterine growth retardation, primordial short stature, microcephaly, mental retardation, high-pitched voice, and characteristic facial appearance (Figs. 10–14 and 10–15). He assumed that the children had Bloom syndrome. In 1971, Grosse et al (8) suggested that the disorder was a distinct entity. Approximately 150 cases have been published to date (25). We cannot accept the case described by Lerman-Sagie et al (13) who may well have had deletion of 22q11.2. Autosomal recessive inheritance has been demonstrated because of multiple sib involvement (5,8,10,12,18,21,24,25,27,29–31) and parental consanguinity (18,31). It has also been documented in identical twins (30) and in one of dizygotic twins (25). The cause remains unknown. There is resemblance with mildly expressed Smith-Lemli-Opitz syndrome, and indeed a moderately lowered cholesterol level has been published in a single case (1). We have not confirmed this among several patients.

Moller and Gorlin (16), Belohradsky et al (2), Ilyina and Lurie (10), and Tsukahara and Opitz (25) surveyed the disorder. Evolution of the phenotype has been demonstrated (6,9,14,16). The major clinical features are summarized in Table 10–4.

Growth. Birth weight is approximately 2.4 kg (males) to 2.2 kg (females), and birth length is approximately 45 cm. Prenatal growth failure has been evident in approximately 70%. Postnatal growth is retarded in 90%. Head circumference at birth averages 31 cm. Delayed bone age has been reported in 72%.

Facies. In nearly all cases there is microcephaly, the degree of which does not correlate with mental retardation. The small head circumference seen at birth remains small. High sloping forehead with sparse frontal hair and flat supraorbital ridges are seen in approximately 90%. Facial asymmetry has been noted occasionally. A broad-based nose and nasal tip are seen in over 50%, especially at a younger age. Telecanthus is very frequent, and ptosis with or without blepharophimosis, often asymmetric, is seen in 65%. Low-set and somewhat dysmorphic pinnae have been noted in about 75%. Approximately 75% have microretrognathia (10). The face elongates with age (Figs. 10–14 and 10–15). Both premature aging (6,14) and an appearance younger than chronologic age (9) have been described. Ocular symptoms have included strabismus, microphthalmia (10), tortuous retinal vessels (10,15,18), hypopigmentation

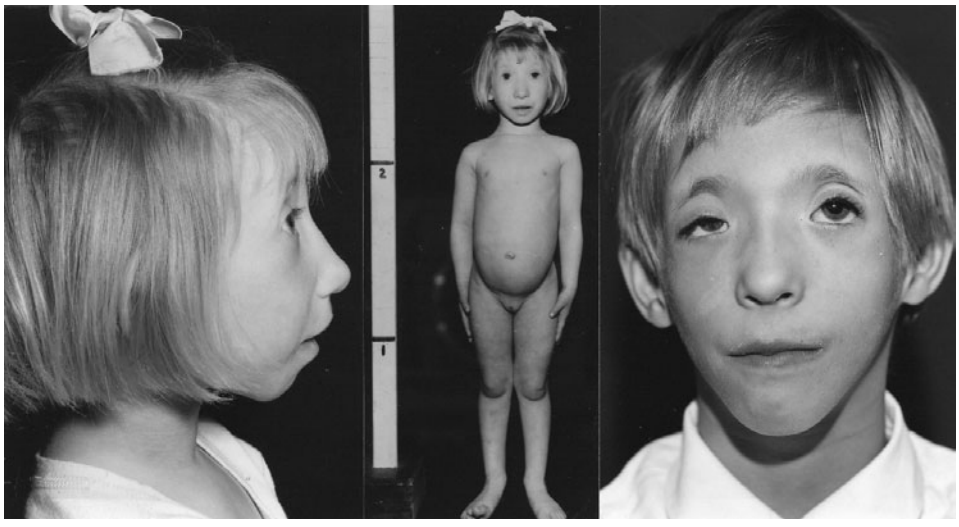
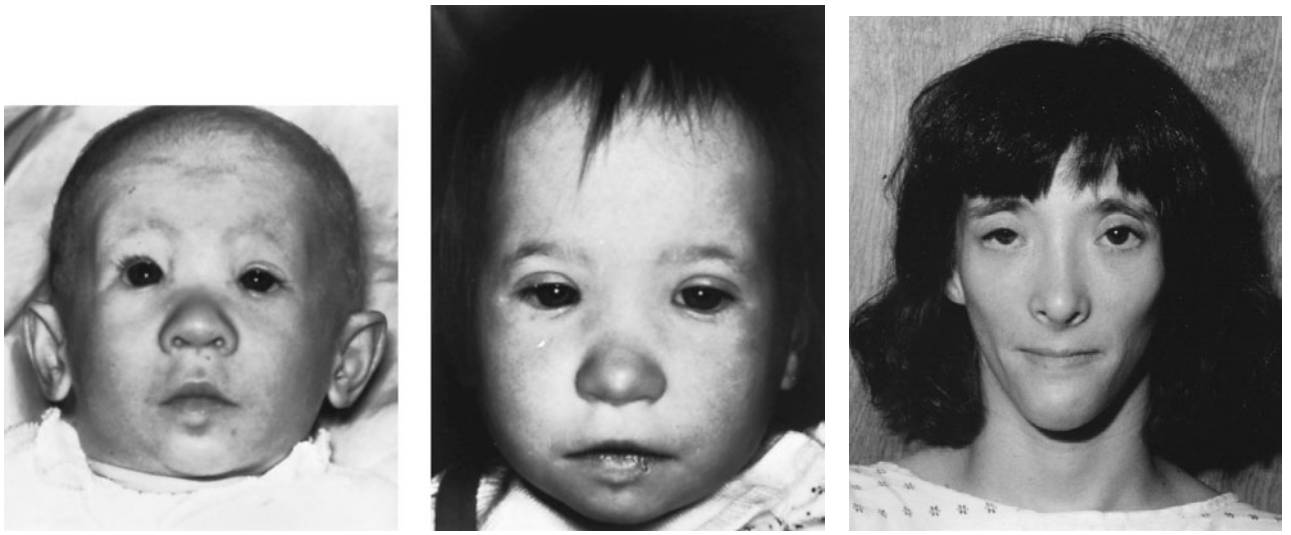


Fig. 10–14. *Dubowitz syndrome*. Primordial shortness of stature, blepharophimosis, ptosis of eyelids, and micrognathia. (From F Grosse et al, Z Kinderheilkd 110:175, 1971.)



A B C

Fig. 10–15. *Dubowitz syndrome*. (A) Note high forehead with flat supraorbital ridges, widely spaced eyes, blepharophimosis, and small mandible. (B) Sister of patient shown in A. Note similar facies. (C) 30-year-old (originally described by Dubowitz in 1965). Note triangular face, laterally sparse eyebrows, asymmetric ptosis, prominent nasal bridge, and narrow chin. (C from KE Hansen et al, Am J Med Genet 55:161, 1995.)

(10,17,18,25), coloboma of iris (23,25), fibrous strands in anterior chamber (19), tapetoretinal degeneration (10), and other anomalies (10,25).

Skin. An eczematous skin eruption, especially of the face and extremities, has been noted in approximately 60%, usually from birth (25). The site of involvement has varied from a limited area to the entire body. It often clears by age 2 to 4 years, but it may last until adulthood. Variable minor soft-tissue syndactyly of the second and third toes has been documented in 25%.

Central nervous system. Motor milestones are reached at normal times. Moderate or severe mental retardation has been evident in 15% and 10%, respectively. Most children have been estimated to be in the dull normal range. However, normal intelligence has been noted (26). Hyperactivity has been manifested by approximately 70% (10,20). Speech is delayed in 60%.

Table 10–4. *Dubowitz syndrome*—clinical findings ($n = 141$)

Feature	Reported cases	%
Prenatal growth retardation	83	(63)
Postnatal growth retardation	119	(86)
Psychomotor retardation	90	(72)
Hyperactivity	50	(36)
Microcephaly	112	(79)
High, sloping forehead	43	(30)
Sparse, thin hair	58	(41)
Blepharophimosis	60	(42)
Ptosis	53	(38)
Broad nasal bridge	31	(22)
Broad nasal tip	20	(14)
High, narrow palate	30	(21)
Cleft palate	22	(16)
High-pitched voice	38	(27)
Micrognathia	81	(57)
Low-set ears	24	(17)
Eczema	59	(42)
Clinodactyly of fifth fingers	48	(34)
Cutaneous syndactyly	22	(16)
Retarded bone maturation	37	(26)
Cryptorchidism	26	(18)

Adapted from M Tsukahara and JM Opitz, Am J Med Genet 63:277, 1996.

Other findings. High-pitched voice has been noted in 50%. Approximately 65% exhibit poor feeding, frequent vomiting, and chronic diarrhea during infancy. The vomiting is usually related to gastroesophageal reflux (25). Approximately 50% of affected males manifest hypospadias or cryptorchidism. Rarely, congenital cardiac defects have been reported (11,12,14,22,25).

Of considerable interest are reports that have noted an association with leukemia (7), lymphoma (2,21), neuroblastoma (21), and aplastic anemia (3,10,28). Although there have been some suggestions that these patients have an immune defect, its precise nature has not been defined (8,15,18,21). Sauer and Spelger (21) noted hypogammaglobulinemia in one sib and IgA deficiency in the other. Both children had malignancies. Thuret et al (24) noted IgA deficiency. Recurrent infections are common in Dubowitz syndrome.

Oral manifestations. Cleft palate, bifid uvula, or submucous cleft palate have been found in approximately 30% (2,4,8,10,18,25,30). Various dental anomalies were described, including oligodontia, microdontia, crowded teeth, macrodontia, and malocclusion (10,25).

Differential diagnosis. Dubowitz syndrome may be confused with *Bloom syndrome, fetal alcohol syndrome*, or Fanconi anemia, and resembles mildly expressed *Smith-Lemli-Opitz syndrome*.

References (Dubowitz syndrome)

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Hallermann-Streiff syndrome

Hallermann-Streiff syndrome is characterized by dyscephaly, hypotrichosis, microphthalmia, congenital cataracts, beaked nose, micrognathia, and proportionate short stature. The condition was probably first described by Aubry (2) in 1893, although he did not report the complete syndrome. Another early report is that of Bergmeister (5). Hallermann (27), in 1948, and especially Streiff (56), in 1950, separated the syndrome from progeria and mandibulofacial dysostosis. An important early paper is that of François (18), who, in 1958, presented two cases, reviewed 22 cases from the literature, and further delineated the syndrome. The condition has also been called François syndrome (3,4,9,19) and oculomandibulodyscephaly (53). Over 180 cases have been recorded to date. Several extensive reviews and surveys are available (3,6,8,12,19,58). A portrait by a contemporary Mexican artist has been documented (44).

Virtually all cases have been sporadic. There is no sex predilection. The syndrome has been described as concordant in monozygotic twins (61) and has been seen in one of dizygotic twins (1). Affected females have had normal children (28,43). We cannot accept any of the familial cases reported to date. For example, Guyard et al (24) described an affected father and daughter and Koliopoulos and Palimeris (35) reported what they called "atypical Hallermann-Streiff-François syndrome" in three successive generations. Neither of these papers describes Hallermann-Streiff syndrome. François (18,19) cited several familial cases as personal communication that have never been published. He further cited two affected sibs reported by Hall et al (26) as examples, although Hall et al (26) specifically recognized the condition they reported as an entity different from Hallermann-Streiff syndrome; they named their disorder pseudoprogeria/Hallermann-Streiff (PHS) syndrome (vide infra).

Table 10–5. *Hallermann-Streiff syndrome*—principal features ($n = 150$)

Abnormality	%
Dyscephaly	98–99
Cataract	81–90
Microphthalmia	78–83
Dental abnormalities	80–85
Hypotrichosis	80–82
Skin atrophy	68–70
Proportionate short stature	45–68

From D Barrucand et al, Rev Oto-Neuro-Ophthalmol 50:305, 1978 and B Carles Mermet, Thesis, Lyon, 1979.

The affected cousins reported by Schanzlin et al (49) do not represent familial examples either. Although a second cousin clearly had Hallermann-Streiff syndrome, the proband had dup(10q) with buphthalmos, sclerocornea, total aniridia, nasal abnormality, micrognathia, and bifid halluces. Chromosomal studies have been normal in almost all instances (3,4,17,21,33,37), with few exceptions (29,34).

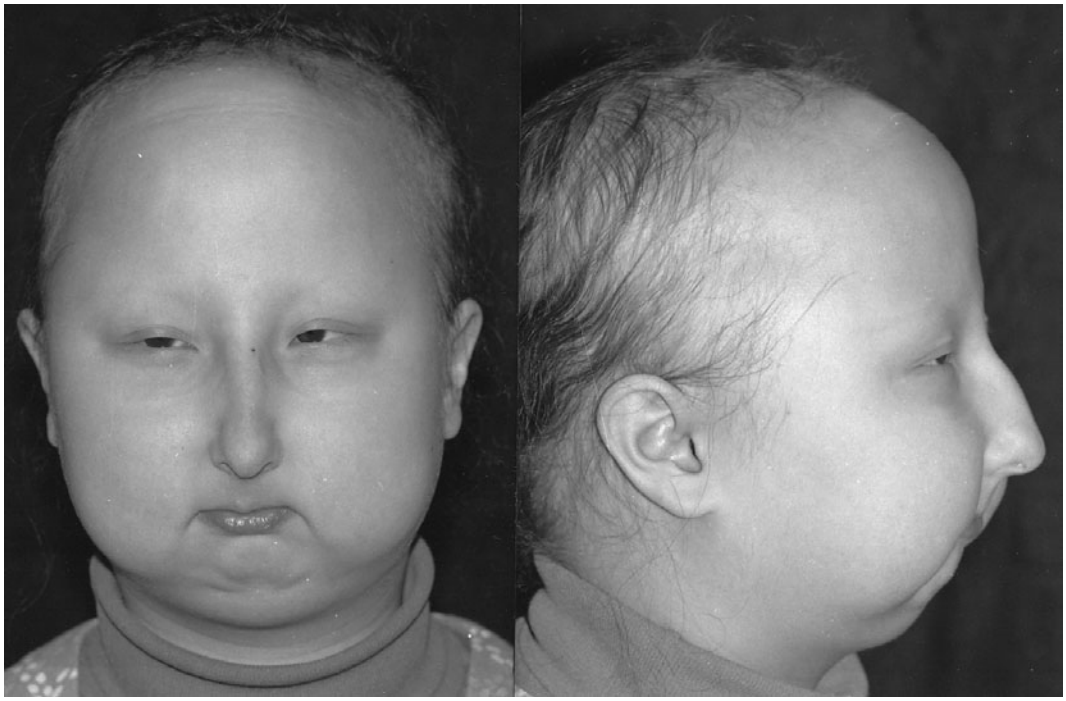
The sporadic cases reported by Scoppetta et al (52) and Steel et al (55) are not examples of the syndrome. Consanguinity was reported by Berbich et al (4), but in their sibship of eight children, only one was affected. François (19) cited a number of other instances of consanguinity. However, families that can be verified had only one affected individual per family.

Natural history. Clinical findings are summarized in Table 10–5. Narrow upper air passages may make feeding difficult during infancy (13a,29,46). Pneumonia and/or severe feeding difficulties have led to the demise of affected infants in several instances. Anesthetic risks have been discussed by Ravindran and Stoops (45) and Sataloff and Roberts (48). Sleep apnea has also been noted (13a,20).

Birth weight is normal in about 65%, prematurity and/or low birth weight occurring in the other 35% (58). Short stature is seen in 45%–68% (19). Growth is diminished proportionately, being at least 2–5 SD below the mean. Final height attainment for females is approximately 152.4 cm, with males being 2.5–5.0 cm taller.

Craniofacial features. The face is small, with a long, thin, tapering, "pinched" nose, and receding chin (51). An odd-shaped, bulging skull with brachycephaly is often accompanied by frontal or parietal bossing (Fig. 10–16). Mild microcephaly and malar bone hypoplasia also occur but are not constant features (19,37). Gaping or dehiscence of sutures, as well as delayed closure of fontanels, has been described by nearly all authors. Increased wormian bones have been reported (11). The nose is thin, pointed, and often curved and may have a tendency to septal deviation (7,43). Hypotrichosis, especially of the scalp, brows, and lashes, occurs in approximately 80% (3,8,21,22,58). Scanning electron microscopy has shown absent or abnormal cuticle development in the hair shafts (21). Alopecia is most prominent about the frontal and occipital areas, but is especially marked along suture lines (57). Cutaneous atrophy and/or atrophic alopecia, present in approximately 70% (3,8,22), is largely limited to the scalp and nose. Scalp skin is thin and taut, and scalp veins are prominent. Similar changes may be observed on the nose.

Previously undiagnosed patients tend to visit ophthalmologists because of visual impairment from congenital cataract. Microphthalmia of variable severity (78%–83%) and bilateral congenital cataracts (81%–90%) occur with high frequency (3,8,58). Cataracts consist of milky white liquefied lens masses that resorb spontaneously in approximately 10% (19,54,64). Blue sclerae have been described in approximately 22%–31%, nystagmus in 32%–45%, strabismus in 33%–37%, glaucoma in 7%–11%, pupillary membrane persistence in 5%, and down-slanting palpebral fissures in 12%–13% (3,8,30,37,57–59,61). Donders (16) published a histopathologic study of the eye from an autopsy case. Anomalies of the fundus, conjunctiva,



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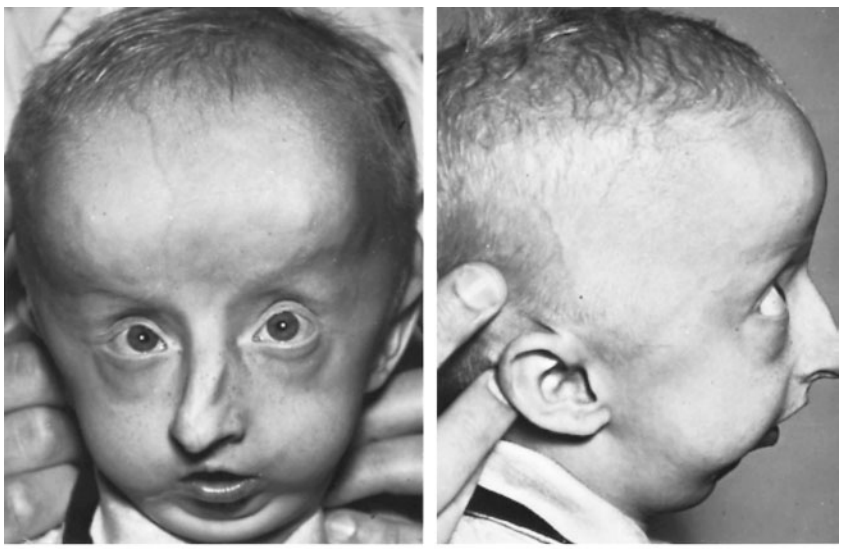

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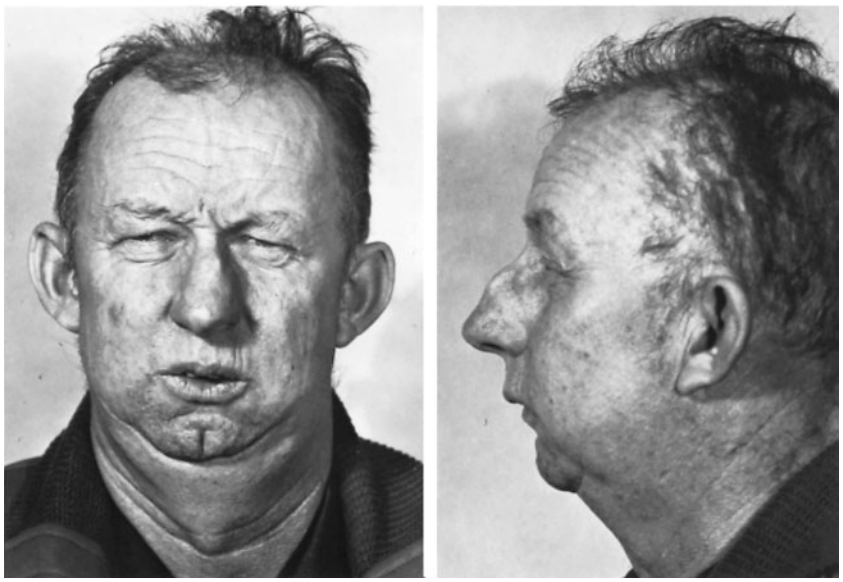

E F

Fig. 10–16. *Hallermann-Streiff syndrome*. (A–F) Characteristic facial appearance with brachycephaly, hypotrichosis, thin pointed nose, and micrognathia. Note posteriorly angulated ears in patient shown in D. Note also chin groove in patient shown in E. [A,B from MM Cohen Jr, Malformation syndromes. In: Surgical Correction of Dentofacial Deformities, WH Bell et al (eds), W.B. Saunders, Philadelphia, 1980, p 35. C,D from D Hoefnagel and K Benirschke, Arch Dis Child 40:57, 1965.]

Table 10–6. *Hallermann-Streiff syndrome*—findings ($n = 150$)

Abnormality	%
Congenital cataract	81–90
Microphthalmia	78–83
Nystagmus	32–34
Strabismus	33–37
Blue sclerae	22–31
Sparse eyelashes and eyebrows	29
Fundus anomalies	18–22
Conjunctival defects	11
Corneal abnormalities	9–14
Downslanting palpebral fissures	12–13
Intraocular hypertension	7–11
Iris atrophy	10–14
Vitreous degeneration	8
Eyelid anomalies	6
Iris coloboma	5
Pupillary membrane persistence	5
Enophthalmos	2.5–4
Hypotelorism	2.5
Epicanthic folds	2–4
Disc coloboma	1
Choroidal coloboma	1
Ptosis of the eyelids	1–3
Hypoplasia of the lacrimal puncta	2
Epibulbar tumor	1

From D Barrucand et al, Rev Oto-Neuro-Ophthalmol 50:305, 1978 and B Carles-Mermet, Thesis, Lyon, 1979.

Table 10–7. *Hallermann-Streiff syndrome*—other abnormalities ($n = 150$)

Abnormalities	%
Mental deficiency	15
Neurological manifestations	Infrequent
Skeletal defects	10–50
Genital anomalies	10–12
Cardiac defects	2–9
Ear anomalies	9
Hematopoietic abnormalities	7
Pulmonary anomalies	3
Digestive system abnormalities	3
Muscular hypotrophy	3
Hepatic anomalies	2
Renal anomalies	1–2

From D Barrucand et al, Rev Oto-Neuro-Ophthalmol 50:305, 1978; B Carles-Merment, Thesis, Lyon, 1979; L Crevits et al, J Neurol 215:225, 1977; and Y Suzuki et al, Dev Med Child Neurol 12:496, 1970.

and cornea as well as miscellaneous ocular findings (Table 10–6) are well documented in several accounts (3,7,8,17–19,23,27,37,39,41,57, 60,61,63,64).

The mandible is hypoplastic with double chin and central clefting or dimpling (7,18,23,27,56). The ascending ramus is usually short, and the condyle may be missing or the fossa hypoplastic (18,34,36). Radiographic examination reveals a characteristic temporomandibular joint displacement of approximately 2 cm forward from its normal position that is located just in front of the external auditory meatus (61). The midface is hypoplastic with a prominent nasal bone. The palate is high and narrow and the paranasal sinuses are diminished in size (17). Microstomia is present in approximately 10% (34,61). The gonial angle is straight. Cephalometric and anthropometric studies have been carried out (20,25,62).

Dental anomalies are common (80%–85%) and may include absence of teeth, persistence of deciduous teeth, malocclusion and open bite, malformed teeth, severe and premature caries, supernumerary teeth, and especially natal teeth (2,3,7,8,17–19,27,29,31,39,40–42,47,50,56). A well-documented histopathologic study of dentoalveolar abnormalities observed at autopsy is available (53).

Central nervous system. Mental deficiency has been noted in approximately 15% (34,58); and although an estimate as high as 31% has been indicated elsewhere (3,8,19), Crevits et al (13) has warned that the psychometric aspects of the syndrome have been treated very subjectively, with only rare instances of psychometric testing. Hyperactivity, choreoathetosis, and generalized tonic-clonic seizures have been noted occasionally (13,17,34).

Other findings. A wide variety of miscellaneous findings has been reported (Table 10–7). Hypogenitalism has been reported in 10%–12% (3,8,29). Also documented have been cryptorchidism, hypospadias, clitoral enlargement, breast asymmetry, and breast atrophy (3,19). Axillary and pubic hair may be scant (17,18).

Various cardiac anomalies including pulmonic stenosis, ASD, VSD, PDA, and tetralogy of Fallot have been reported in approximately 5% (15,32,65).

Chandra et al (10) reported a case with deficiency of humoral immunity and hypoparathyroidism. Although immunodeficiency, hypoparathyroidism, and cardiac anomalies have now been observed in Hallermann-Streiff syndrome, true DiGeorge sequence has not occurred. The patient reported by Chandra et al (10) had normal cell-mediated immunity with reduced serum IgG and plasma opsonic function.

A great many other abnormalities have been observed, including occipital bossing, hydrocephaly, calcification of falx cerebri (3,19,38,65), osteoporosis (41), syndactyly (61), lordosis and/or scoliosis (39,50), spina bifida, winging of scapula (34,43,58,61), pectus carinatum or excavatum (19,61) and thin gracile bones (11). Vitiligo and livedo have also been noted (18,37,65).

Differential diagnosis. *Progeria* differs from the Hallermann-Streiff syndrome by having premature arteriosclerosis, nail dystrophy, acromicria, and chronic deforming arthritis. In addition, the eyes are normal. *Wiedemann-Rautenstrauch syndrome* should also be excluded.

Mandibulofacial dysostosis shares in common with the Hallermann-Streiff syndrome micrognathia, high palatal vault, and malar hypoplasia, but usually has lower eyelid colobomas and associated ear anomalies.

The autosomal recessive pseudoprogeria/Hallermann-Streiff (PHS syndrome) (26) has similarities to the Hallermann-Streiff syndrome but has, in addition, severe spastic quadriplegia. Furthermore, appearance at birth is normal except for absence of eyebrows and eyelashes. The disorder is progressive, with limb spasticity and psychomotor delay evident by 6 months of age. Dennis et al (14) described a lethal recessive disorder characterized by slender long bones, underossified skull, and congenital cataracts.

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Rubinstein-Taybi syndrome

In 1963, Rubinstein and Taybi (93) observed a combination of broad thumbs and halluces, characteristic facial dysmorphism, growth retardation, and mental deficiency (Figs. 10–17 to 10–19). However, the syndrome had been described as early as 1957 in the French literature by Michail et al (74). Rubinstein (92) reviewed 571 patients in 1989. The syndrome has been observed in whites, blacks, and Orientals (47,92). The reader is referred to the following sources for detailed coverage: extensive review (92), genetic aspects (47), growth (106), craniofacial features (4), natural history (2,43,48,105), neoplasias (75), oral characteristics (44), cardiac aspects (104), psychological investigations (50), and bibliography (42).

The prevalence in the general population has been estimated to range from 1/300,000 to 1/720,000 (101). As several of the patients used in this study proved to have a different diagnosis on careful follow-up (81), these figures are no longer usable. Hennekam et al (47) estimated a birth prevalence of 1/125,000 in the Netherlands. This figure has proved to be correct for the Netherlands in the period 1988–1998 (RCM Hennekam, unpublished data, 2000).

Genetics. The overwhelming majority of reported cases are sporadic. Fourteen MZ concordant, one MZ discordant, and four discordant DZ twins have been recorded (6,33,47,48,53,54,59,64,83,85,97). Affected sibs were noted by Johnson (57). Apparent dominant transmission has been described (31,45,70). In several other reports (23,35,41,108), familial recurrence was unconvincing or the diagnosis unlikely (47). The

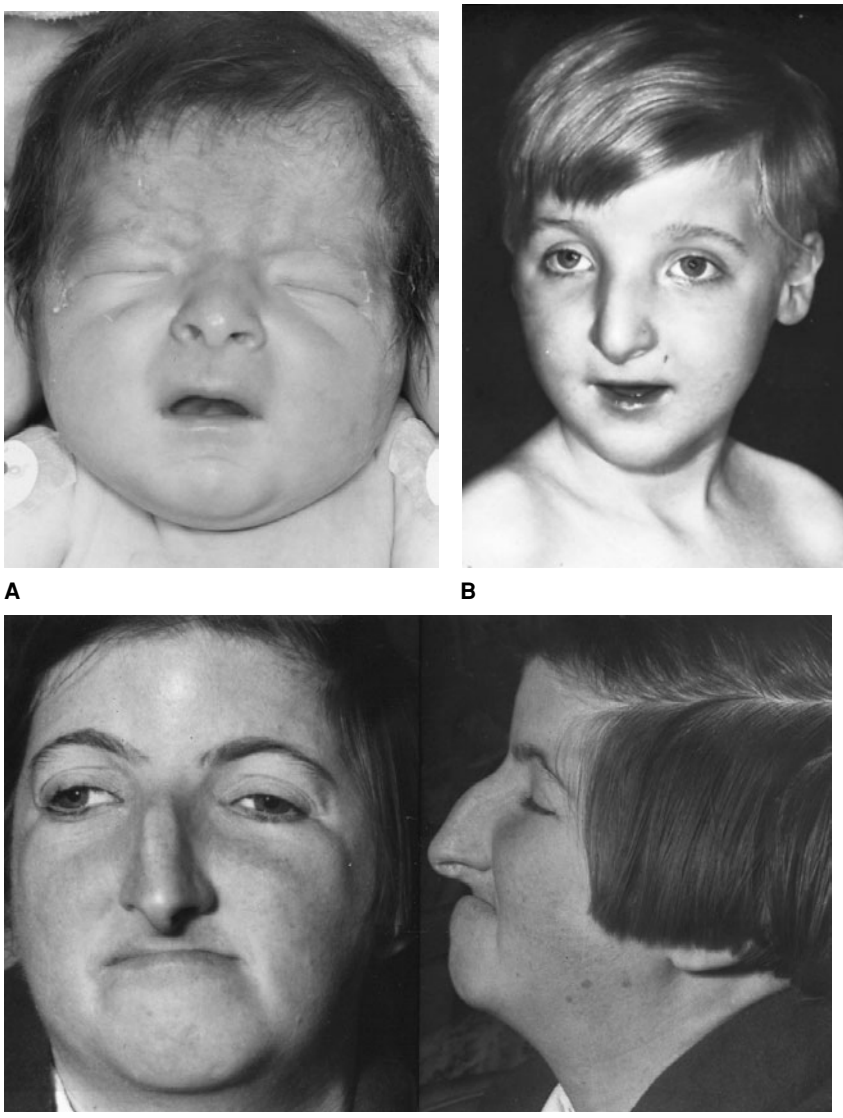


Fig. 10–17. *Rubinstein-Taybi syndrome*. (A–E) Characteristic facial appearance at different ages. Note septum extending below nasal alae. (B,C from R Weiland, Arch Kinderheilkd 179:78, 1969. D,E from JM Berg et al, J Ment Defic Res 10:204, 1966.)

parents in ten families (47) were consanguineous. Several family histories are noteworthy because of the presence of broad thumbs in relatives (47,92).

Hennekam et al (47) reviewed the cytogenetic findings in 306 patients in 1990: 295 had normal karyotype and nine had (inconsistent) chromosome anomaly. Imaizumi et al (55) and, later on, Tommerup (112), Lacombe (65), and Hennekam (unpublished observation) described translocations or inversions involving locus 16p13.3. This allowed for the detection of submicroscopie deletions by fluorescence in situ hybridization (17,51).

Several series of patients have been investigated for microdeletions at 16p13.3 (17,51,71,73,107,116), in which deletions could be demonstrated in approximately 15% of the cases, depending on the reliability of the clinical diagnosis. For an analysis of specific mutations, see Blough et al (12a). No major differences were found in patients with and without deletion, with the possible exception that more frequent microcephaly and angulated halluces were noted in those with the deletion (51,107). The empiric recurrence risk for sibs was calculated to be 0.1% (47).

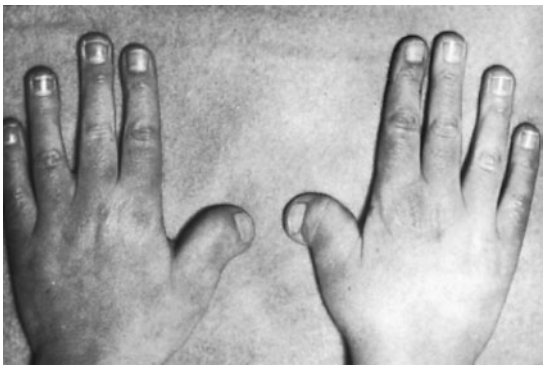
Eventually, Petrij et al (82) described mutations in two patients in the transcription cofactor CBP (CREB binding protein), making the Rubinstein-Taybi syndrome a haplo-insufficiency disorder. The mechanism by which decreased CBP levels affect pattern formation is unclear. In Drosophila, CBP was shown to be a cofactor in the hedgehog signaling pathway (1), which may explain in part the pleiotropic effects of CBP. Five cosmids may be used for detection of microdeletion (82a).

Systemic manifestations. Natural history has been well documented (48,105). Various findings are listed in Table 10–8. Polyhydramnios has been reported in 30%. Two patients have been described with both an aged appearance and a meningioma (11,48).

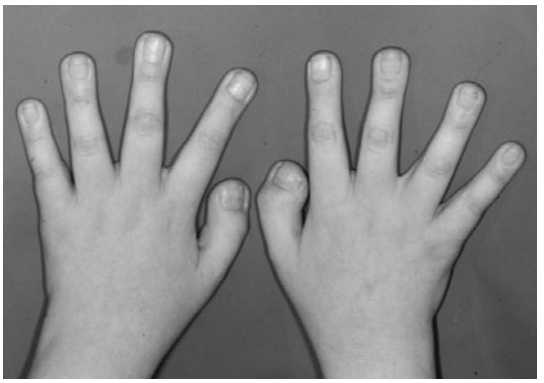
Growth. Length, weight, and head circumference at birth are between the 25th and 50th centiles. Average birth length is 49 cm, with a range of 43.9–53.3 cm. Average birth weight is 31 kg, with a range of 2.05–4.28 kg. Mean head circumference is 34.2 cm (males) and 32.2 cm (females), with a range of 29–38 cm (106). Often there is poor weight gain during infancy (106). Males are often overweight for height during childhood, while females are overweight during adolescence.

Values for final height attainment for males are 153.1 cm and for females 146.7 cm (106). Mean head circumference at adulthood is 54.7 cm (males) and 52.4 cm (females)(3).

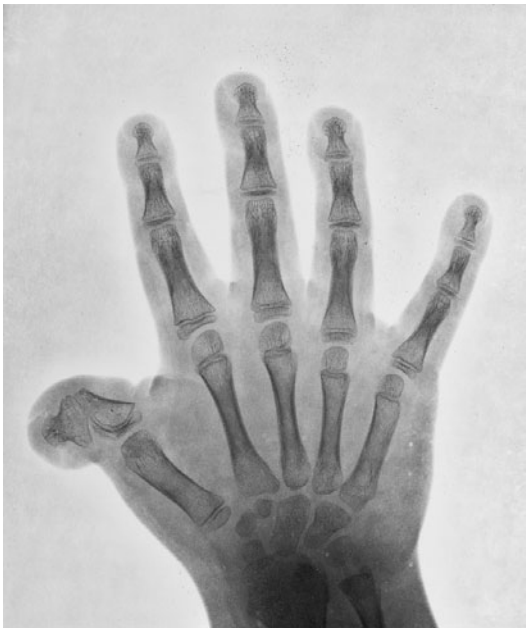
Performance and central nervous system. Global mental deficiency is characteristic with the most severe delay in expressive speech (50). The average IQ has been reported to be 51 (range 33–72) (n = 37) (48) or 36 (range 25–79) (n = 40) (50). Affected individuals tend to be loving and friendly, although maladaptive behavior has also



A

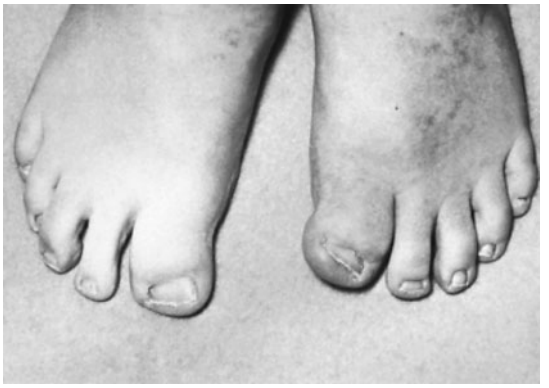


B



C

Fig. 10–18. *Rubinstein-Taybi syndrome*. (A) Broad and radially deviated thumbs. (B) Compare with A. (C) Radiograph showing broad short terminal phalanges and triangular proximal phalanges of thumbs. (A from JM Berg et al, J Ment Defic Res 10:204, 1966. C from A Neuhold et al, Rofo Fortsch Geb Rontgenstr Neuen Bildgeb Verfahr 150:49, 1989.)



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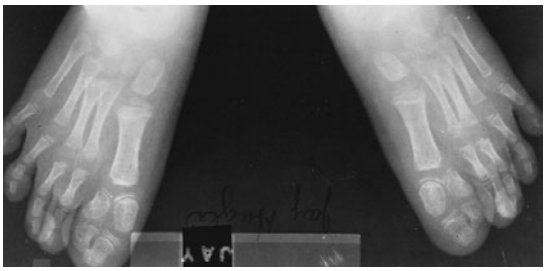

B

Fig. 10–19. *Rubinstein-Taybi syndrome*. (A) Broad and tibially deviated halluces. (B) Radiograph showing broad great toes with duplication of halluces. (A from JM Berg et al, J Ment Defic Res 10:204, 1966.)

Table 10–8. *Rubinstein-Taybi syndrome*—medical problems ($n = 95$)

Feature	%
Pregnancy	
Gestational length	39.9 weeks (range 32–44 weeks)
Polyhydramnios	30
Infancy history	
Respiratory problems	51
Feeding problems	80
Constipation	71
Poor weight gain	80
Medical history	
Visual problems	84
Strabismus	(58)
Refractive error	(41)
Astigmatism	(18)
Other	(4)
Cataracts	7
Glaucoma	8
Coloboma	5
Tear duct obstruction	39
Ptosis	45
Hearing loss	24
Frequent middle ear infections	60
Congenital heart defects	32
PDA	(13)
VSD	(12)
ASD	(10)
Coarctation	(3)
Pulmonic stenosis	(2)
Urinary tract infection	22
Keloids or hypertrophic scarring	25
Severe constipation	44
Epilepsy	23

Based on CA Stevens et al, Am J Med Genet 72:188, 1997; RCM Hennekam and JM Van Doorne, Am J Med Genet Suppl 6:42, 1990; and RCM Hennekam et al, Am J Med Genet 6:17, 1990.

been noted. Persistence is low. A specific behavioral phenotype has been described (50). Despite their limited verbal abilities, the communicative level is good.

Electroencephalographic abnormalities, seizures, absence of corpus callosum, and hyperactive deep-tendon reflexes have been noted (39,48,87,93,105). Rarely, other abnormalities such as Dandy-Walker anomaly (7,14) and myelinization defects (84) are found.

Craniofacial features. The facial appearance is striking, with microcephaly, prominent forehead, down-slanting palpebral fissures, epicanthal folds, strabismus, broad nasal bridge, beaked nose with the nasal septum extending below the alae, highly arched palate, and mild micrognathia (Fig. 10–17). The features are recognizable in the newborn. Facial changes with time have been studied by Allanson (2) and Hennekam (43,48). Grimacing or unusual smile has been observed frequently. Other findings may include long eyelashes, nasolacrimal duct obstruction, ptosis of eyelids, congenital or juvenile glaucoma, refractive error, and minor abnormalities in shape, position, and degree of rotation of ears (9,12,14, 16,18,26,29,39,48,62,67,69,78,92,93,114). Van Genderen et al (114) described an abnormal waveform of Visual Evoked Potentials, and cone or cone–rod dysfunction on electroretinography. Low-frequency abnormalities have included bifid uvula, submucous palatal cleft, bifid tongue, macroglossia, short lingual frenum, natal teeth, and thin upper lip (44,92, 95,105). Talon cusps (markedly enlarged cingulum on maxillary incisor teeth) have been observed in over 90% (32,44,62) (Fig. 10–20), necessitating specific dental care (20,44). Talon cusps are found in 1% of the normal population. Cephalometric studies (49) and objective evaluation of craniofacial structures (4) are available.

Hands and feet. Broad thumbs and great toes have been present in almost all reported cases. In most instances, the terminal phalanges of the fingers are also broad. Persistent fetal pads are common. Clinodactyly of fifth fingers and overlapping of toes are present in over half the cases. Angulation deformities of the thumbs and halluces, together with abnormally shaped proximal phalanges, occur in approximately 35% (48,92, 105,118). Abnormally shaped first metatarsals and duplication of the proximal or distal phalanx of the halluces have also been reported. Rarely, postaxial polydactyly of the feet, partial cutaneous syndactyly involving the toes, and absence of the distal phalanx of the hallux have been noted (18,26,48,92,93,105,110) (Figs. 10–18 and 10–19). There is no description of a proven case with preaxial polydactyly. The metacarpophalangeal pattern profile may be specific (46).

Alterations in the frequency of various fingerprint patterns have been observed, but findings have been inconsistent (5,26,36,53,87,92,93).

Skeletal system. Growth retardation and delayed bone age are common. Large anterior fontanel or delay in closure, large foramen magnum, and parietal foramens have been reported in some cases. Other skeletal anomalies have included pectus excavatum, other sternal abnormalities, rib defects, scoliosis, kyphosis, lordosis, spina bifida, flat acetabular angles, slipped capital femoral epiphysis (15), flaring of ilia, and notched ischia (48,92). Various other low-frequency anomalies have been discussed by Rubinstein (92), Robson (88), and Hennekam (48).

The gait is commonly stiff. Hypotonia, lax ligaments, increased fracture frequency, and hyperextensible joints have also been noted (92). Patellar dislocation can be bothersome (48,76,103). Several pubertal patients have severe aseptic hip joint inflammations (RCM Hennekam, personal observation). A tethered cord has been described (90).

Fig. 10–20. *Rubinstein-Taybi syndrome*. Talon cusps of four maxillary permanent incisors, marked distal marginal ridge on left lateral incisor. (From DG Gardner and SS Girgis, Oral Surg 47:519, 1979.)

Genitourinary system. Probably all male patients have incomplete or delayed descent of the testes. Anomalies of the urinary tract, including duplication of the kidney and ureter, renal agenesis, nephrotic syndrome, and other abnormalities, have been recorded in a number of cases (34,48,108,115). Urinary tract infections occur in approximately 20%–25% (48,105). Rarely, angulated penis and hypospadias have been noted (48,92).

Other findings. A variety of congenital heart defects have been found in approximately 35% (104). Abnormal lung lobulation, supernumerary nipples, nevus flammeus of the forehead, nape, or back (60%), hirsutism (75%), and other abnormalities have been described (18,20,48,57,92,105). Supernumerary nipples are found in 15% (19). Precocious puberty has also been noted (54a). Multiple pilomatrixomas have been reported (19,72,75). Herranz et al (52) reported a patient with piebaldism. An increased tumor risk (75), such as nasopharyngeal rhabdomyosarcoma (102), intraspinal neurilemoma (94), neuroblastoma (54a,75), pheochromocytoma (13), angioblastic meningioma (11,48,RCM Hennekam, unpublished observation), and acute leukemia (58), has been recognized (75). Keloids or hypertrophic scarring has been described in 5%–20% (37,48,89,98,105). Gastroesophageal reflux (38) and megacolon (39,48) are rarely found. Other rare complications are thymus hypoplasia (61), IgA deficiency and other immunologic disorders (48,115a), bifid uterus and menstruation problems (66), migraine (48,105), branchial arch anomalies (48), and ankyloblepharon filiforme adnatum (48,108).

Obstructive sleep apnea may cause considerable problems (24,48,119). In a single report, cardiac arrhythmias due to neuromuscular blocking agents (succinylcholine) were described (105). Another anaesthetic problem may be difficulties in intubation due to easy collapsibility of the laryngeal walls (22,48). Fryns et al (28) observed that maternal serum screening tests may be positive in pregnancies with the entity.

Differential diagnosis. Although many components of the syndrome may occur as isolated findings or as features of various other syndromes, the overall pattern of anomalies is sufficiently distinctive to permit diagnosis in most instances. The authors have seen numerous patients who have exhibited only some of the stigmata of the Rubinstein-Taybi syndrome (47,92). Some may represent incomplete forms. Differential diagnosis can be a problem in the newborn period. Occasionally, some cases have been confused with de *Lange syndrome* (64), *Saethre-Chotzen syndrome* (68), or with *trisomy 13* (117). Broad thumbs may be observed in *Apert syndrome* and *Pfeiffer syndrome*, and short thumbs and fingers are seen in Type D brachydactyly. Cotsirilos et al (21) reported a mother and two sibs affected with a Rubinstein-Taybi–like disorder. Six other relatives of the mother were reported to have broad thumbs and halluces. The family with broad thumbs and mental deficiency reported by Robinow (86) probably represents a separate entity. Prieto syndrome has a similar facies but X-linked inheritance (86).

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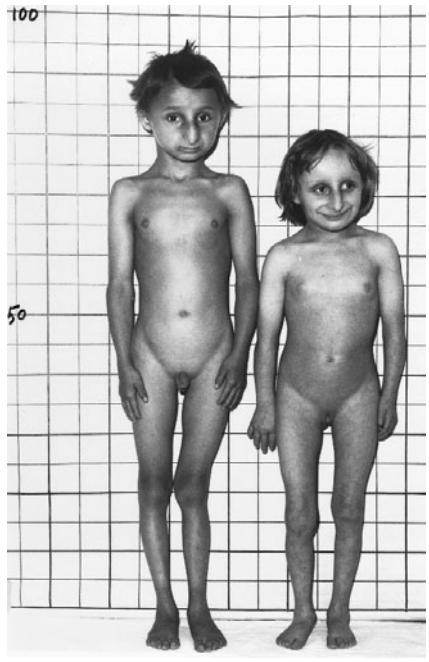
Seckel syndrome and other microcephalic primordial dwarfisms

Seckel syndrome. Seckel syndrome is characterized by marked intrauterine and postnatal growth retardation, microcephaly, mental retardation, and typical facial appearance with a beaklike protruding nose (Figs. 10–21 and 10–22). In the past, the condition has been overdiagnosed (41,81). Of Seckel's two original patients (68), only case 1 fits the proper diagnostic criteria. Seckel syndrome is compared to the other major forms of microcephalic primordial dwarfism in Table 10–9.

Fig. 10–21. *Seckel syndrome*. Proportionate short stature, microcephaly, curved nose, and small mandible in two affected sibs. (From B Boscherini et al, Eur J Pediatr 137:237, 1981.)



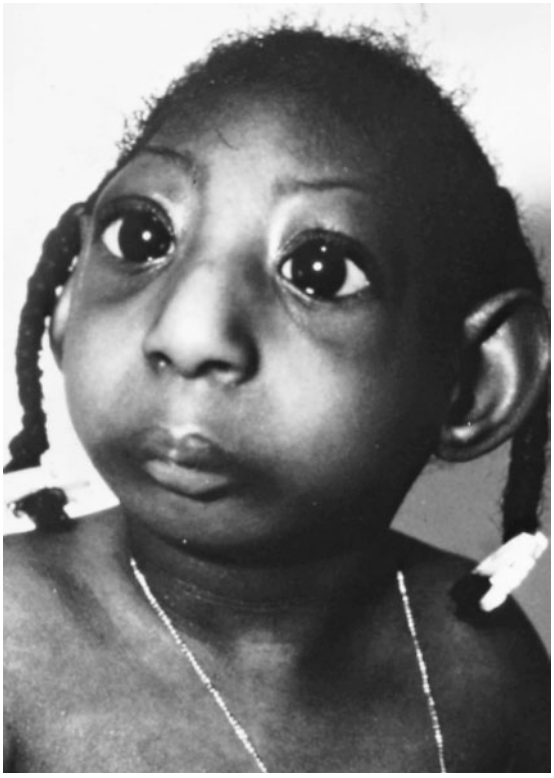


Fig. 10–22. *Seckel syndrome*. Characteristic facies, with small head circumference and micrognathia, lending prominence to the midface. (Courtesy of JJ Sauk, Baltimore, Maryland.)

Table 10–9. Major manifestations of Seckel syndrome compared to those in osteodysplastic primordial dwarfism

	Seckel Syndrome	OPD I	OPD II
Prenatal growth retardation	+++	21/21	17/17
Postnatal growth retardation	+++	11/11	17/17
Moderate/severe MR	+++	10/10	15/16
Microcephaly	+++	21/21	16/17
Sparse/absent scalp hair	−	14/15	5/14
Small anterior fontanel	++	18/18	4/9
Receding forehead	+++	14/15	7/12
Prominent eyes	++	21/21	6/14
Blepharophimosis	++	0/10	3/11
Prominent nose	+++	16/17	15/16
Teeth anomalies	++	2/2	2/8
Micrognathia	+++	16/18	16/17
Dysplastic, low-set ears	+++	12/13	9/13
Short neck	−	14/15	4/11
Relatively large hands/feet	−	7/10	0/12
Short fingers	+	14/14	6/8
Hyperkeratosis	−	10/12	0/9
Dislocations	++	9/11	1/14
Contractures	+	7/12	1/13
Delayed osseous maturation	+++	19/19	16/16
Disproportionate short long bones	−	13/14	15/17
Bowed long bones	−	9/13	2/13
Brachymesophalangy	−	5/8	12/14
Brachymetacarpy I	−	5/7	4/9
Pelvis anomalies	+/−	17/17	9/14

Key: +++, 75–100; ++ 50–75; + 25–50; +/− 25 or less; −, absent.

Adapted from RCM Hennekam and K De Geest, Dysmorphol Clin Genet 3:39, 1989; S Sigaudy et al, Am J Med Genet 80:16, 1998; and F Majewski and T Goecke, Am J Med Genet 80:25, 1998.

From the literature, only 30 cases qualify as examples of Seckel syndrome [2 (case 1),3,7 (case 1–2),9,12,13,17,27,28,35,37 (case 2),44, 50,59 (case 2),63 65,68 (case 1),69,75,77,78,82 (case 1–3)]. The male-to-female sex ratio is equal, and both sexes are equally severely affected. All parents have been normal. Consanguinity has been described in two Yemeni Arab families (36,69). Affected sibs have been reported by eight authors (3,7,13,27,36,63,69,82). The syndrome has autosomal recessive inheritance. Courtens et al (16) reported a boy with a Seckel-like phenotype and interstitial deletion of 2q33.3q34. Another family maps to 3q22.1–q24 (24). A great many cases from the literature do not qualify as examples of Seckel syndrome [6,7 (case 3),10,14,20,21–24,29,40,42,53,57,59 (case 1,3),60,61,66,68 (case 2–4,6–15),72,73,82 (case 4,5),84,92].

Growth and development. Striking features of Seckel syndrome are listed in Table 10–9. Mean birth weight of affected newborns at term is approximately 1540 g (range 1000–2055 g). Postnatal growth deficiency is, on average, 7.1 SD below the mean, with a range of −5.1 to −13.5 SD. Head circumference is as retarded as height in half the cases; in the remaining instances, head circumference is the singularly most retarded parameter. All patients are mentally retarded, with half having an IQ below 50. Moderate mental deficiency has been observed in some instances (44).

In addition to delayed osseous maturation, the phalanges exhibit ivory epiphyses and cone-shaped epiphysis in the proximal phalanges. The carpal bones are relatively small, and disharmony occurs in maturation between the carpals and phalanges (62).

Craniofacial features. Craniofacial features are striking, with severe microcephaly, receding forehead, relatively large eyes, and micrognathia, lending prominence to the midface and curved nose (Fig. 10–22). Synostosis of cranial sutures occurs in approximately 50%. Other craniofacial features may include facial asymmetry, down-slanting palpebral fissures, lobeless ears, highly arched or cleft palate, enamel hypoplasia, crowded teeth, and class II malocclusion (27,44,82). Bilateral optic atrophy and tapetoretinal degeneration and mild nerve deafness have been reported (36).

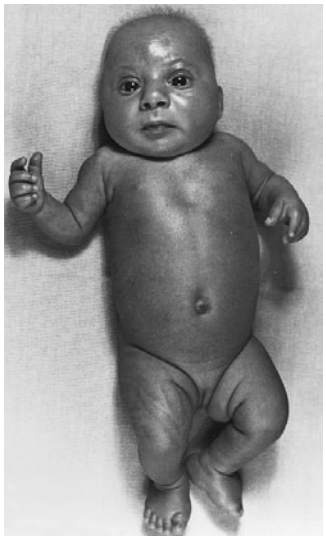
Other findings. Limb anomalies include clinodactyly of fifth finger, abnormal finger flexion creases, dislocation of radial head, and hip dysplasia. Other findings may include cryptorchidism, clitoromegaly, hypospadias, and hirsutism (44,69). Case 1 of Sugio et al (76) had hydronephrosis. Butler et al (12) reported pancytopenia in one patient and chromosome instability in two; other reported hematologic anomalies were increased sister chromatid exchange (13) and acute myeloid leukemia (28). Woods et al (90) reported a patient with Seckel-like features, who showed an increased mitomycin C sensitivity. Central nervous system anomalies included agenesis of the callosal body, hypoplasia of the cerebellar vermis or complete cerebellum, pachygyria, large basal ganglia, and arachnoidal cysts (36,69,76).

Findings not previously emphasized have been discussed by Thompson and Pembrey (82).

Osteodysplastic primordial dwarfism. In a series of papers, Majewski and coworkers suggested a subdivision of the other forms of microcephalic primordial dwarfism in three types (44–48). Later, it appeared that types I and III were, in fact, identical (25,43,89). Majewski (43) proposed to reclassify type III, and to designate the form of dwarfism present in Caroline Crachami (8), two German sibs, and possibly several patients from the ancient literature (43) as such.

Osteodysplastic primordial dwarfism (OPD) type I (formerly termed types I and III, and also called Taybi-Linder syndrome) has been described in approximately 30 cases (4,5,21,25,35,47,48,51,54,55,71,80, 81,87a,89); we are uncertain about the diagnosis in one case [2 (case 1)] due to insufficiency of data.

The disorder was comprehensively reviewed by Sigaudy et al (71). The major characteristics that separate type I osteodysplastic primordial



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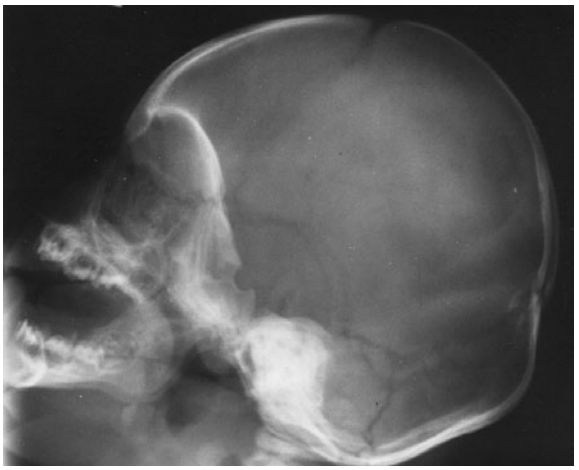

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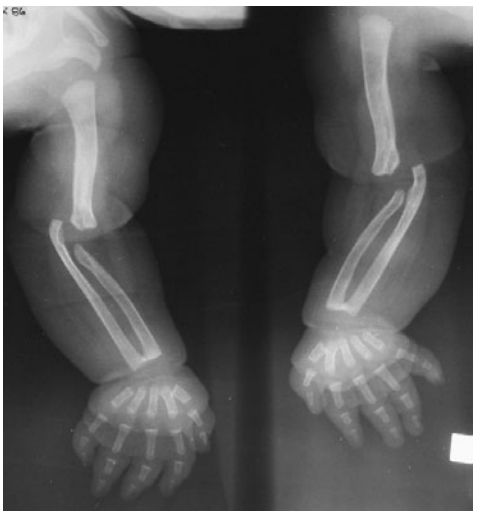

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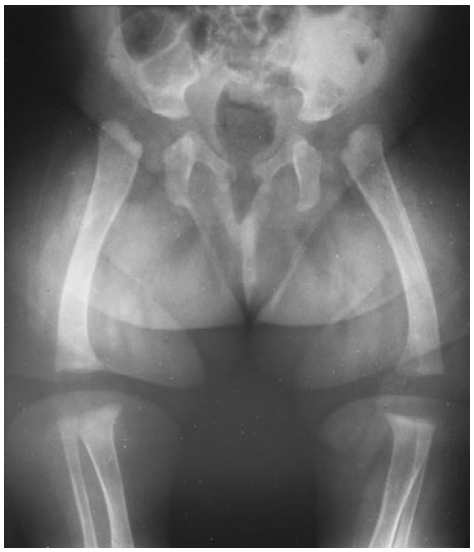

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Fig. 10–23. *Microcephalic primordial dwarfism (osteodysplastic type I).* (A) Microcephaly, hypotrichosis, prominent eyes, large fleshy nose, small dysplastic ears, and micrognathia. (B) Radiograph showing microcephaly, steep skull base. (C) Radiograph showing shortened humeri, bilateral dislocation at elbows, short metacarpals, absence of secondary ossification centers in humeral heads, carpals, and capitellum. (D) Hypoplasia of lower ilia, widened iliac angle, lateral bending of femoras, absent epiphyses at knees. [A courtesy of F Majewski and J Spranger, Mainz, Germany. B courtesy of HN Bass and RS Sparkes, Los Angeles, California. C,D from HN Bass, Syndrome Ident 3(2):12, 1975.]

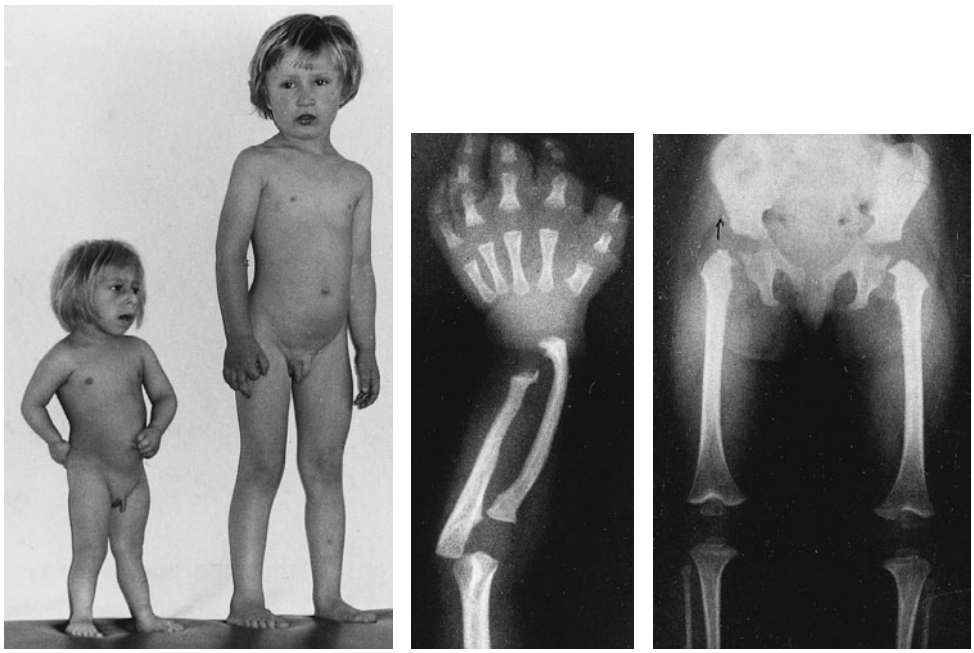
dwarfism from Seckel syndrome are the sparse or absent scalp hair, low-set ears, short neck, relatively large hands and feet, and hyperkeratosis (Fig. 10–23 and Table 10–9). Malformations of the central nervous system have included brain dysgenesis, pachygyria, heterotopias, agenesis of corpus callosum or cerebellar vermis, and hypoplastic frontal lobes (25,38,54,55,71,80,81,89), which are similar to the brain findings in Seckel syndrome. Other anomalies have included neonatal cholestasis (5), tetralogy of Fallot (46), atrial septal defect and coarctation of aorta (71), and renal tubular leakage (21), focal medullary hypoplasia (5), renal cysts (71), or renal hypoplasia (71).

Radiographic features have included delayed osseous maturation, generalized shortening of long bones that are often bowed and show enlarged metaphyses, and pelvic anomalies (hypoplasia of iliac wings and acetabulae; horizontal acetabular fossae). The clavicles may be elongated, and some platyspondyly has been described (48,89). One patient had multiple fractures (5), at least in part due to renal problems. Type I has autosomal recessive inheritance (71). Prenatal diagnosis has been accomplished (71).

Type II has been reported 18 times [1,2 (case 2),10,26,31,44,45,47,48, 52,70,74,87,88]. Masuno et al (52) and Majewski and Goecke (45) provided an overview. Besides pre- and postnatal failure, microcephaly, moderate developmental delay, except in one case (26), and facial features, type II has been characterized by somewhat sparse scalp hair (but less expressed compared to type I), disproportionately short forearms and legs that were generally not bowed, brachymesophalangy, brachymetacarpy I, metacarpal pseudoepiphyses, V-shaped flaring of distal femoral metaphyses, and high, narrow pelvis, proximal femoral epiphysiolysis and coxa vara (Fig. 10–24). Internal malformations are uncommon, and have included hypospadias (74) and partial callosal body agenesis (74). Consanguinity in 6 of 10 parents (1,45,70,87,88), affected sibs (87), and equal number of affected males and females, all point to autosomal recessive inheritance.

Several other patients with microcephalic osteodysplastic dwarfism have been described that we are unable to classify further (11,15,21,29, 31,32,41,44,49,64,83,91).

Differential diagnosis. The craniofacial features of Seckel syndrome allow differentiation from other syndromes of growth deficiency with microcephaly such as *Dubowitz syndrome, fetal alcohol syndrome, trisomy 18, de Lange syndrome, Bloom syndrome, Nijmegen breakage syndrome*, and Fanconi syndrome. The sibs with microcephaly, cataracts, spasticity, kyphoscoliosis, and severe mental retardation described by Scott-Emuakpor et al (67) and later called CAM(F)AK syndrome (79) probably had early-onset *Cockayne syndrome* (75). Mutchinick (58)



A B C

Fig. 10–24. *Microcephalic primordial dwarfism (osteodysplastic type II).* (A) Patient next to age-matched control child. In addition to mental retardation, marked growth retardation, microcephaly, small forehead, moderately prominent nose, and micrognathia. (B) Note disproportionate shortness of forearms, brachymesophalangy, brachmetacarpy I. (C) Observe V-shaped flare of distal femoral metaphyses, triangular distal femoral epiphyses, proximal femoral epiphysiolysis, and coxa vara. (From F Majewski et al, Am J Med Genet 12:23, 1982.)

described two sisters with microcephaly, postnatal growth retardation, mental retardation, speech delay, and facial dysmorphia. The entity was later confirmed in three brothers (19), one of whom had, in addition, internal hydrocephaly, atrial septal defect, situs abdominalis inversus, and biliary duct agenesis. It has been called Mutchinick syndrome.

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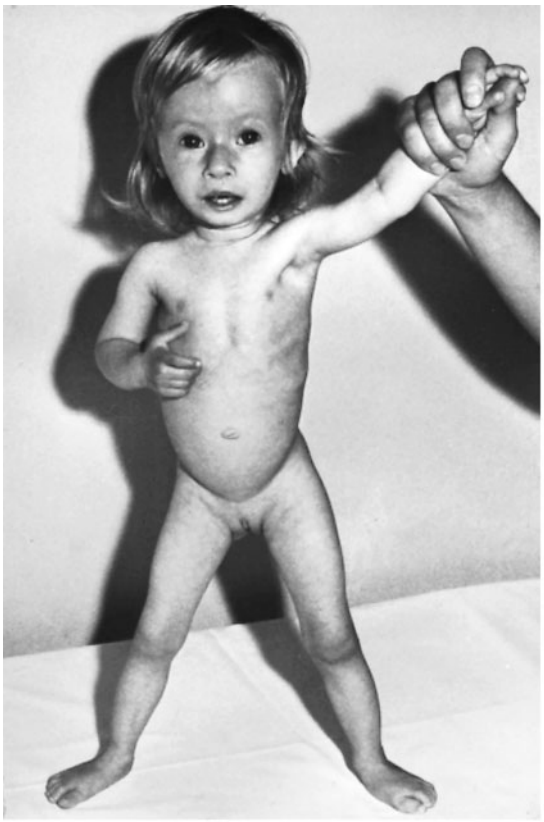
Silver-Russell syndrome

The syndrome of short stature of prenatal onset, triangular facies, body asymmetry, variation in pattern of sexual development, café-au-lait pigmentation, and clinodactyly of fifth fingers (Figs. 10–25 to 10–27) was independently described by Silver (59) in 1953 and by Russell (53) in 1954. Most authors regard the Silver-Russell syndrome as a single entity (22,27,38,51,63), although some have argued that it is not clearly separable from low-birth-weight infants (63). Donnai et al (16) described a more severe form. A survey of 368 cases is that of Wollmann et al (67).

The etiology is unknown and is probably heterogeneous. Syndrome heterogeneity has been discussed by several authors (43,54,61). More than 500 cases, in all racial groups, have been reported (18,35,38,



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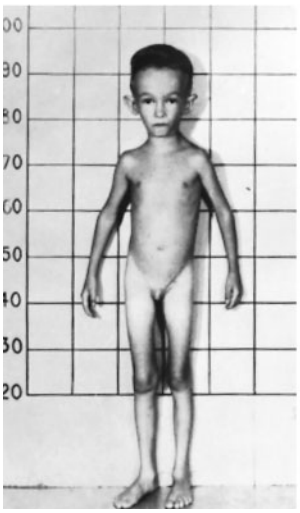

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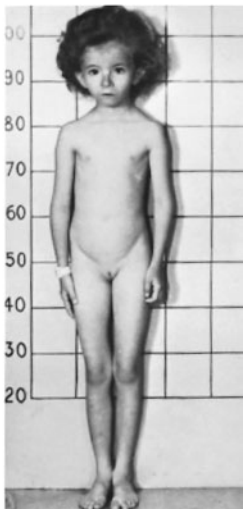


C

Fig. 10–25. *Silver-Russell syndrome*. (A–C) Proportionate short stature. Note leg asymmetry and similar facies. (A from G Schumacher and H Niederhoff, Helv Paediatr Acta 22:404, 1967. B,C from RH Haslam et al, Pediatrics 51:216, 1973.)

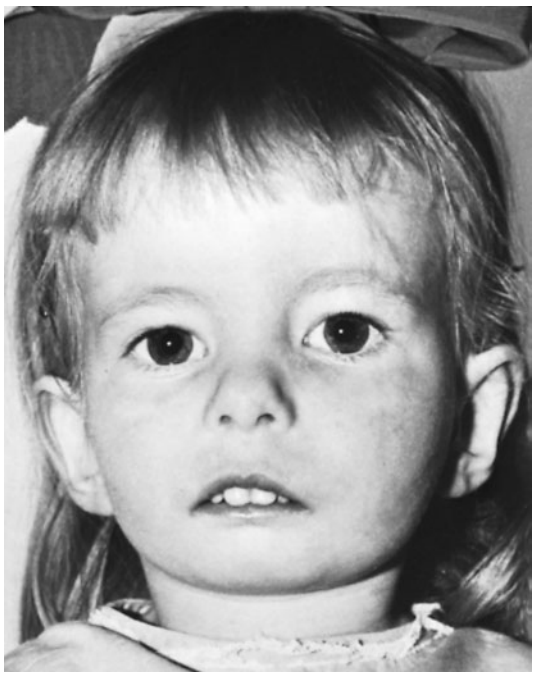


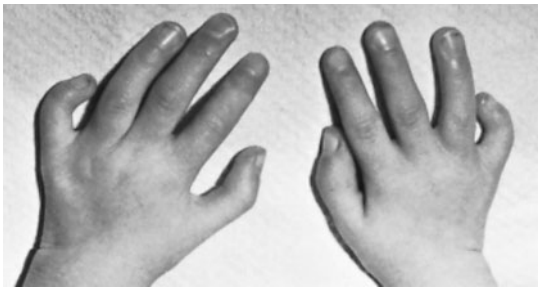
Fig. 10–26. *Silver-Russell syndrome*. Normal-sized cranium with disproportionately small facial bones. Note downturned angles of mouth. (Courtesy of A Russell, London, England.)

44,51,67). Most have been sporadic, but familial occurrence has been noted (18). In several instances, the mother was stated to be short or showed other minimal signs (10,22,35,43). Autosomal dominant inheritance with most cases representing fresh mutations is possible (2,18). However, approximately 7%–16% exhibit maternal uniparental disomy for chromosome 7q31-qter (6,20,28,29,34,45–47,68); uniparental disomy for chromosomes 2,7,8,11,14,16, and 20 was not found (4,20). Insulinlike growth factor 1 receptor (TGF1R) was thought to be a likely candidate gene on chromosome 7, but in 33 patients biallelic expression was found (1,24,62). Miyoshi et al (37) suggested that one of the maternally expressed genes (MEG1) is apparently identical to growth factor receptor-bound protein 10 (GRB10), which is homologous to human chromosome 7p11.2 (37a,64a). GRB10 binds to the insulin receptor and to IGF1R, and inhibits its growth-promoting activities. Eggerman et al (21) found a paternally inherited deletion of the chorionic somatomammotrophin hormone 1 (CSH1) gene, which maps to 17q22–24, in one patient with Silver-Russell syndrome. Although deletions of GSH1 without phenotypic consequences have been described, the role of a heterozygous deletion in the entity was considered possible.

Concordant monozygotic twins (50) and dizygotic twins (58) have been documented as well as discordant monozygotic twins (5,40,55). Autosomal recessive inheritance has been suggested in a Yemenite Arab family (64). The sibs described by Fuleihan et al (25) probably had 3-M syndrome, and the sibs reported by Schwingshackl et al (56) appears to have had Bloom syndrome. Our collective experience suggests that the diagnosis is overused.

More than 10 cases with a chromosomal anomaly involving mosaicism for trisomy 18 (12,29,31), del (18p) syndrome (13), diploid-triploid mosaicism, ring chromosome 15 (9,24,32,51,62,66), and two apparently balanced translocations involving 17q25 (36,48) and a Silver-Russell–like phenotype have been reported.

Fig. 10–27. *Silver-Russell syndrome*. Clinodactyly of fifth fingers. (Courtesy of A Russell, London, England.)



Growth. Mean birth weight is 1940 ± 353 g in males and 1897 ± 325 g in females at full term, and birth length is approximately 43.1 ± 3.7 cm (67). The placenta is small. Short stature is maintained throughout childhood, height usually being below the third centile. Adult height averages 151.2 cm in males and 140 cm in females, or approximately −4.3 SD (15,27,44,50,63,67). Females seem to gain some subcutaneous fat after puberty (15).

Facies. The facies is characterized by pseudohydrocephaly due to relative smallness of the face (Figs. 10–25 and 10–26). The calvaria, while appearing large, is really somewhat smaller than normal (23,33). The forehead is prominent or bossed and the face triangular, with the chin small and pointed in approximately 65% (22). The sclerae may be bluish in infancy (35). The eyes seem large (44). In one case, marked asymmetry of the optic nerve was found (57).The mouth appears wide and the corners are often turned downward. The upper lip vermilion is thin. The pinnae may protrude. Appearance becomes markedly less striking with age.

Musculoskeletal system. Congenital asymmetry has been noted in 65%–80% (22) (Fig. 10–25). Although occasionally total, it may involve only the head, trunk, or limbs. Rarely, asymmetry becomes evident only with growth (58). Poor muscular development and delay in early gross motor performance are common.

Delayed closure of the anterior fontanel is found in 20% (22,27). Occasionally, there is hip or elbow dislocation. The fifth fingers are abbreviated and exhibit clinodactyly in over 75% (53,63) (Fig. 10–27).

Radiographically, bone age is retarded in relation to both sexual development and chronological age until puberty in 50% (27,30,63). The long bones tend to be slender. The humerus is somewhat shortened in 20% (22). Hypoplasia of the middle phalanges of the fifth fingers is evident in 80%. Pseudoepiphyses are found more often at the base of the second metacarpal than in the normal population (63), and frequently there are distal phalangeal ivory epiphyses (30). Soft-tissue syndactyly between the second and third toes is seen in approximately 20% (22). The total and posterior cranial base are reduced in length (33).

Urogenital anomalies. Variation is sexual development has been found in over 30% (58), but there is usually normal puberty (63). Cryptorchidism and/or hypospadias are present in over 35% of males (16,35,48,52,58,65). Females have exhibited premature estrogenation of the urethral or vaginal mucosa in approximately 25% (22). Ambiguous genitalia have also been reported (26,28,35). Renal and/or ureteral anomalies such as hydronephrosis, ureteropelvic obstruction, pyelonephritis with reflux, renal tubular acidosis, and enlarged kidneys have been found (3,29,60).

Other findings. Café-au-lait spots have been noted in approximately 25% (22). Hyperhidrosis and tachypnea are frequent findings in the neonatal period due to hypoglycemia (23,27,43). Dermatoglyphics are not specific (7). Mild developmental delay or mental retardation has been reported in approximately 35% (22,64). Testicular cancer, hepatocellular carcinoma, testicular seminoma, and craniopharyngioma have been reported (8,13,17,65).

Oral manifestations. Downturned corners of the mouth have been noted in over 60% (58). The maxilla and mandible are small, the palate is high and narrow, and the teeth are crowded and may show enamel defects (33).

Differential diagnosis. Silver-Russell syndrome is one of a large group of conditions categorized as "intrauterine growth retardation" or "low-birth-weight dwarfism." Differential diagnosis includes a plethora of conditions with short stature and precocious sexual development (58). To be excluded are *mulibrey nanism*, an autosomal recessive disorder associated with pericardial constriction and characteristic eye findings, and *3-M syndrome*, another autosomal recessive condition. An X-linked disorder of short stature with skin pigmentation has also been described (43). The authors suggested that other examples may be of this type (10,22,25).

Café-au-lait pigmentation and/or body asymmetry may be seen with *neurofibromatosis, hemihyperplasia (hemihypertrophy), McCune-Albright syndrome, Klippel-Trenaunay syndrome, Proteus syndrome*, and several chromosome anomalies.

Laboratory findings. Urinary gonadotropin levels have been elevated in approximately 10% (14,58,60). Hypoglycemia following short periods of fasting has been described (22,27,28), and growth hormone deficiency has been reported in a few cases (17,19,28,39,41). Cassidy et al (11) and Okabe and Ueda (42) have discussed hypopituitarism in the syndrome.

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3-M syndrome

Although first described by Fuhrmann et al (5) in 1972, Miller et al (11), in 1975, rediscovered this distinct type of low-birth-weight proportionate dwarfism and named the syndrome after the initials of the first three authors of the paper. Spranger et al (15) independently observed the same condition. Additional cases have been reported (3,6–8,12–14,16,17). Hennekam et al (8) reported three affected sibs and reviewed the findings in previously recorded cases. To date there have been approximately 30 examples noted.

Inheritance is autosomal recessive. Presumably heterozygotes have thinner bones and a prominent talus (7) and may show some facial characteristics (8). A preliminary report mentioned a decreased production of collagen type III (9).

Low birth weight at full term and proportionate small size characterize the disorder. Dolichocephaly and triangular facies are evident (Figs. 10–28 to 10–30). The malar region is flat, the ears outstanding, the lips patulous, and the chin pointed and prominent. The dental arch is V-shaped with malocclusion and anterior crowding. Frontal bossing and short broad neck with prominent trapezius muscles are evident. The shoulders are square and high, and the thorax short. Pectus carinatum or

Fig. 10–28. *3-M syndrome*. Low-birth-weight proportionate dwarfism in 4- and 15-year-old sibs. Note triangular face, outstanding pinnae, patulous lips, pointed outstanding chin. (From J Spranger, Eur J Pediatr 123:115, 1976.)

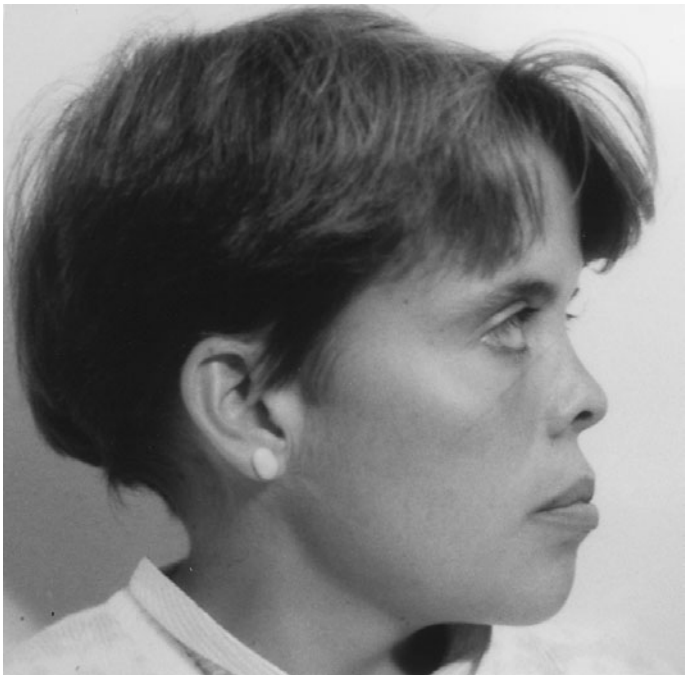
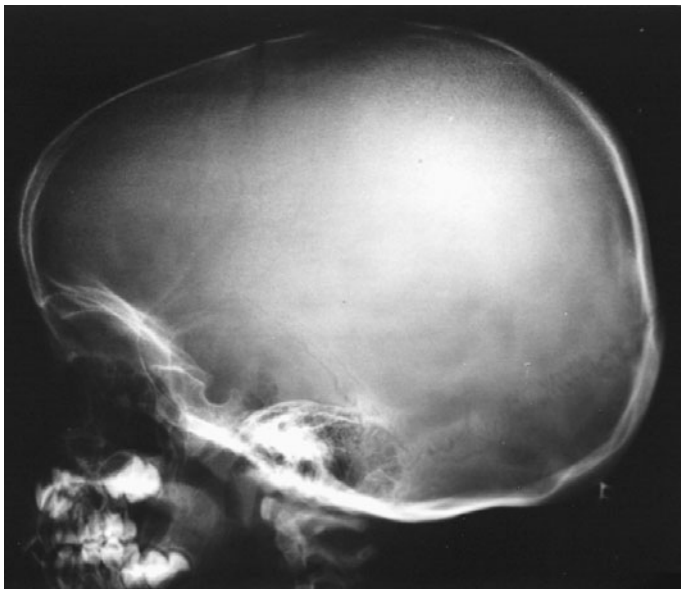


Fig. 10–29. *3-M syndrome*. Note flattened malar region, upturned nares, long philtrum and full lips. (From RCM Hennekam et al, Am J Med Genet 28:195, 1987).

excavatum is common and there may be transverse grooves above the costal margins. The scapulae are winged, the joints are hyperextensible, and the fifth fingers are short. Recurrent dislocations and fractures have been described (8), as were gonadal fusion and hypospadias (17). In a single case, intracerebral aneurysms have been present (12), but these were not found in others (9).

Radiographically, the bones are slender, especially the diaphyses. This becomes more prominent with age. The vertebral bodies are tall (3,13). The pubic and ischial bones are small, the iliac wings flared, the femoral neck short, and the talus prominent (Figs. 10–31 to 10–33). Bone age is slightly delayed.

Fig. 10–30. *3-M syndrome*. Marked dolichocephaly. (From RM Winter et al, J Med Genet 21:124, 1984.)



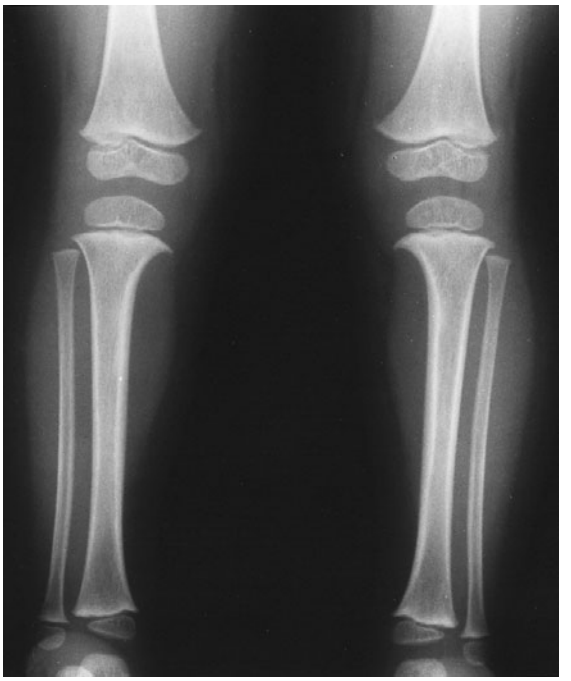
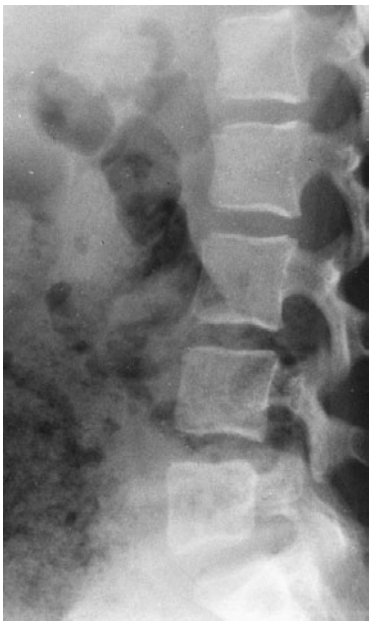


Fig. 10–31. *3-M syndrome*. Narrow long bones with overconstriction of diaphyses and metaphyseal flaring. (From RM Winter et al, J Med Genet 21:124, 1984.)

Several patients with 3M-syndrome have been erroneously labeled as having *Silver-Russell syndrome* (6). Body asymmetry is not seen in 3-M syndrome. Furthermore, there is no altered pattern of sexual development, craniofacial disproportion (pseudohydrocephaly), or delayed closure of the anterior fontanel. Height is shorter than in those with Silver-Russell syndrome (14). The facies somewhat resembles that seen in *Bloom syndrome*, and the two conditions have been confused (13). Gracile bones are frequently found in any abnormality in which fetal hypokinesia is found. Le Merrer et al (10) delineated an autosomal recessive syndrome, similar to 3-M syndrome, which can be differentiated by a round face

Fig. 10–32. *3-M syndrome*. Tall vertebral bodies. (From RM Winter et al, J Med Genet 21:124, 1984.)



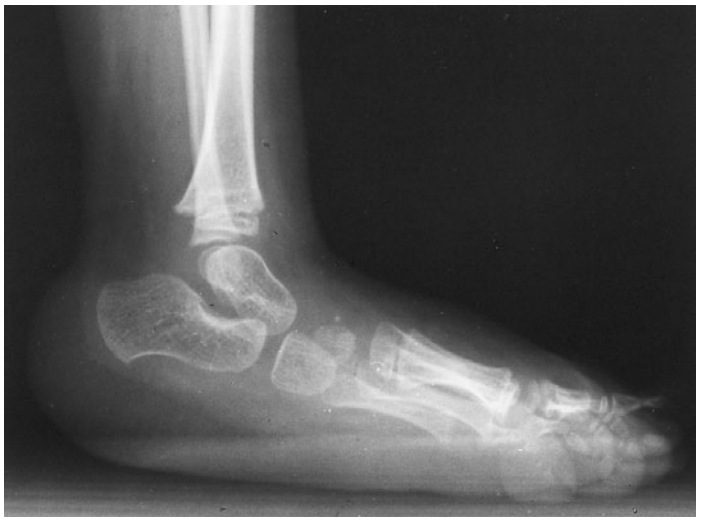


Fig. 10–33. *3-M syndrome*. Vertical talus with prominent calcaneus. (From RM Winter et al, J Med Genet 21:124, 1984.)

and full lips ("gloomy face") and absence of any radiologic abnormality. Several cases described as having the 3-M syndrome [4,16 (3rd case),17 (4th case)] have been said to have dwarfism with *gloomy face*. Cameron et al (2) described a still-different entity in two sisters, who have a somewhat different face, no square shoulders or prominent heels, and with short, broad long bones, square iliac bones, short femoral necks, and narrowing of the interpedicular distance inferiorly. We cannot identify the disorder described by Callaghan (1). Also to be excluded is *mulibrey nanism*.

Prenatal diagnosis of 3-M has been noted (10a).

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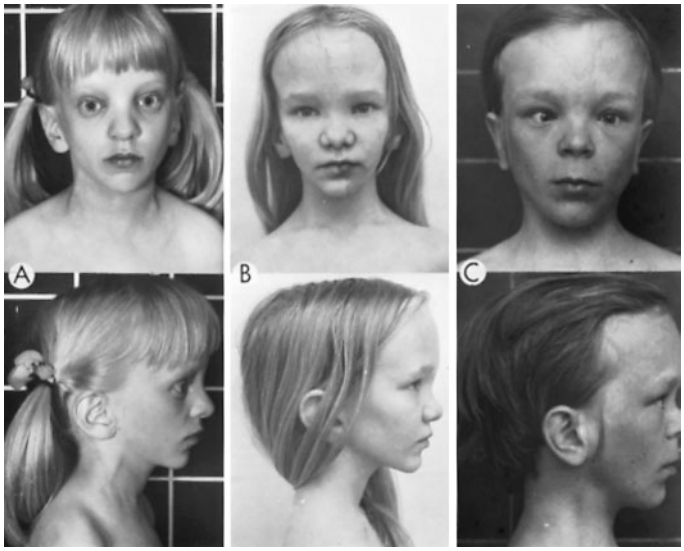


Fig. 10–34. *Mulibrey nanism.* (A–C) Three unrelated adolescent patients exhibiting similar facies. (From J Perheentupa et al, Lancet 2:351, 1973.)

Mulibrey nanism

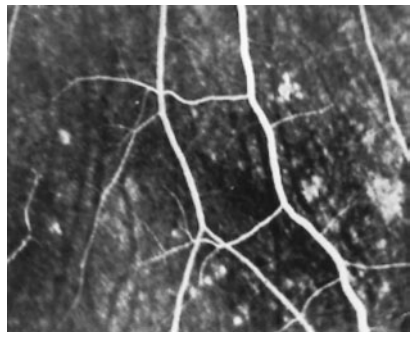
Perheentupa et al (11), in 1973, described a form of prenatal growth retardation associated with anomalies of *MU*scle, *LI*ver, *BR*ain, and *EY*e, employing the mnemonic "mulibrey" (Figs. 10–34 to 10–36).

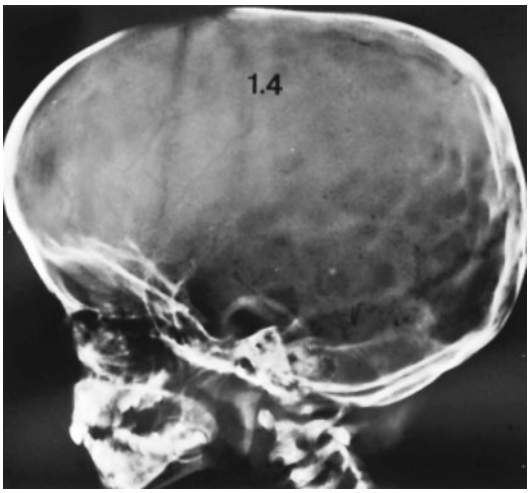
More than 40 patients have been described, most stemming from Finland (8,12) but also from Argentina, Canada, Egypt, France, Mexico, the Netherlands, Spain, and the United States (5,6). It should be considered as part of the differential diagnosis in children with short stature (17). The disorder has autosomal recessive inheritance. There is an increased risk for miscarriages (3). The gene for mulibrey nanism has been assigned to 17q22–q23 (1,10). The gene is a zinc finger transcription factor (1a). An exhaustive review is provided by Lapunzina et al (6).

Weight and length at birth are usually 1.5 to 2 SD below the mean. With time, growth becomes progressively retarded. Adult males vary from 136 to 161 cm; adult females range from 126 to 151 cm. Some have shown a good response on growth hormone supplementation (5,7). Patients may die in childhood from cardiac involvement or pulmonary infections, but most survive to adulthood without incapacity. A humeral immunodeficiency has been described (5).

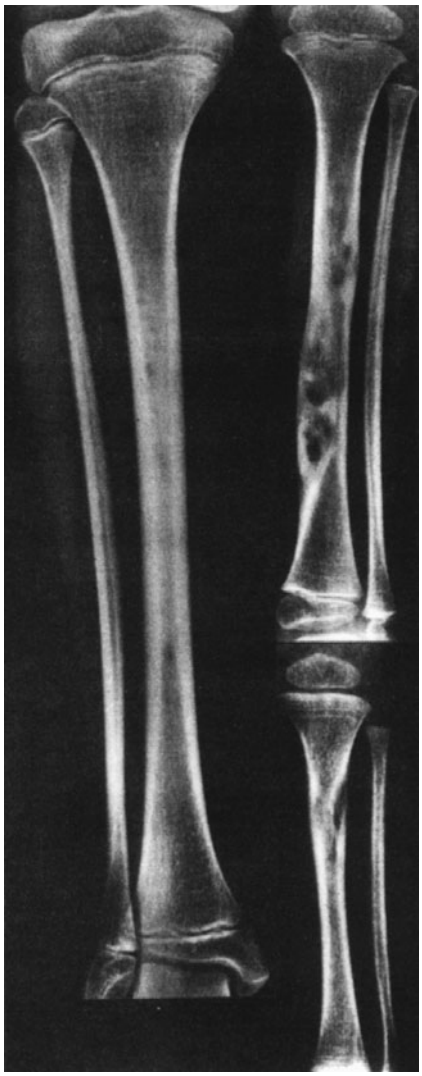
Facies. The face is triangular and the forehead is prominent and high. The size relationship between skull and face resembles those seen normally in young infants. The nasal bridge is deep and broad (Fig. 10–34).

Fig. 10–35. *Mulibrey nanism*. Fluorescein angiogram of fundus showing conglomerate of dots and severe hypoplasia of choroid. (From J Perheentupa et al, Lancet 2:351, 1973.)





A



B

Fig. 10–36. *Mulibrey nanism.* (A) Typical skull radiograph at 1.4 years exhibiting abnormal cranial form, J-shaped sella, and increased basilar angle. (B) Fibrous dysplasia lesions of the tibia have been found in about 30%. (From J Perheentupa et al, Lancet 2:351, 1973).

Eyes. There is mild hypertelorism. Aggregation and dispersion of pigment in the midperiphery and more peripheral areas of the fundus, with yellow dots are characteristic (Fig. 10–35). Other findings are hypoplasia of the choroid (4), colobomata (8), and corneal dystrophy (13,16). The optic discs, maculae, and the ERG are normal.

Heart. Thickened and adherent pericardium results in cardiac constriction in 35%, visible in prominent jugular veins, enlarged liver (6,11,18–20), and, in some cases, ascites with congestive heart failure (2,20). Radiographically, this gives the heart a globular shape.

The myocardium is usually normal, although myocardial fibrosis has been described (4,19).

Liver. The liver is enlarged, especially in the neonatal period, probably due to passive venous congestion, secondary to the constrictive pericarditis.

Central nervous system. Intelligence is normal. Some patients have dysarthria (9). Abnormal large ventricles can also be found (11).

Skin. Naevi flammei, found in half of the patients, are mostly located on the limbs (3).

Musculoskeletal system. The extremities are thin and short. About 70% are mildly hypotonic. Radiographically, bone age is normal. There are frequent absent or small frontal and sphenoidal sinuses (9) and J-shaped sella turcica. Fibrous dysplastic lesions of the tibia have been found in approximately 30% (4,19) (Fig. 10–36).

Miscellaneous findings. Wilms tumor has been reported in about 4% of patients (1a,14,15).

Oral manifestations. Dental malocclusion has been noted in approximately 40% and hypodontia in approximately 20% (3,9). The tongue appears small (9). The voice is usually weak and high-pitched (3,4,9). In 30%, the paranasal sinuses are small.

Differential diagnosis. There is considerable overlap with *Silver-Russell syndrome*.

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Chapter 11
Overgrowth Syndromes and Postnatal Onset Obesity Syndromes

Beckwith-Wiedemann syndrome [EMG (exomphalos-macroglossia-gigantism) syndrome]

In 1963, Beckwith (2) reported three cases of a newly recognized syndrome consisting of macroglossia, omphalocele, cytomegaly of adrenal cortex, hyperplasia of gonadal interstitial cells, renal medullary dysplasia, and hyperplastic visceromegaly (Figs. 11–1 to 11–5). Subsequently, Beckwith (3) enlarged his series of patients, noting postnatal somatic gigantism, mild microcephaly, and severe hypoglycemia. In 1964, Wiedemann (107) independently reported the syndrome in three sibs and observed a further component—a dome-shaped defect of the diaphragm. Other important contributions have been made by many investigators (5,6,8,9,13,18,30,35,38–48,54,55,66–70,73,76,81,88,90,101,108–110,113,115). Over 500 cases have been reported. The frequency has been estimated at 1 per 12,000 births (31,112). Exhaustive reviews have been published (14,15,28,29,31,33,44,73,79). The most recent update is that of Cohen (17). Early diagnosis of this striking condition alerts the clinician to the dual threat of hypoglycemia and possible neoplasia. Clinical and laboratory findings are listed in Table 11–1.

Etiology. The molecular aspects of the Beckwith-Wiedemann syndrome have been extensively studied by Weksberg and colleagues (56,57,105). The syndrome is caused by alterations in chromosome region 11p15, which is subject to imprinting (80,96). Particularly implicated are mutations in (CDKNIC) $p57^{KIP2}$ (approximately 5%) and biallelic expression of IGF2 (approximately 50%) (51). Other genes are also found in the 11p15 region: KVLQT1, HASH2, INS, and H19. It is possible that Beckwith-Wiedemann syndrome, with its pronounced variability in clinical expression, is caused by imbalance of growth-promoting and growth-inhibiting genes in the 11p15 region (16,17,40,52,56,57, 104,105). The proportion of cells with paternal uniparental disomy correlates with organ size (44a). Unbalanced translocation involving the area has been reported (32a).

Cases of Beckwith-Wiedemann syndrome can be classified on the basis of family history, karyotype, and molecular testing. Findings do not have to be mutually exclusive. Autosomal dominant pedigrees account for about 15% of cases and expression is almost always found in individuals born to female carriers (5,6,9,47,61,71,73,82). Paternal imprinting is involved (100). Karyotypes are normal in about 98% of patients. Paternally derived duplications and maternally derived translocations and inversions account for the other 2% of cases (65,95). Uniparental paternal disomy is present in about 10%–20% of patients (43). Female monozygotic twins have occurred with high frequency. Most have been discordant for the syndrome (12,53,60,74). Overexpression of IGF2 has been implicated in several subsets of Beckwith-Wiedemann patients: (*a*) those with paternal uniparental disomy; (*b*) those with somatic mosaicism for partial paternal isodisomy, which can explain some instances of hemihyperplasia; and (*c*) those with disruption of maternal imprinting with both paternal and maternal alleles active, which can explain patients with and without hemihyperplasia and even patients with crossed hemihyperplasia (87). There is anthropometric evidence of heterogeneity (70a). Embryonal tumors reported in Beckwith-Wiedemann syndrome (Wilms tumor, adrenal cortical carcinoma, hepatoblastoma, and rhabomyosarcoma) retain paternal alleles but lose heterozygosity, specifically maternal alleles (56,57,105).

Pathogenesis. Growth hormone production has been normal in patients with the Beckwith-Wiedemann syndrome (91). Because of endocrine cytomegaly, Beckwith (3) suggested that the fetal adrenal cortex is either overactive or underactive, with excess stimulation caused by a feedback mechanism similar to that found in adrenogenital syndrome. He further noted that the abnormalities observed in the hypophysis, gonads, islets of Langerhans, and paraganglia should be considered in evaluating the abnormal growth present in the syndrome and that altered placental endocrine physiology could conceivably play a role in producing many of the features found during the neonatal period.

The visceromegaly of the syndrome may possibly result in omphalocele and diaphragmatic eventration. Against this view is Beckwith's observation (personal communication, 1969) in affected premature cadavers that profound visceromegaly is absent as well as the absence of abdominal and diaphragmatic defects in other conditions with early, increased abdominal pressure, such as infantile polycystic disease, universal nephroblastomatosis, and low intestinal atresia.

Infant mortality. The infant death rate is approximately 20%, usually resulting from either congestive heart failure or severe malformations associated with the syndrome (79).

Growth. Polyhydramnios is frequent and the placenta tends to be about twice normal weight (106). This has led to the diagnosis of the syndrome using FISH technique (25). Average length for males at birth is above the 95th centile and growth throughout adolescence parallels the normal growth curve at or above the 95th centile. Average birth length for females is at the 75th centile and length increases to the 95th centile by 18 months. Female height then remains at or above the 95th centile throughout adolescence, again paralleling the normal growth curve (79,106). Gigantism is not always present at birth. Growth may even be subnormal for a few months, although somatic gigantism eventually results in most cases (3,33). Advanced bone age is usually present and there may be widening of the metaphyses and cortical thickening of long bones. Hemihyperplasia (hemihypertrophy) has been a feature in approximately 20% of cases (3,28,29,33,44,90,110).

Sippell et al (85) studied the growth of seven patients longitudinally. They found that growth velocity remained above the 90th centile up to 4–6 years of age. After puberty it was +2.5 SD, or about 13.2 cm greater than their parents' height. Bone age was markedly advanced, especially during the first 4 years. Weight was above the 90th–97th centile during infancy and early childhood and remained there, usually being appropriate or slightly subnormal for height, until adulthood. Three girls, however, reached and maintained the 50th centile during or after puberty. Spontaneous pubertal development occurred within normal limits.

Performance and central nervous system. Intelligence is usually normal (33), although mild to moderate retardation was a regular feature in Beckwith's series (3). Mild microcephaly has been an associated feature in some cases (3,18). In other cases, mental deficiency may be due, in part, to undetected hypoglycemic episodes during infancy. Seizures have been a feature in some instances.

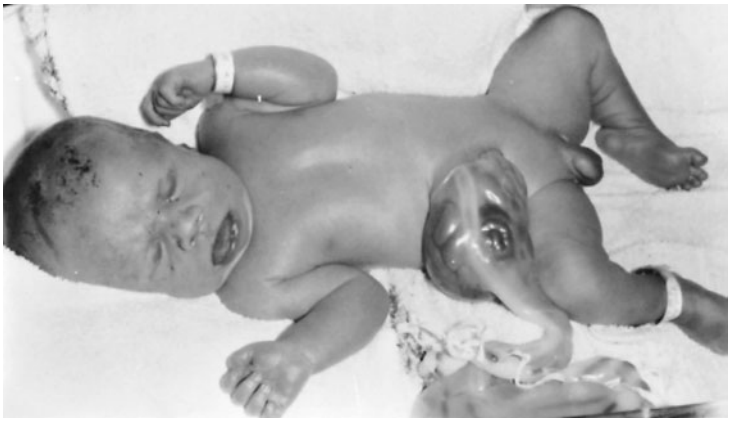
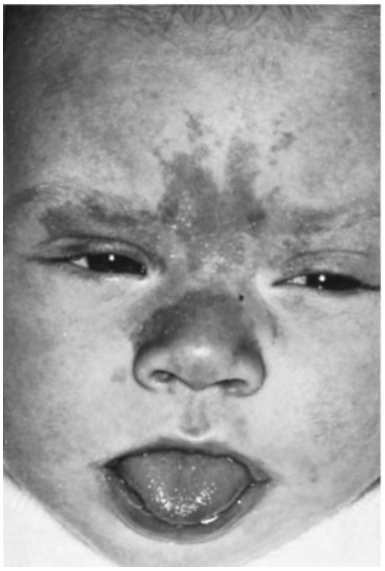


Fig. 11–1. *Beckwith-Wiedemann syndrome.* Note large tongue and omphalocele. (From MW Moncrieff et al, Postgrad Med J 46:162, 1970.)

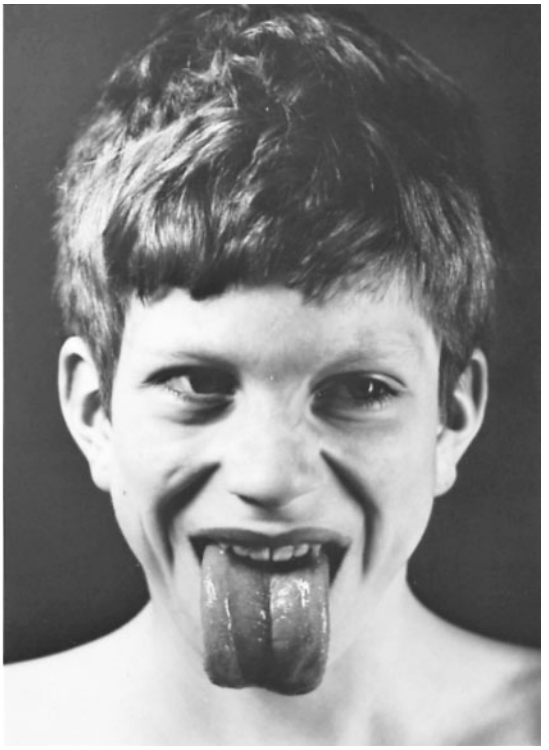
Craniofacial features. Macroglossia (Figs. 11–1 and 11–2) is very common at birth (70) but is not an obligatory feature of the syndrome, and it may not present until the first few months of life (11). Chronic alveolar hypoventilation has been reported secondary to macroglossia on occasion (88). Tongue biopsies have been normal. In some cases, macroglossia tends to regress, with gradual accommodation of the tongue to the oral cavity. At present, it is not known whether this is caused by enlargement of the oral cavity relative to the tongue, shrinkage of the tongue relative to the oral cavity, or a combination of both processes. Persistent macroglossia, seen in almost 100%, leads to anterior open-bite, and requires surgical intervention (34). Patients with the syndrome have also been observed to be prognathic. Is macroglossia directly responsible for the prognathic mandible? Some authors have noted cessation of prognathic growth following partial glossectomy. However, careful long-term studies of many patients are needed. It is conceivable that prognathism may reflect the generalized somatic gigantism that occurs in the syndrome. Further, is the prognathism a true mandibular prognathism, or is it relative to hypoplastic changes in the midface?

Facial nevus flammeus (Fig. 11–2A), a feature seen in 60%, tends to become less prominent during the first year of life. Ear lobe grooves (Fig. 11–3A) are very distinctive, consisting of slitlike linear indentations. Indented ear lesions on the posterior rim of the helix or concha (Fig. 11–3B) have been observed in 75% (47). Because of the rarity of these anomalies in the general population (1), they serve as valuable diagnostic signs of the Beckwith-Wiedemann syndrome when they are present. Mild microcephaly has been a feature of some cases (3,18). Cleft palate or submucous cleft palate has been noted in 3% (23,93). Various other low-frequency anomalies of the head and neck are listed under *Other abnormalities*.

Visceromegaly. Omphalocele (Fig. 11–1) or umbilical hernia or diastasis recti are noted in 75%. Omphalocele is especially frequent with CDKNIC mutations (51). Malrotation anomalies may be a feature. In considering the visceromegaly noted in the syndrome, hepatomegaly and nephromegaly occur in about 60%, but cardiomegaly is found in no more than 15%. Pancreatomegaly has been a feature of autopsied



A



B

Fig. 11–2. *Beckwith-Wiedemann syndrome.* (A) Glabellar nevus flammeus and macroglossia. (B) Tongue with macroglossia and remarkable extensibility. (A from H-R Wiedemann, Z Kinderheilkd 106:171, 1969. B courtesy of H-R Wiedemann, Kiel, Germany.)

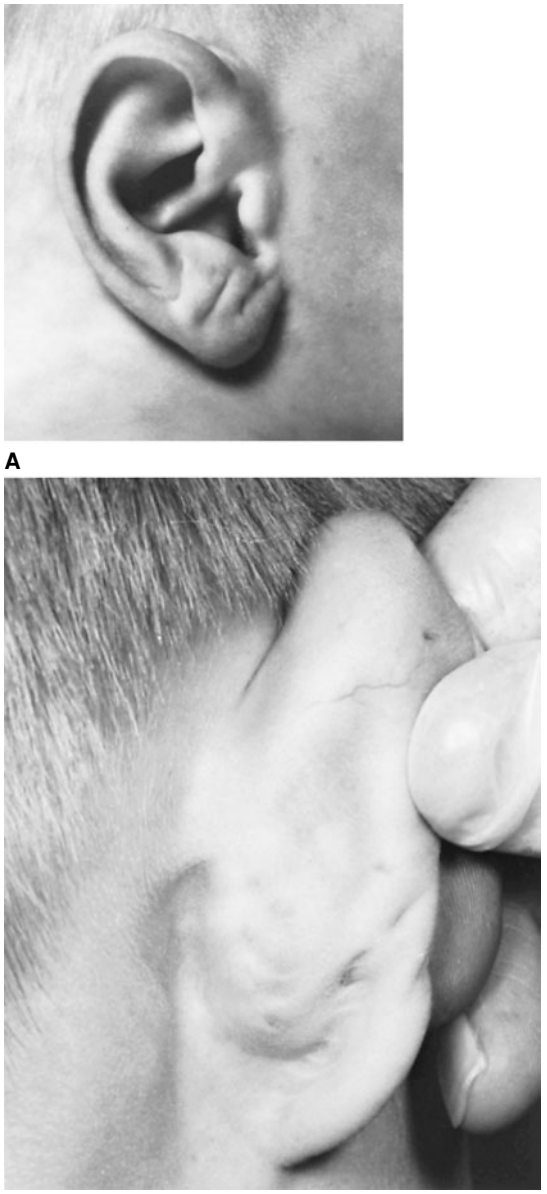


Fig. 11–3. *Beckwith-Wiedemann syndrome.* (A) Linear grooves on earlobe. (B) Punched-out depressions of posterior pinna. (A from H-R Wiedemann, Z Kinderheilkd 106:171, 1969.)

cases. Medullary sponge kidney has been observed on occasion (4). Genital overgrowth has been noted in some instances. Hyperplastic bladder, uterus, and thymus have also been reported (3,44,69,101,107). A dome-shaped defect of the diaphragm (Fig. 11–4) has been seen in a number of cases. In this defect, the posterior part of the diaphragmatic leaf is elevated.

Histopathology. The histopathologic features of the syndrome reflect the visceromegaly observed grossly. In the pancreas, hyperplastic changes are evident in the acini, islets, and ducts. In the kidney, the lobular arrangement is disordered. Each lobule is capped by a wide, persistent nephrogenic activity zone. Medullary dysplasia is evident with most pyramids showing an increased amount of stroma. Cytomegaly of the fetal adrenal cortex (Fig. 11–5) is prominent, the cells containing sudanophilic droplets. The adrenal cortex is cystic and the medulla is hyperplastic. In the pituitary gland, cells resembling amphophiles are increased in number. Gonadal interstitial cells are hyperplastic. The paraganglia are

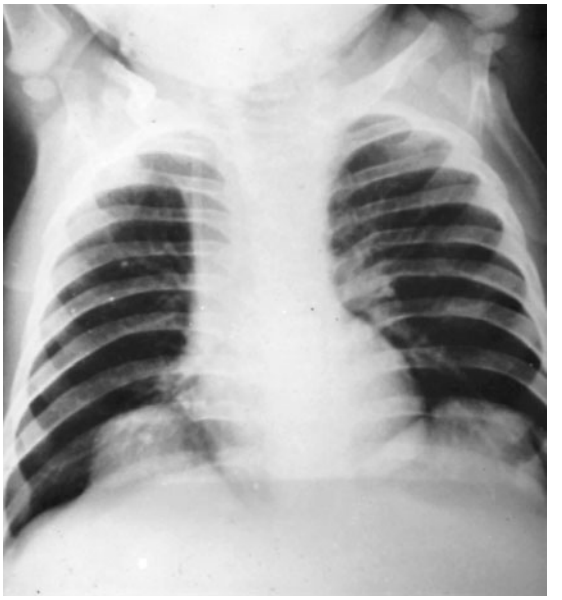


Fig. 11–4. *Beckwith-Wiedemann syndrome.* Bilateral diaphragmatic eventration (From I Irving, J Pediatr Surg 2:499, 1967.)

also hyperplastic (3). In some cases, both macroglossia and omphalocele are absent, but the visceral histologic lesions are florid (114).

Cardiovascular anomalies. Greenwood and associates (38) reported cardiovascular abnormalities in 12 of 13 patients. Seven had congenital heart defects, including ASD, VSD, PDA, hypoplastic left heart, and tetralogy of Fallot; the other five had idiopathic cardiomegaly.

Fig. 11–5. *Beckwith-Wiedemann syndrome.* Adrenocytomegaly. (From K Bech, Acta Pathol Microbiol Scand 79A:279, 1971.)

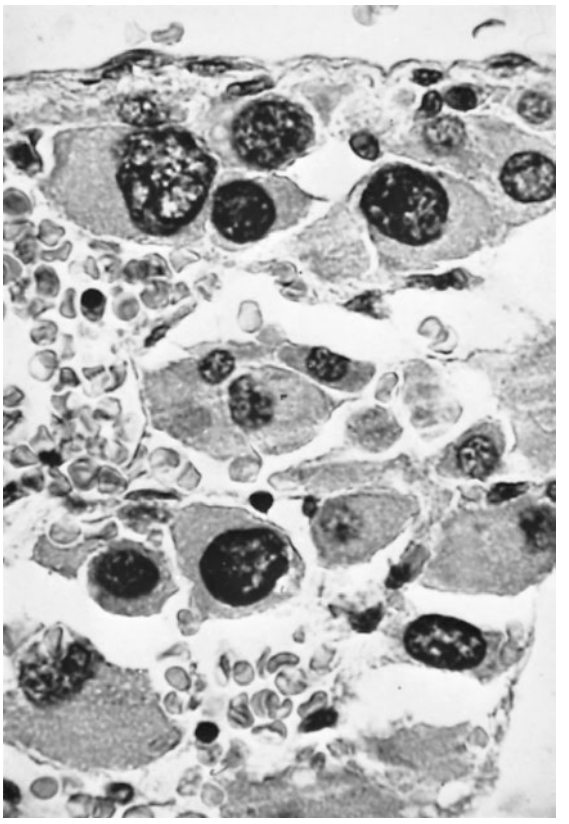


Table 11–1. *Beckwith-Wiedemann syndrome*[a]. Estimated frequencies of clinical and laboratory findings

Finding	Percentages
Growth/skeletal	
Increased birth weight	39
Postnatal gigantism	33
Accelerated osseous maturation	21
Asymmetry	13
Skeletal anomalies	14
Performance	
Seizures, apnea, cyanosis	22
Mental deficiency	12
Craniofacial	
Macroglossia	82
Ear lobe grooves	38
Flame nevus	32
Craniofacial dysmorphism[b]	39
Mild microcephaly	14
Abdominal/genitourinary	
Omphalocele, umbilical hernia	75
Gastrointestinal anomalies	13
Hepatomegaly	32
Splenomegaly	14
Nephromegaly	23
Genitourinary anomalies	24
Cardiac anomalies	16
Diaphragmatic anomalies	7
Inguinal hernia	6
Laboratory findings	
Hypoglycemia	30
Polycythemia	20
Hypocalcemia	5
Hypercholesterolemia, hyperlipidemia	2

[a]Frequencies estimated from 174 cases from the literature tabulated by C Sotelo-Avila et al, J Pediatr 96:47, 1980. See MJ Pettenati et al, Hum Genet 74:143, 1986 for different percentages. There is an obvious ascertainment bias in the frequencies of various findings from reported cases. On the one hand, the more severe cases are most likely to be reported. On the other hand, the presence or absence of various findings may be omitted from some reports.

[b]Includes maxillary hypoplasia, prominent occiput, flat nasal bridge, highly arched palate, frontal ridge, downslanting palpebral fissures, etc.

VSD was observed in three patients by Kosseff et al (48) and in five patients by Niikawa et al (73). ASD has been noted (73,81), as has coarctation of the aorta (6,45). Pulmonary artery stenosis was reported by Raine et al (81).

Other abnormalities. Polyhydramnios has been found in about 50% (106). Various low-frequency anomalies have been reported, including, among others, persistent anterior fontanel, prominent metopic ridge, meningomyelocele, malformed cerebellum, preauricular pits, cleft palate, conductive hearing loss from fixation of the stapes, accessory nipples, pectus excavatum, pectus carinatum, congenital hip dislocation, clinodactyly, postaxial polydactyly, pyloric stenosis, ileal stenosis, atresia of colon, imperforate anus, pyelocalyceal diverticula, other renal and ureteral malformations, prune belly, inguinal hernia, hypospadias, cryptorchidism, unicornuate uterus, and bicornuate uterus (6,7,18,21,44,45, 48,73,75,89,94). Wales et al (102) reported a premature Beckwith-Wiedemann infant who developed bronze baby syndrome when exposed to phototherapy.

Neoplasms. Wiedemann (110,112) noted that of 388 reported and personally observed cases, 29 developed a total of 32 neoplasms. Of these, 26 were intra-abdominal, 5 were extra-abdominal, and 1 was a malignant lymphoma, giving a total reported tumor percent of 7.5%. It is important to emphasize that reported cases of Beckwith-Wiedemann syndrome with neoplasia have an ascertainment bias that favors the reporting of cases with tumors; the true frequency of neoplasia may be lower. Although approximately 13% of patients have hemihyperplasia (hemihypertrophy) (90,110), 40% with neoplasia have hemihyperplasia (110). Thus, Beckwith-Wiedemann patients with hemihyperplasia have an increased risk for developing tumors.

Nephroblastoma is reported most commonly followed by adrenal cortical carcinoma, followed by hepatoblastoma. Other reported neoplasms have included malignant lymphoma, neuroblastoma, glioblastoma, renal cell carcinoma, rhabdomyosarcoma, pancreatoblastoma, gastric teratoma, adenoma of adrenal cortex, fibroma of the heart, umbilical myxoma, retroperitoneal ganglioneuroma, carcinoid tumor of the appendix, and fibroadenoma of the breast (10,26,30,32,59,79,81,86,90,110, 115,116). Tumors found with the syndrome are compared with tumors associated with hemihyperplasia (hemihypertrophy) and with Sotos syndrome in Table 11–2. Perhaps there is a common mechanism involving

Table 11–2. A comparison of reported neoplasms associated with the Beckwith-Wiedemann syndrome, hemihyperplasia (hemihypertrophy), and Sotos syndrome[a]

	Beckwith-Wiedemann syndrome[b]	Hemihyperplasia (hemihypertrophy)[b]	Sotos syndrome[c]
Tumor frequency	7.5%	3.8%	3.9%
Method of study	Retrospective literature review	Prospective mail survey	Retrospective literature review
Bias	Possible overestimate	Possibly none	Possible overestimate
Malignant tumors	Nephroblastoma[d] Adrenal cortical carcinoma[d] Hepatoblastoma[d] Hepatocellular carcinoma Gliobastoma Neuroblastoma Rhabdomyosarcoma Malignant lymphoma Pancreatoblastoma Teratoma	Nephroblastoma[d] Adrenal cortical carcinoma[d] Hepatoblastoma[d] Neuroblastoma Pheochromocytoma Testicular carcinoma Undifferentiated sarcoma	Nephroblastoma[d] Hepatocellular carcinoma[d] Epidermoid carcinoma
Benign tumors	Adrenal adenoma Carcinoid tumor Fibroadenoma Fibrous hamartoma Ganglioneuroma Myxoma	Adrenal adenoma	Cavernous hemangioma Hairy pigmented nevus Osteochondroma

[a]See text and references provided (From MM Cohen, Jr, Adv Hum Genet 18:181, 1989.)

[b]Not all cases of hemihypertrophy are part of the Beckwith-Wiedemann spectrum.

[c]Tumors occur with lower frequency in Sotos syndrome than with either Beckwith-Wiedemann syndrome or hemihyperplasia (hemihypertrophy).

[d]Most commonly observed neoplasms in descending order of frequency.

development of Beckwith-Wiedemann syndrome and embryonal tumors that represents somatic development of homozygosity for a mutant allele at a locus on chromosome 11 (49). Those with Wilms tumor do especially well when compared to those who have the tumor but not the syndrome (80a).

Prenatal diagnosis. Ultrasound monitoring of fetal size, organ size, and abdominal wall contour may be useful for families with a positive history of the syndrome. Weinstein and Anderson (103) noted increased amniotic fluid, bilateral cystic kidneys, and a larger-than-expected fetus at 20 weeks. Winter et al (113), using serial ultrasound monitoring, showed enlarged abdominal circumference and an omphalocele at 18 weeks. Omphalocele has also been detected by α-fetoprotein (15). Shapiro et al (84) detected a large placenta in a Beckwith-Wiedemann fetus by ultrasound.

Differential diagnosis. The facial features and large tongue may, at times, suggest a *mucopolysaccharidosis,* an *oligosaccharidosis,* or hypothyroidism. The combination of macroglossia and umbilical hernia can be seen in both *trisomy 21 syndrome* and hypothyroidism. The syndrome of macroglossia, intrauterine growth retardation, and transient neonatal diabetes mellitus has been discussed by Dacou-Voutetakis et al (20). Autosomal dominant inheritance of macroglossia has been observed (82). Omphalocele may occur alone or with a variety of associated anomalies and syndromes (14). Familial omphalocele (24,63) and familial gastroschisis and abdominal hernia (97) are also known to occur.

Perlman and others (36,37,42,58,72,77,78,82a) reported an autosomal recessive syndrome consisting of polyhydramnios, visceromegaly, macrosomia, macrocephaly, nephromegaly, hepatomegaly, renal hamartomas, nephroblastoma, and Wilms tumor in the absence of macroglossia, omphalocele, and hemihyperplasia. Wilms tumor and abnormal sexual differentiation occur in Drash syndrome (64).

In 1934, de Lange (22) described three children with a distinctive condition that bears some superficial resemblance to Beckwith-Wiedemann syndrome. Findings include congenital muscular hypertrophy, hypertrophy, hypertonia, and developmental retardation. Macroglossia and large ears were observed in two of the three patients, and overgrowth at birth was a feature in one instance. Autopsy findings in one case demonstrated polymicrogyria and a widespread porencephalic process.

Infants of diabetic mothers sometimes resemble infants with Beckwith-Wiedemann syndrome in being gigantic and hypoglycemic. Combs et al (18) have pointed out that newborn infants of diabetic mothers are overweight for their length, whereas Beckwith-Wiedemann syndrome patients are not. They further noted that the hypoglycemia seen in Beckwith-Wiedemann syndrome may persist beyond the immediate neonatal period, whereas the hypoglycemia found in infants of diabetic mothers occurs very early and is of brief duration. Infant giants represent a rarely encountered disorder in which gross macrosomia occurs without associated malformations. Overgrowth is based on prenatal hyperinsulinism that persists into postnatal life. A history of maternal diabetes is always negative and maternal glucose tolerance tests are always normal (14).

Sotelo-Avila and his coworkers (90) have noted that Beckwith-Wiedemann syndrome and hemihyperplasia (hemihypertrophy) are probably at either end of the same spectrum, intermediate forms being the connecting links. In our opinion, *hemihyperplasia* (*hemihypertrophy*) is etiologically heterogeneous and although some cases represent the Beckwith-Wiedemann spectrum, other cases do not. There have been mislabelings and overlap of patients with *Simpson-Golabi-Behmel syndrome*. This has been extensively discussed by Elliott and Maher (28), Verloes et al (98), and Coppin et al (19).

Laboratory findings. Approximately 60% of reported cases have neonatal hypoglycemia (29,90). The condition is transitory, being responsive to medical therapy with spontaneous regression usually occurring during the first 4 months of life. Polycythemia has been noted in 20% of the cases. Also reported in a few instances are hypocalcemia, hypercholesterolemia, and hyperlipidemia (90).

High-resolution chromosome banding studies should be carried out.

High maternal serum α-fetoprotein levels have been recorded in some instances (31a) and may indicate the presence of nephroblastoma (8), gigantism with visceromegaly (76), or possibly Beckwith-Wiedemann syndrome with associated hypothyroidism. On occasion, hypothyroidism (67), thyroxine-binding globulin deficiency (2), or low uptake with normal levels of protein-bound iodine have been noted. Beckwith-Wiedemann syndrome patients with low serum thyroxine levels should be further evaluated for frank hypothyroidism or simply thyroxine-binding globulin deficiency (54). Shah (83) recommends abdominal and renal ultrasound scans at 3-month intervals up to age 5, or more frequently if necessary, and then scans at 6-month intervals until adolescence. Daugbjerg and Everberg (21) recommend hearing tests at intervals from early childhood.

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Hemihyperplasia (hemihypertrophy)

Hemihyperplasia (hemihypertrophy), described in 1822 by Meckel (32) and in 1839 by Wagner (49), gained widespread recognition after the studies of Gesell (12) and Lenstrup (28) during the 1920s. Comprehensive reviews carried out since 1965 include those of Ringrose et al (39), Parker and Skalko (35), Gorlin and Meskin (15), Cohen (6,8), Bell and McTigue (2), and Pollock et al (37). Contributions have been made by many authors (11,14,16,17,19,45).

Although the term *hemihypertrophy* has been used conventionally and frequently in the medical literature, it is inappropriate, as the condition so obviously refers to hemihyperplasia. The differences between common asymmetry, hemihyperplasia, hypertrophy, hemiatrophy, and preferential laterality have been discussed by Cohen (7). In hemihyperplasia, the enlarged area may vary from a single digit, a single limb, or unilateral facial enlargement to involvement of half the body (14,15,39,47,48). Hemihyperplasia may be segmental, unilateral, or crossed. About 2% are crossed (37). In some cases, the defect is limited to a single system—for example, muscular, vascular, skeletal, or nervous system—but it may frequently involve multiple systems (Figs. 11–6 to 11–9) (48).

Almost all cases are sporadic if incomplete forms of the Beckwith-Wiedemann syndrome and neurofibromatosis are excluded. Tomooka et al (47) estimated a birth prevalence of 1/86,000 livebirths. Increased birth weight has been observed (mean, 3.8 kg) (28). A 2:1 female predominance for hemihyperplasia has been noted (23).

The etiology and pathogenesis are poorly understood. A tendency toward dizygotic twinning has been observed (12). Various chromosomal mosaicisms have been occasionally found, including diploid/triploid mosaicism and trisomy 18 mosaicism. Many other theories have been advanced to explain hemihyperplasia, including anatomic and functional vascular or lymphatic abnormalities; lesions of the central nervous system, leading to altered neurotrophic action; endocrine abnormalities; asymmetric cell division and deviation of the twinning process; fusion of two eggs following fertilization, leading to unequal regulative ability in the two halves; mitochondrial damage to an overripened egg, leading to overregeneration and unilateral enlargement of the neural tube; and proliferation of neural crest cells (34,37). The range and variability of clinical abnormalities, together with the large number of sporadic cases, suggest etiologic heterogeneity. One subset of hemihyperplasia overlaps and is continuous with the Beckwith-Wiedemann syndrome.

Clinical manifestations. Asymmetry is usually evident at birth and may become accentuated with age, especially at puberty. Occasionally, asymmetry has been stated not to be present at birth, but to develop later. However, such observations are valid only when measurements are

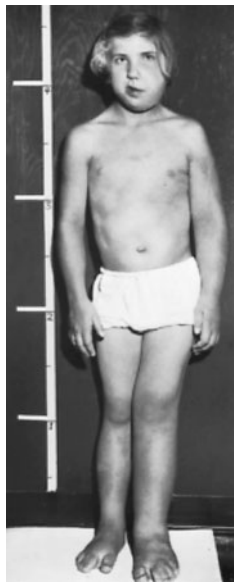


Fig. 11–6. *Hemihyperplasia.* Note asymmetry of body, with complete left-sided hemihyperplasia. Note also syndactyly of toes.

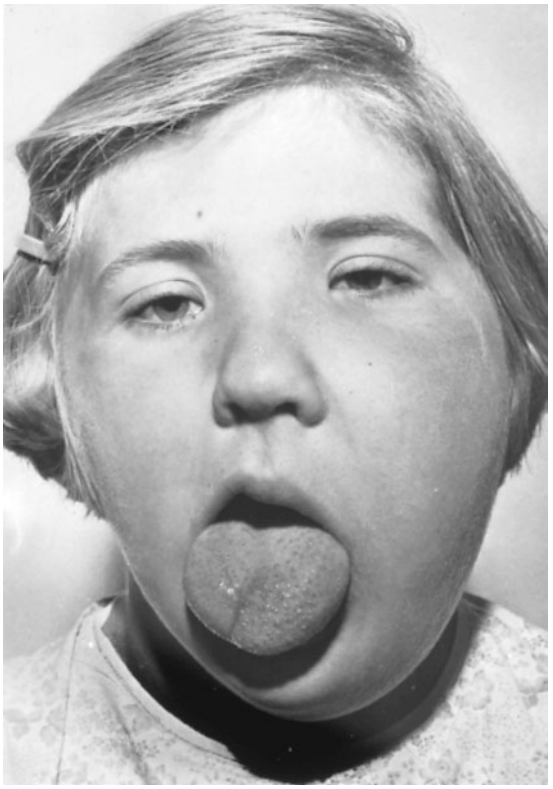


Fig. 11–7. *Hemihyperplasia.* Unilateral hyperplasia of face and tongue.

taken at birth. The bones have been found to be unilaterally enlarged with increased bone age on the affected side reported (35). A variety of nonneoplastic abnormalities have been observed to affect the limbs, teeth, skin, central nervous system, cardiovascular system, liver, kidneys, and genitalia (Figs. 11–6 to 11–9; Table 11–3).

Cutaneous anomalies include telangiectasia, nevus flammeus, and hirsutism (39). Oral and dental anomalies include enlarged hemitongue and enlarged teeth on affected side with early eruption (15,22,33). Medullary sponge kidney is a frequent finding (16,19,41,44). Many miscellaneous anomalies have also been noted. The most extensive reviews of abnormalities by system and miscellaneous anomalies are those of Ringrose et al (39), Parker and Skalko (35), Gorlin and Meskin (15), Bell and McTigue (2), and Cohen (8).

Neoplasms. Various neoplasms have been reported in association with hemihyperplasia, including, most commonly, Wilms tumor, adrenal cortical carcinoma, and hepatoblastoma, in that order. Other tumors have also been noted: neuroblastoma, pheochromocytoma, testicular carcinoma, undifferentiated sarcoma of the lung, cyst of liver, and adrenal adenoma (11,15,20,23,29,31,35,36,38,42,43,46). Hoyme et al (21) reported a tumor incidence of 5.9%. A 1.36:1 right-sided predominance and a 1.88:1 female-to-male sex ratio were found in 168 patients. Tumors occurred ipsilateral and sometimes contralateral to the hemihyperplastic side (23).

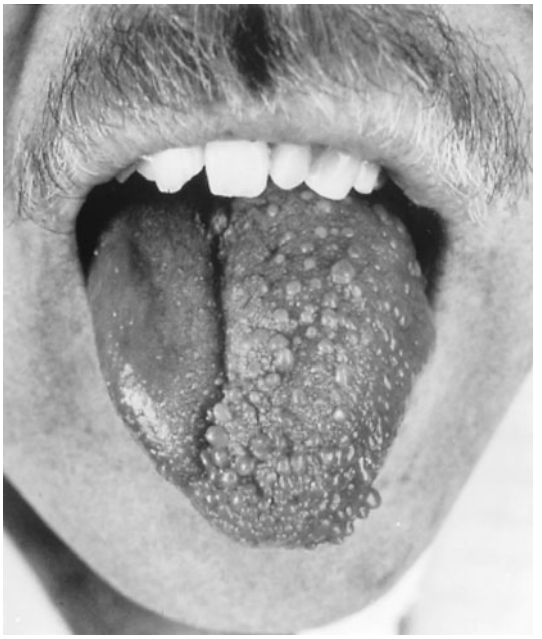
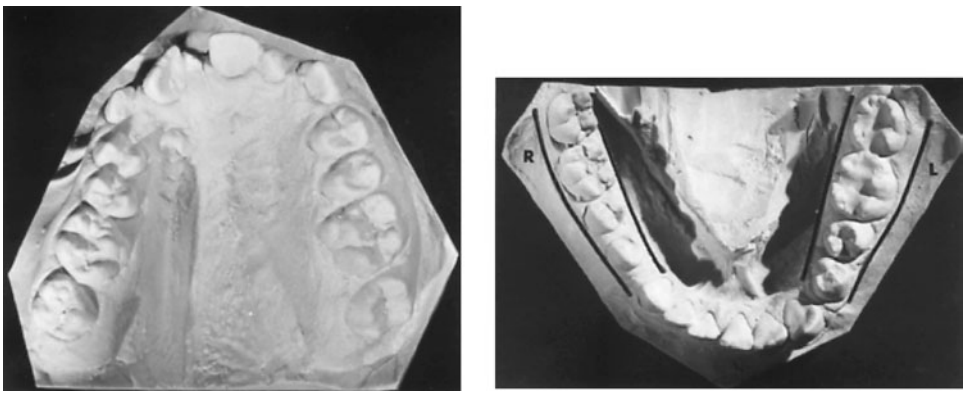


Fig. 11–8. *Hemihyperplasia.* Marked hemihyperplasia of tongue with enlargement of fungiform papillae. Note sharp demarcation at midline. (Courtesy of BB Horswell, Farmington, Connecticut.)

Differential diagnosis. So-called familial instances of hemihyperplasia are frequently incompletely documented and may represent other disorders, particularly *neurofibromatosis.* There is no question that the spectrum of the *Beckwith-Wiedemann syndrome* shades into hemihyperplasia. However, not all cases of hemihyperplasia represent the Beckwith-Wiedemann syndrome, particularly those sporadically occurring cases with no other signs and symptoms of the latter (6). Hemihyperplasia may also be observed with the *linear verrucous epidermal nevus syndrome* (13,33) and with the syndrome of hemihypesthesia, hemiareflexia, and scoliosis (1). The HIPO syndrome consists of hemihyperplasia, intestinal webs, preauricular tags, and cloudy cornea (18). There may be an autosomal dominant form of facial hemihyperplasia (5). Hennekam et al (19a) and Biesecker et al (4) described a somewhat Proteus-like disorder with arteriovenous and lymphatic malformations, linear verrucous epidermal nevus, and mild overgrowth. K. Jones and R. Gorlin have seen such a child but a unique PTEN mutation was found.



A B

Fig. 11–9. *Hemihyperplasia.* (A,B) Casts of jaws. Note differences in width of bone and size of teeth on affected and normal sides. (From RJ Gorlin and L Meskin, J Pediatr 61:870, 1962.)

Table 11–3. Hemihyperplasia (hemihypertrophy)—miscellaneous findings

Skin	*Central nervous system*
Nevi (39)	Hemimegalencephaly (12,39)
Pigmentation (30,39)	Cerebral hemiatrophy
Cutis marmorata (39)	Macrocephaly (43)
Telangiectasis (39,48)	Cyst of septum pellucidum (35)
Nevus flammeus (12,39,43)	Mental deficiency (48)
Coarse skin on affected side (39)	Seizures (35,43,48)
Ichthyosis on affected side (9)	*Cardiovascular*
Hirsutism (39)	Congenital heart defects (39, 48)
Hypertrichosis (24)	*Liver*
Thicker hair on affected side (39)	Cyst (38)
Excessive secretions of sebaceous and sweat glands	Focal nodular hyperplasia
Increased skin temperature on affected side (39)	*Kidney*
Limb	Medullary sponge kidney (16,19,41,44,47)
Macrodactyly (16,39)	Unilateral nephromegaly
Polydactyly (39)	Abnormal collecting system (35)
Syndactyly (39)	Polycystic kidneys (40)
Clubfoot (39)	*Genitalia*
Skeletal	Hypospadias (35,39)
Increased bone age on affected side (12)	Cryptorchidism (35,39)
Compensatory scoliosis (39)	Macropenis (39)
Hip dysplasia (39)	Enlarged testis on affected side (35)
Dental, oral	Clitoromegaly (39)
Enlarged teeth on affected side (15)	*Other*
Early eruption of teeth on affected side (15)	Strabismus (39)
Abnormal tooth roots	Tracheoesophageal fistula (35)
Enlarged alveolar ridge on affected side (15)	Supernumerary nipples (39)
Enlarged tongue on affected side (15)	Umbilical hernia (39)
	Inguinal hernia (34,39)
	Short stature (39)

Asymmetry may also occur with arteriovenous aneurysm, congenital lymphedema, *Silver-Russell syndrome, McCune-Albright syndrome, Klippel-Trenaunay syndrome, Proteus syndrome,* multiple exostoses, Ollier syndrome, *Maffucci syndrome, Langer-Giedion syndrome*, hemihyperplasia/lipomatosis syndrome, and facial tumors of childhood (4). Hemiatrophy may occur secondarily to early central nervous system insult and may also occur in *Romberg syndrome, Sturge-Weber syndrome*, and unilateral ichthyosiform erythroderma (9). *Bencze syndrome* (3,26) is an autosomal dominantly inherited form of facial asymmetry associated with esotropia, amblyopia, and submucous cleft palate.

Laboratory aids. Patients with isolated, nonsyndromic hemihyperplasia should be screened with ultrasound for tumors, especially Wilms tumor, every 6 months for the first 4 years of life and probably less frequently thereafter until age 7. Chromosome studies may, on occasion, reveal mosaicism of various types.

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Sotos syndrome

Sotos syndrome (cerebral gigantism), described by Sotos et al (31) in 1965, is an overgrowth syndrome characterized by increased birth length, increased birth weight, excessive growth during the first four years of life, advanced bone age, and distinctive facial features including macrodolichocephaly, ocular hypertelorism, and prominent mandible. Opitz et al (25) critically reviewed the syndrome. An extensive update is that of Cohen (9). Over 300 cases are found in the literature. Sotos syndrome is relatively common among overgrowth syndromes and appears to occur ten times more frequently than Weaver syndrome. Most cases are sporadic, and increased paternal age has been noted (11). Identical twins have been discordant for the syndrome (3). Several reported families have been consistent with autosomal dominant inheritance (25,28,37). Schrander-Stumpel et al (30) found a balanced translocation: t(3;6)(p21;p21). Breakpoint mapping has been carried out on this patient (19a). This is in part supported by the observation of Cole et al (13) that there is loss of heterozygosity at 3p21 in small cell lung carcinoma that has been found in Sotos syndrome.

Most patients can be diagnosed by craniofacial gestalt accompanied by significant overgrowth (1). Occasional patients have been confused as having Weaver syndrome. Still other patients cannot be confidently diagnosed as having either syndrome. Opitz et al (25) suggested that the many similarities between Sotos syndrome and Weaver syndrome may possibly indicate allelic rather than locus heterogeneity. Boys with fragile X may overlap phenotypically with those having Sotos syndrome (2,33). Clinical findings are listed in Table 11–4.

Table 11–4. Clinical findings in Sotos syndrome[a]

	Total number of patients	Percentage with finding
Growth		
Large birth weight	19	84
Excessive growth	102	97
Accelerated osseous maturation	102	79
Large hands and feet	80	83
Performance		
Developmental retardation	100	84
Lack of fine motor control	92	72
Neonatal adaptation and/or feeding difficulties	80	44
Craniofacial		
Macrocrania	20	90
Dolichocephaly	100	85
Receding hairline	18	94
Prominent forehead	101	96
Ocular hypertelorism	98	92
Downslanting palpebral fissures	20	65
Pointed chin	101	79
Highly arched palate	97	96
Premature eruption of teeth	80	57

[a] Based on 80 cases reviewed by Jaeken et al (18), and 22 cases reviewed by Wit et al (36). Because the findings are based on sporadic cases, there is an obvious ascertainment bias toward the severe end of the phenotypic spectrum.

Growth and skeletal findings. Overgrowth is commonly evident in the newborn, birth weight averaging 4200 g in males and 4000 g in females. Birth length, birth weight, and head circumference are, respectively, 3.2, 1.0, and 1.8 standard deviations above the mean (12). Excessive growth is particularly pronounced during the first four years of life. Bone age is advanced and gradually increases until the fifth year, after which the difference between bone age and chronological age stabilizes (35). From four years onward, growth curves usually remain above the 97th centile. Midparental height of affected individuals is similar to the normal mean midparental height. A small percentage of affected individuals have more extreme final height attainment (35). Early feeding problems are seen in 35% (11).

The hands and feet are large (6). Dysharmonic maturation and abnormal sequences in the appearance of carpal bones occur in some affected individuals (8). A characteristic metacarpophalangeal pattern has been reported (4,5,14). Joint laxity is frequent with pes planus especially common. Rarely, there is significant scoliosis (16a).

Performance and CNS abnormalities. Most patients have nonprogressive neurologic dysfunction manifested by unusual clumsiness which improves with age. Cole and Hughes (12) reported a mean DQ/IQ of 78 with a range of 40–129 (n = 23), but indicated that their figures probably underestimated ability in Sotos syndrome because some children from regular schools could not be formally assessed. Delay in expressive language and motor development during infancy is particularly common and in some instances may be followed by attainment of normal or near normal intelligence. Cole and Hughes (12) have observed that patients with Sotos syndrome tend to improve as they get older. Delay in walking until after 15 months of age and speech delay until after two and one half years are usual. Autism has been seen (21). Seizures and respiratory and feeding problems have been noted in about 20%. Often drooling is observed. Attention deficit may also be a component in some instances. Occasionally, other neurological signs have been reported, including nystagmus, strabismus, increased deep tendon reflexes, hypotonia, and muscle weakness (8,9).

Dilatation of the cerebral ventricles is seen in 70%–100% (20a,26,36). Other abnormalities include absent corpus callosum, prominent cortical sulci, cavum septum pellucidum, and cavum velum interpositi (20a,29). Schaefer et al (29) in a neuroimaging study of 40 patients, found prominence of the trigone in 90%, prominence of the occipital horns in 75%, and ventriculomegaly in 63%.

Craniofacial features. Dolichocephaly and marked frontal bossing are accentuated by frontoparietal balding (Fig. 11–10). The head circumference is usually well above the 97th centile. Narrow temples make the eyes appear wide-set, but true ocular hypertelorism is not found. Strabismus is noted in 40%. The cheeks are full. Although the mandible is long and narrow inferiorly, squared, or pointed, true prognathism is rare. The palate is highly arched, and prematurely erupted deciduous teeth are observed in more than 50% of cases (8,9). Cephalometric analyses are available (22,34).

Other findings. Congenital heart defects have been discussed by Keneko et al (19), Cole and Hughes (12), Noreau et al (24), and Tsukahara et al (32). Many low-frequency abnormalities have been reported, including, among others, juvenile macular degeneration, optic disc pallor, glaucoma, bones in the anterior fontanelle, vertebra plana, kyphoscoliosis, brittle nails, syndactyly, functional megacolon, and autonomic failure with persistent fever (8,9,17a,37).

Neoplasms. Cohen (10) critically reviewed neoplasms reported to occur with Sotos syndrome. Retrospective literature review suggests a

A B

Fig. 11–10. *Sotos syndrome.* (A) Eighteen-month-old male showing typical facies. Note receding hairline and small nose. (B) Six-month-old female with characteristic facies. (A courtesy of MM Steiner, Chicago, Illinois.)

tumor frequency of about 3.9% (7,9,17,23). Tumors have included Wilms tumor, hepatocellular carcinoma, neuroblastoma, vaginal epidermoid carcinoma, small cell carcinoma of lung, sacrococcygeal teratoma, giant cell granuloma of the mandible, and acute lymphatic leukemia (10,17,19b).

Laboratory findings. A 14% frequency of glucose intolerance has been demonstrated in Sotos syndrome by numerous investigators (8,18).

Differential diagnosis. Enlarged head circumference may be seen in several other conditions: hydrocephalus, *neurofibromatosis, achondroplasia,* autosomal dominant macrocephaly, and so on. Although some syndromes occur with overgrowth and others are associated with macrocephaly, Sotos syndrome is a distinctive condition. Several syndromes have been confused with Sotos syndrome (7,11). Cole and Hughes (12), evaluating 79 patients, found that 50% were misdiagnosed. Cole and Hughes (11a) and others (23a,31a) proposed that autosomal dominant macrocephaly, obesity, unusual facies, delayed bone age, mental retardation and autism is a distinct entity. This has come to be known as Cole-Hughes macrocephaly syndrome. *Nevo syndrome* (8), in addition to Sotosoid features, has generalized edema at birth, severe muscular hypotonia, contractures of the feet, wrist drop, and clinodactyly. The condition has autosomal recessive inheritance. *Weaver syndrome* has a distinctive facial appearance, widened distal long bones, and more accelerated osseous maturation. The *Bannayan-Riley-Ruvalcaba syndrome* (8,9) has some Sotosoid features but has distinctive pigmentary spotting of the penis and intestinal polyposis, especially of the colon. Inheritance is autosomal dominant. Some patients clinically suspected of having Sotos syndrome have also been reported with *fragile X syndrome* (2,33). Goldstein et al (16) observed two patients with overgrowth, congenital hypotonia, nystagmus, strabismus, and mental deficiency; they were thought to bear some resemblance to those with Sotos syndrome. The patient reported by Evans (15) probably had *pseudohypoparathyroidism* or *acrodysostosis.* Although there is stated to be resemblance to the autosomal dominant Siena-type overgrowth syndrome, we do not think there is overlap (20). We are not able to identify the Sotosoid syndrome with redundant skin folds and vesicoureteris reflux (27).

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Nevo syndrome

The syndrome was observed by Nevo et al (6) in 1974 in three sibs among a large inbred family from Israel. Whereas Nevo and coworkers (6) described their patients as having cerebral gigantism, Cohen pointed out that the condition was clearly at variance with cerebral gigantism (2) and named the condition Nevo syndrome (3).

Al-Gazali et al (1) reported two further children from two unrelated families. Hilderink and Brunner (5) observed a patient from a consanguineous Dutch family. Another patient was noted by Dumić (4). To date, seven children have been reported from five families; three of these families are Arabic. Autosomal recessive inheritance is established.

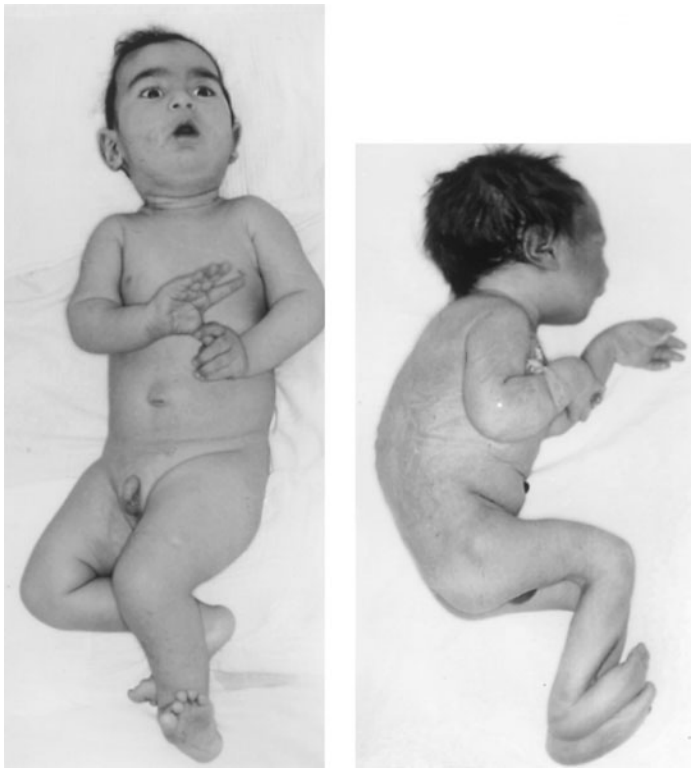

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Fig. 11–11. *Nevo syndrome.* (A) Large infant. (B) Second affected infant. Note contractures and puffy hands. (From S Nevo et al, J Med Genet 11:158, 1974.)

Features of Nevo syndrome similar to those found in *Sotos syndrome* include intrauterine overgrowth, accelerated osseous maturation, dolichocephaly, large extremities, clumsiness, and retarded motor and speech development. Nevo syndrome has, in addition, generalized edema at birth, severe muscular hypotonia, contractures of the feet, wrist drop, and clinodactyly (Fig. 11–11). Large, low-set, malformed ears and cryptorchidism were observed in some patients (6).

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Bannayan-Riley-Ruvalcaba syndrome (Bannayan-Zonana syndrome, Ruvalcaba-Myhre syndrome, Riley-Smith syndrome)

Riley and Smith (30) in 1960, observed the association of macrocephaly, pseudopapilledema, and multiple hemangiomas. Bannayan (2), in 1971, and Zonana et al (41), in 1976, described macrocephaly with multiple subcutaneous and visceral lipomas and hemangiomas. Ruvalcaba et al (31), in 1980, reported patients with macrocephaly, intestinal polyposis, and pigmented spotting of the penis. Gorlin et al (14) extended the

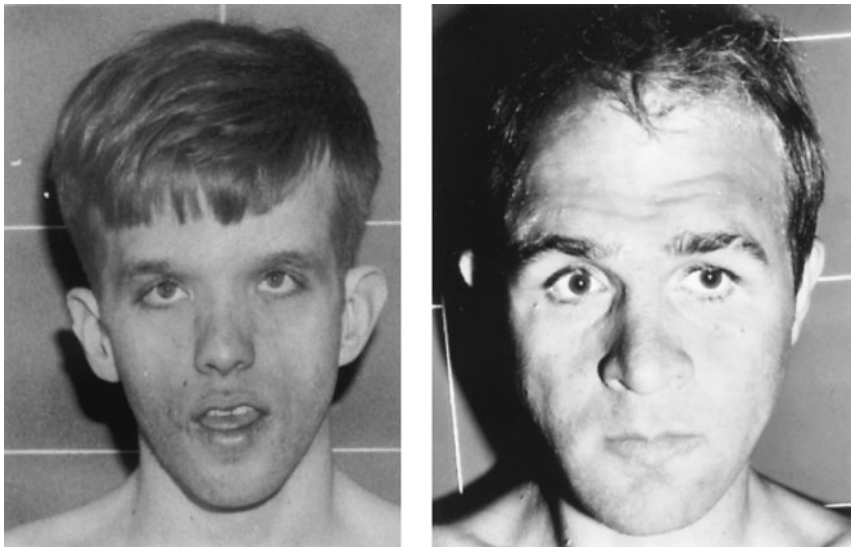

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Fig. 11–12. *Bannayan-Riley-Ruvalcaba syndrome.* (A,B) Macrocephaly, prominent mandible. (From R Ruvalcaba et al, Clin Genet 18:413, 1980.)

syndrome to include Hashimoto thyroiditis and suggested a relationship to juvenile polyposis of infancy. At least 45 cases have been described (1–40). Cohen (5) proposed the syndrome be named for the first authors of the three original reports. Of interest to the reader are the editorial comments of Cohen and MacLean (6).

Inheritance is autosomal dominant. More males than females have been reported (10,29). The syndrome, mapping to 10q23, is due to mutations in a tumor suppressor gene, PTEN, a dual specificity phosphatase. Bannayan-Riley-Ruvalcaba syndrome is allelic to Cowden syndrome. Phenotypic and molecular overlap have been recorded (28b). Germline mutations have been found in almost 60% of cases, none within the PTPase core motif as yet (1a,24,25). In fact, there are examples of overlapping phenotypes (1a,12,42), and families in which the two phenotypes exist (3). Translocation causing the syndrome has been noted (1). The PTEN gene is expressed in the embryo in areas other than those affected by the syndrome (13a).

Birth weight is usually in excess of 4000 g, with birth length above the 97th centile. Postnatal growth decelerates, older children and adults both being well within the normal range (9,10,31).

Hypotonia, gross motor delay, mild-to-severe mental deficiency, and cognitive speech delay have been reported in approximately 70% (9,17,22,26,27,29,34). About 25% exhibit seizures (9,29). DiLiberti and Budden (8) and Powell et al (29) reported asymmetric motor development. These minor motor asymmetries were transient and improved with age. Deep tendon reflexes are diminished.

Craniofacial features. Head circumference is at least 4.5 SD above the mean in nearly all affected. A few patients have exhibited delayed closure of the anterior fontanel. Ocular hypertelorism has been noted in some instances (Fig. 11–12). Downslanting palpebral fissures and strabismus or amblyopia are frequently noted. Examination of the eyes under slit lamp has demonstrated prominent Schwalbe lines and clearly visible corneal nerves in approximately 35% of patients (9,15). Pseudopapilledema has been found in some cases (11,30).

Skin. Pigmented macules are found on the penile gland and shaft in 25% of affected males (7,14) (Fig. 11–13). This spotting is often subtle and may be missed if not specifically looked for. The macules may not appear until mid-childhood or later.

Cutaneous angiolipomas with a vascular component that vary in number, size, and location have been observed in over half the patients (9). About 25% have a small number of café-au-lait spots on the trunk and lower limbs (29). One patient had acanthosis nigricans-like lesions of the face. Another patient had accessory nipples (31).

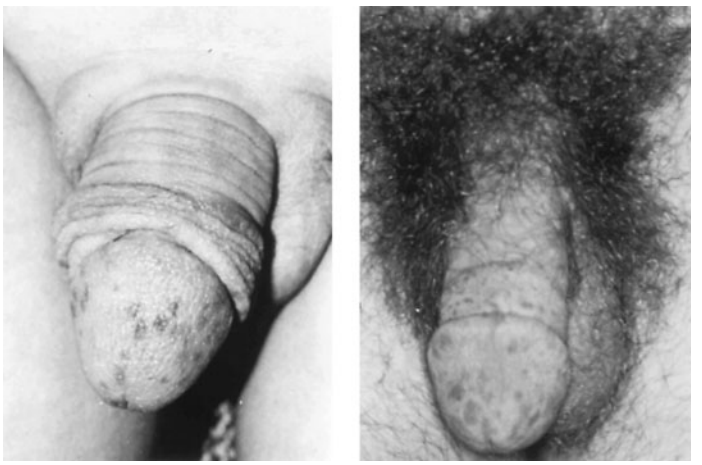
Hashimoto thyroiditis. Hashimoto thyroiditis, an autoimmune disorder of delayed hypersensitivity, is characterized by euthyroid or mildly hypothyroid goiter. It occurs predominantly in middle-age females, although it may be seen in adolescent or preadolescent females. Gorlin et al (14) expanded the syndrome to include Hashimoto thyroiditis.

Goiter or fullness in the throat with mild dysphagia is usually present. Onset is insidious. The gland is 2–5 times normal size, firm to rubbery in consistency, and painless. Asymmetric enlargement is noted in about 35%.

Microscopically there is diffuse involvement of the entire gland marked by a dense infiltration of lymphocytes throughout the parenchyma and in focal collections with true germinal centers. Fibrous connective tissue is not significantly increased. The acinar lining cells are swollen with granular, eosinophilic (oncocytic) cytoplasm and large hypochromatic nuclei. The acini are small with slitlike lumina containing almost no colloid (14).

Gastrointestinal system. Hamartomatous (juvenile) polyps, usually multiple and limited to the distal ileum and colon, may be associated with intussusception and/or rectal bleeding. Polyps have been found in 45% of all patients. Polyps other than juvenile type have been found (23a).

Fig. 11–13. *Bannayan-Rily-Ruvalcaba syndrome*. (A,B) Pigmented macules on penile shaft. (A form J DiLiberti, Am J Med Genet 15:491, 1983. B from R Ruvalcaba et al, Clin Genet 18:413, 1980.)



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While some become manifested in childhood, others have not become evident until middle age (9,13). Protein-losing enteropathy has been observed (14,22,23,32,33,35–38).

Musculoskeletal system. At least 60% of patients had a myopathic process in the proximal muscles (4,10) which manifests as delayed motor development. There is exercise intolerance. Muscle biopsy has shown intracellular lipid accumulation, predominantly in enlarged type I muscle fibers (7,29), Type II fibers are smaller than normal and contain less fat (10). Metacarpophalangeal profile patterns show accelerated growth of the first metacarpal and first and second middle phalanges (16). Joint hyperextensibility, pectus excavatum, and scoliosis have been reported in about 50% (9,18).

Neoplasms. Mesodermal hamartomatous masses are usually discrete lipomas (75%). Capillary or venous malformations (10%) and lymphatic malformations (10%) are seen. In 20% of patients, the vascular malformations are of the combined type (21). Most of the hamartomas are subcutaneous, but may be intracranial (20%) or osseous (10%). Some lipomas may be aggressive and can cause serious complications (26). The puzzling patient of Okumura et al (28) had manifestations of Bannayan-Riley-Ruvalcaba syndrome, Klippel-Trenaunay syndrome, and Proteus syndrome. A Proteus-like syndrome was noted by Zhou et al (40a). Hamartomatous polyposis has already been discussed in the section on the gastrointestinal system.

Malignant tumors have been noted in some patients. One adult male had a thyroid tumor and two other affected males had thyroidectomies at a young age. One affected female has had rapid onset of bilateral invasive breast cancer at age 34 (DiLiberti, personal communication, 1986).

Other abnormalities. Adult males had enlarged testes (9,13). A patient seen by one of us (RJG) had a painful testis due to fatty infiltration. We have also noted hemihyperplasia in a few patients.

Differential diagnosis. An exhaustive discussion of conditions associated with macrocephaly is that of Gorlin et al (14). The most common cause is autosomal dominant macrocephaly. Other syndromes are those of *Sotos, Weaver, Marshall-Smith*, and *macrocephaly-cutis marmorata*. Lipomas, hemangiomas, and lymphangiomas may also occur in *Proteus syndrome.* The combination of macrocephaly, angiomatosis, and limb asymmetry in sporadic cases has been discussed by Stephan et al (39). Hashimoto thyroiditis has been reported in association with familial adenomatous polyposis and with generalized hypertrophic myopathy and chorioretinal dystrophy (14).

Familial juvenile polyposis, an autosomal dominant disorder which maps to 18q21.1, placed the affected at increased risk for gastrointestinal adenocarcinoma (20). Hereditary mixed polyposis maps to 6q (40). There has been considerable argument whether the gene for some patients with juvenile polyposis is the PTEN gene (20).

Laboratory aids. Electromyography, muscle biopsy, and mutational analysis should be performed on all infants with macrocephaly, normal CT scans, and hypotonia. Patients with Bannayan-Riley-Ruvalcaba syndrome should be monitored for gastrointestinal polyposis and thyroid neoplasms. Muscle-free carnitine levels have been reduced (29).

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Weaver syndrome

In 1974, Weaver et al (38) reported a syndrome of persistent overgrowth of prenatal onset, accelerated osseous maturation, distinctive craniofacial appearance, developmental delay, widened distal long bones, and camptodactyly (Table 11–5). Most cases are sporadic. Parent-to-child transmission has been recorded on several occasions (10,16,28). Fitch (12,13) and Ardinger et al (2) reported cases and reviewed the literature. Recent critical reviews are those of Opitz et al (28) and Cole et al (8). A recent update is that of Cohen (7). Many cases have been reported (1,2,4–21, 23,27–29,32,38–40). There is a 3:1 male-to-female ratio (2,5,28), and females have been noted to be more mildly affected (2,7,28,35).

Table 11–5. Features of Weaver syndrome

Findings	Frequencies
Growth	
Prenatal growth excess	16/20
Postnatal growth excess	19/20
Accelerated osseous maturation	19/19
Performance	
Hypertonia	10/18
Hypotonia	5/18
Developmental delay	19/19
Hoarse, low-pitched cry	14/17
Craniofacial	
Broad forehead	18/19
Flat occiput	6/11
Large ears	15/17
Ocular hypertelorism	19/19
Prominent or long philtrum	10/14
Relative micrognathia	17/19
Limbs	
Camptodactyly	11/16
Prominent fingerpads	6/9
Thin, deeply set nails	9/10
Broad thumbs	4/6
Clinodactyly, toes	4/5
Limited elbow or knee extension	10/13
Widened distal long bones	16/18
Foot deformities[a]	7/10
Other	
Excess loose skin	11/12
Umbilical hernia or diastasis recti	12/17
Inguinal hernia	4/14
Inverted nipples	3/4

[a] Talipes equinovarus, talipes calcaneovalgus, metatarsus adductus.

Growth and skeletal findings. Mean birth weight is 4785 g in males and 3883 g in females. Birth length is 56 cm in males and 53 cm in females. Head circumference at birth is 36.6 cm in males and 35.2 cm in females. Adult head circumference is 61 cm in males and 59.5 cm in females (28). Final height attainment is 194.2 cm in males and 176.3 cm in females. Adult weight is 102.2 kg in males and 87.6 kg in females.

Performance and central nervous system. Mild hypertonia (75%) or hypotonia is common, and motor development is mildly to moderately retarded. The cry is low-pitched and hoarse (100%). Although the appetite is voracious, hypothalamic dysregulation has not been demonstrated. Difficulty in swallowing or breathing has been noted in several cases. Other findings have included cysts of the septum pellucidum, pachygyria, dilation of the ventricles, basal cisterns, sylvian cistern, and interhemispheric fissure, consistent with nonspecific cerebral atrophy, and enlarged vessels and hypervascularization in the areas of the middle and left posterior cerebral arteries (2,7,28).

Craniofacial features. Macrocephaly (90%), broad forehead (100%), and flattened occiput are characteristic. Scalp hair is moderately thin. The ears are large (95%) and may be mildly dysmorphic or low-set (Fig. 11–14). Other features include hypertelorism, long prominent philtrum (90%), depressed nasal bridge (80%), relative micrognathia, and redundant nuchal skin folds. Low-frequency findings have been noted such as mild craniofacial asymmetry, upslanting or downslanting palpebral fissures, small palpebral fissures, ptosis, strabismus, and highly arched palate (2,5,28).

Limbs. Common findings include camptodactyly (65%), prominent finger pads, thin deeply set nails, broad thumbs, clinodactyly of toes, and limited extension at elbows and knees. Foot deformities have been noted such as talipes equinovarus, talipes calcaneovalgus, metatarsus adductus, pes adductus, and pes cavus. Deep creases may be observed on the palmar and plantar surfaces (2,7,28).

Bone age is remarkably advanced; the growth parameters of head circumference, length, and weight are two-to-three times the expected rate. Carpal maturation is accelerated over that of phalanges and metacarpals (Fig. 11–15). Other skeletal findings include abnormal cervical vertebrae, widened or splayed long bone metaphyses, especially of the femurs, and somewhat mottled epiphyses. The iliac wings may be broad and low (2,6,28).

Neoplasms. Although many overgrowth syndromes are associated with neoplasia, two neuroblastomas (17,19a), one ovarian yolk sac tumor (9), and one sacrococcygeal teratoma (22a) have been reported with Weaver syndrome.

Differential diagnosis. Weaver syndrome should be differentiated from *Sotos syndrome,* with which it is sometimes confused (28). There are Weaver-like syndromes and misdiagnosed Weaver syndrome cases from the literature (15,22,24,30,31,33,34,36,37). These have been reviewed by Cohen (7). Van Asperen et al (3) reported familial type 1 *neurofibromatosis* associated with an overgrowth syndrome resembling Weaver syndrome. Some patients cannot be diagnosed confidently as having either Sotos syndrome or Weaver syndrome (28).

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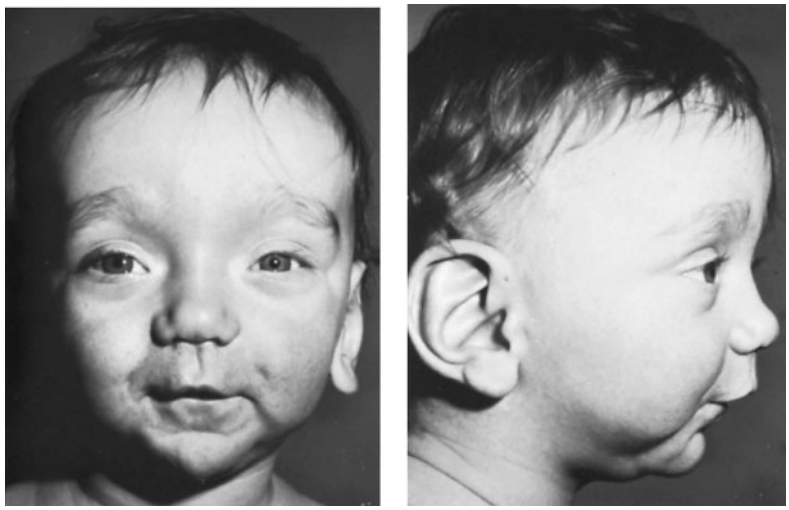

A B

Fig. 11–14. *Weaver syndrome.* (A,B) Note broad forehead, hypertelorism, large ears, long philtrum, and micrognathia. (From DD Weaver et al, J Pediatr 84:547, 1974.)

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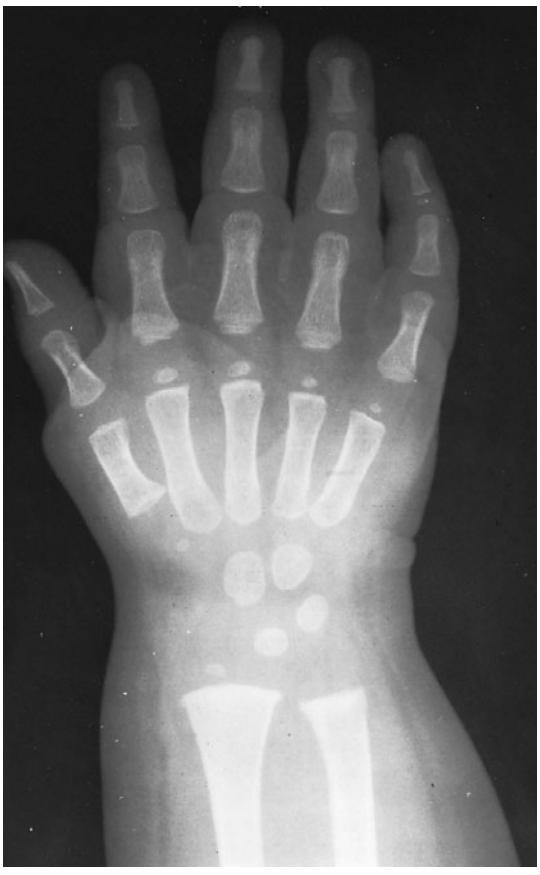
Fig. 11–15. *Weaver syndrome*. Hand-wrist radiograph at 11 months showing carpal bone age of a 4-year-old. (Courtesy of DD Weaver, Indianapolis, Indiana.)



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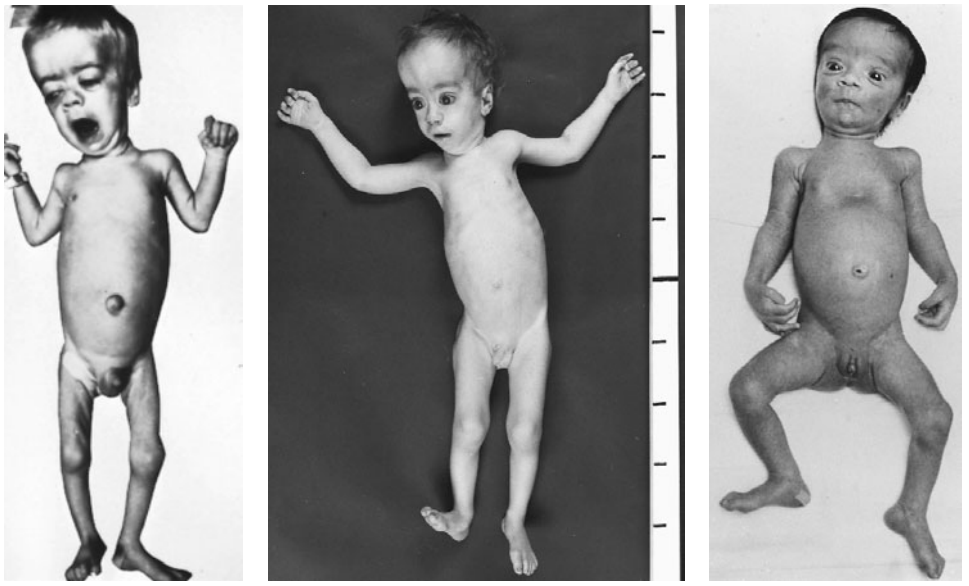

A B C

Fig. 11–16. *Marshall-Smith syndrome.* (A–C) Prominent forehead, bushy eyebrows, bulging eyes in patients with failure to thrive. (A from RE Marshall et al, J Pediatr 78:95, 1971. B from E de Toni et al, Minerva Pediatr 28:1499, 1976. C from S Flatz and J Natzschka, Klin Padiatr 190:592, 1978.)

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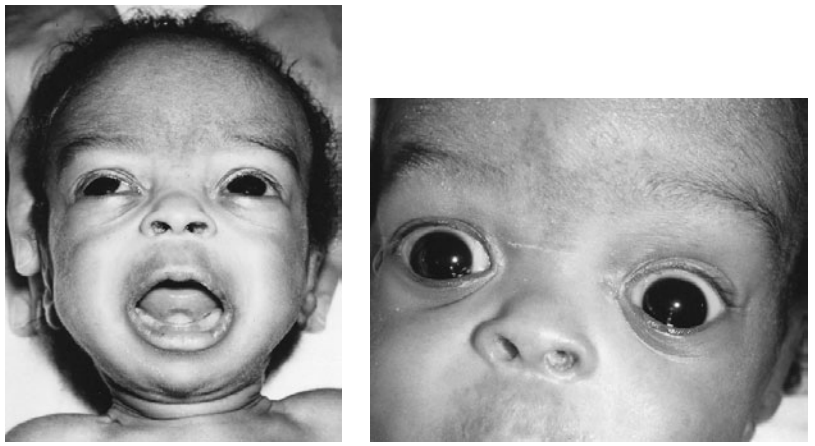
Marshall-Smith syndrome

In 1971, Marshall et al (18) first reported a disorder characterized by accelerated skeletal maturation, mental and somatic retardation, failure to thrive with chronic respiratory distress and early death, characteristic facial appearance, and remarkable skeletal alterations (Figs. 11–16 to 11–18). At least 25 cases have been reported (1–9,12–23,25–31) and all have been isolated examples. Perhaps it represents a new lethal dominant mutation. Findings have been summarized by Hoyme et al (14) (Table 11–6).

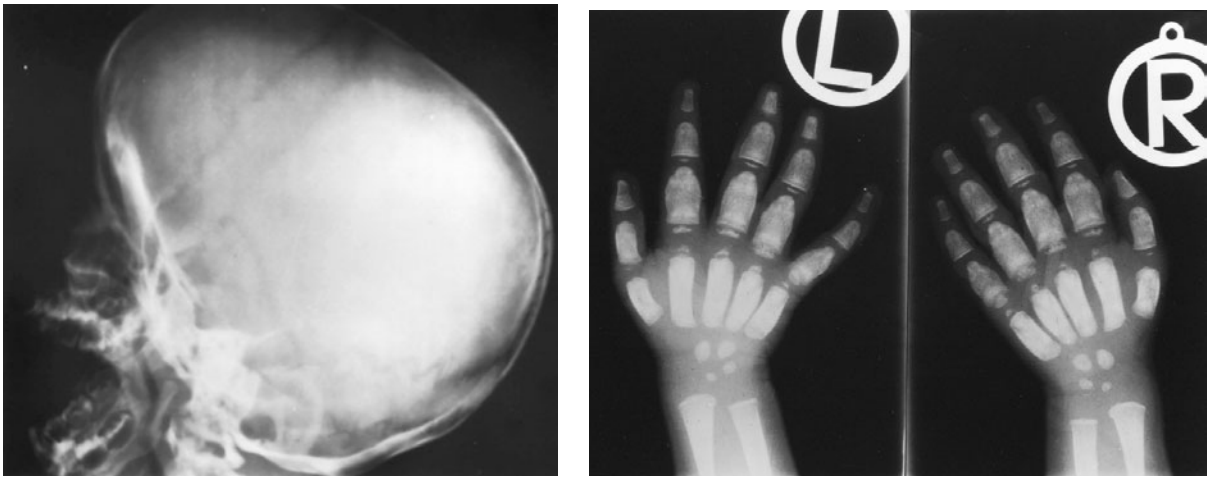
Growth, performance, and natural history. Moderate to severe respiratory distress accompanied by noisy stridor may necessitate intubation. There is failure to thrive, and death due to pneumonia occurs almost always within months. However, a few children have survived for up to 7 years (14,26). The child will often lie with the head extended due to laryngeal hypoplasia (6,18,29). Speech is poor and frequently the child is hypotonic. Psychomotor delay is common. Partial growth hormone deficiency was found by Roodhooft et al (23).

Craniofacial features. The forehead is prominent with frontal ridging, while the supraorbital ridges are flattened in 85%. The eyes bulge or are proptosed in nearly all affected and there may be megalocornea (Fig. 11–17). The sclerae are blue in 60%. Optic atrophy has been found (26,30). The eyebrows are bushy with synophrys. The nose is small with a low nasal bridge and anteverted nostrils in essentially all patients. Unilateral or bilateral choanal stenosis or atresia has been reported (12,15,22,28,29). The helices of the pinnae are often folded with hypoplastic cartilages (8), and the ears may be low-set. The mandible is



A B

Fig. 11–17. *Marshall-Smith syndrome.* (A,B) Bulging eyes, coarse eyebrows, low nasal bridge, micrognathia. (A,B from JCS Perrin et al, Birth Defects 12(5):209, 1976.)



A B

Fig. 11–18. *Marshall-Smith syndrome.* Radiographs. (A) Prominent calvaria, small facial bones, and hypoplastic mandibular rami. (B) Radiograph of hand at 22 days. Note enlarged bullet-shaped proximal and middle phalanges, very small distal phalanges; phalangeal epiphyses, curved first metacarpal, and advanced bone age. (A from RE Marshall et al, J Pediatr 78:95, 1971. B from M Hassan et al, Pediatr Radiol 5:53, 1976.)

small in 85%. The mouth is small and the palate may be highly arched. Stridor appears to be related both to glossoptosis (documented in 35%), rudimentary epiglottis, and hypoplastic larynx (6,12,13,16,29). Hearing loss may be part of the syndrome (14,30).

Musculoskeletal system. The hands and feet and/or digits are often stated to be long. Radiographically, carpal and tarsal bone age is markedly advanced (15,19,22,28). At birth, the phalangeal epiphyses, femoral heads, and patellae are usually ossified, suggesting a bone age of 4 years or more (17,19,20). The frontal bone is prominent and the calvaria thickened and prominent. The orbits are shallow and the facial bones small or hypoplastic. The mandibular rami are underdeveloped with absence of the angle (9,12,13,18,28) (Fig. 11–18A).

Table 11–6. Features of the Marshall-Smith syndrome[a]

Findings	Frequencies
Growth, skeletal	
Accelerated linear growth	2/18
Accelerated osseous maturation	18/18
Broad phalanges	17/17
Failure to thrive	11/13
Performance	
Neurodevelopmental abnormalities	13/13
Structural brain anomalies	7/14
Respiratory	
Respiratory tract abnormalities	15/18
Recurrent pneumonia	14/18
Pulmonary hypertension	4/18
Death in early infancy	10/18
Craniofacial	
Prominent forehead	15/18
Small face	12/18
Prominent eyes	17/18
Blue sclerae	11/18
Flat nasal bridge	17/18
Anteverted nares	15/16
Micrognathia	14/18
Glossoptosis	6/17
Choanal atresia/stenosis	3/17
Other	
Hypertrichosis	7/18
Umbilical hernia	6/18

[a] Adapted from HE Hoyme and MJ Bull; Eighth David W. Smith Workshop on Malformations and Morphogenesis, Greenville, South Carolina, August 15–19, 1987.

Long bones tend to be thin (7,13,16–31). The proximal and middle phalanges of the hands are remarkably thick. The former are rectangular; the latter are bullet-shaped. The terminal phalanges are greatly reduced in size. The metacarpals are also widened distally and are poorly modeled (Fig. 11–18B). Scoliosis has been noted in a few cases. Severe spinal stenosis and instability at the craniocervical junction have been documented (8). One of us (RCM Hennekam) has observed increased fractures.

Muscle biopsy showed hypoplasia of type IIa and IIb fibers (23).

Other abnormalities. Umbilical hernia or omphalocele is present in approximately 35% (16,18,26,29). Generalized hypertrichosis occurs in about 50% (16). Pachygyria of the occipital and temporal areas of the brain has been documented in some instances (18,28). Only a few children have had cardiovascular defects and these have included PDA, ASD, and hypertrophy of the pulmonary arteries (12).

Differential diagnosis. Comparison is sometimes made with *Weaver syndrome,* but except for accelerated osseous maturation, the phenotypes are distinct. Differences have been well reviewed by Fitch (10,11). In *Sotos syndrome,* phalangeal age is ahead of carpal age, but in Marshall-Smith syndrome the opposite occurs. The case reported by Shimura et al (24) as an example of overlap between Marshall-Smith syndrome and Weaver syndrome represents simply Weaver syndrome, in our opinion. The case of Smyth et al (25) appears to represent Marshall-Smith syndrome.

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Table 11–7. Simpson-Golabi-Behmel syndrome—major findings

Clinical findings	Frequency[a]
Neonatal	
Macrosomia	+++
Hydrops fetalis	+
Craniofacial	
Macrocephaly	+++
"Coarse" face	+++
Downslanting palpebral fissures	++
Macrostomia/macroglossia	++
Dental malocclusion	++
Cleft lip/palate	+
Central groove of lower lip	++
Hands	
Polydactyly	++
Fingernail hypoplasia	++
Cutaneous syndactyly/webbing	+
Chest/abdomen	
Supernumerary nipples	+++
Pectus excavatum	+++
Rib/vertebral abnormalities	++
Diastasis recti	++
Coccygeal skin tags	+
Umbilical/inguinal hernias	++
Genitalia	
Hypospadias	+
Cryptorchidism	++
Internal organs	
Congenital heart defect	++
Heart arrhythmias	++
Diaphragmatic defect	+
Hepatosplenomegaly	++
Hyperplastic islets of Langerhans	+
Cystic dysplasia of kidneys	++
Neurological	
Muscular hypotonia	+++
Mental retardation	+/−
Other	
Advanced bone age	++
Neonatal death	++
Neoplasia	+/++

[a]Frequency of clinical findings approximately estimated as: nearly constant (+++), frequent (++), occasionally reported (+), and absent (−). (From G Neri et al, Am J Med Genet 79:279, 1998.)

Simpson-Golabi-Behmel syndrome

The syndrome is an X-linked disorder characterized by prenatal and postnatal overgrowth, intellectual impairment, characteristic facial appearance, and a variety of other anomalies. Golabi and Rosen (4) reported the disorder in four affected males with partial manifestations in a female obligate carrier. Striking features of the syndrome consisted of macrosomia, mental deficiency, broad nose, wide mouth, cleft palate, large cystic kidneys, and musculoskeletal and limb abnormalities. Neri et al (13) noted that the precedent set by Simpson et al (20) and the contribution made by Behmel et al (1,2) necessitated a change in eponymic designation from Golabi-Rosen syndrome to Simpson-Golabi-Behmel syndrome. Neri et al (14) recently reviewed the clinical and molecular aspects of the syndrome. About 35 examples have been described (3,12). A good general discussion of gene regulation is that of Selleck (19a).

Etiology. The Simpson-Golabi-Behmel gene maps to chromosome region Xq25–q27 (17,19,24). Pilia et al (18) identified different microdeletions in three families. Mutations in a cell surface heparan sulfate proteoglycan, glypican-3 (GPC3) play an important role in controlling the growth of mesodermal and endodermal tissues. Veugelers et al (22) reported deletion of the GPC3-GPC4 gene cluster in one family. However, not all families show a deletion (12).

Simpson-Golabi-Behmel syndrome and Beckwith-Wiedemann syndrome share some clinical similarities, but there are also differences. GPC3 binds to IGF2 and it may modulate IGF2 action. It is not known whether the IGF2 receptor and GPC3 compete for IGF2 ligand or whether a trimolecular complex is formed (23). This has importance in clinical overlap of Beckwith-Wiedemann, Perlman, and Simpson-Golabi-Behmel syndromes (6,21).

Clinical findings. Many cases have been reported. Clinical findings are summarized in Table 11–7. Recently, Lin et al (11) reported cardiac abnormalities in 36% (n = 99). Simpson-Golabi-Behmel syndrome has a number of features in common with *Beckwith-Wiedemann syndrome* and clinical differentiation can be challenging, but can be resolved at the molecular level.

Growth. Overgrowth is impressive at birth and continues postnatally in almost 100%. Birth weights of 4000–5000 g have been noted (4,13).

Central nervous system. Mild to moderate mental retardation has been present in most (4,13–15), but there has been severe delay in others (5,16). Hypotonia is common. Speech is delayed in almost all patients.

Craniofacial abnormalities. Macrocephaly and coarse facies are common. The palpebral fissures tend to slant downward. The nose is

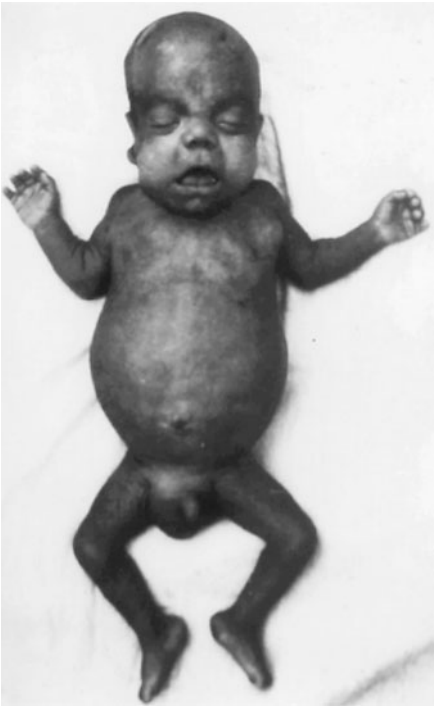


Fig. 11–19. *Simpson-Golabi-Behmel syndrome.* Note hypertelorism, broad flat nasal bridge, short upturned nose, large mouth. Weight greater than 90th percentile at birth. (From M Golabi and L Rosen, Am J Med Genet 17:345, 1984.)

broad and the mouth wide. The tongue is large and malocclusion is common. Several patients had a central groove of the lower lip. Cleft lip and/or palate have been documented (10) (Figs. 11–19 and 11–20). Odontogenic keratocysts have been described, but possibly the patient has Gorlin syndrome (9a).

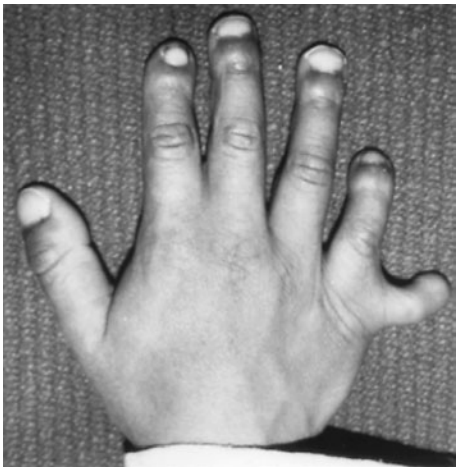


Fig. 11–21. *Simpson-Golabi-Behmel syndrome.* Postaxial hexadactyly, mild soft tissue syndactyly between second and third digits. (From M Golabi and L Rosen, Am J Med Genet 17:345, 1984.)

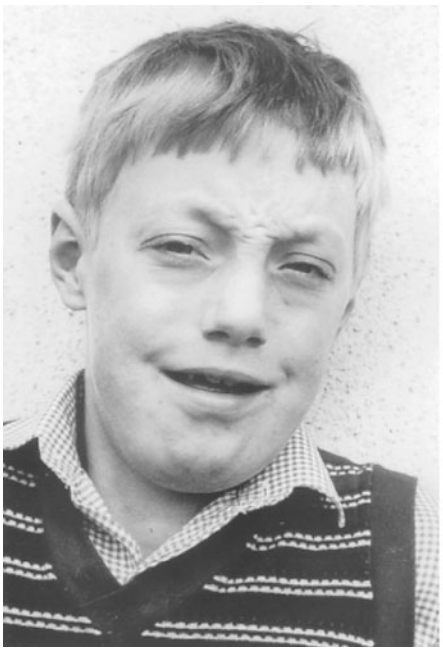
Extremities. The hands are large and square. The thumbs and halluces are broad. Postaxial hexadactyly and 2–3 manual soft-tissue syndactyly are frequent (Fig. 11–21). The nails may be hypoplastic, especially those of the index fingers.

Musculoskeletal anomalies. Pectus excavatum, various rib and vertebral anomalies, and clefting of the xiphisternum have been noted (4,13). Umbilical/unguinal hernias have been documented in 35%. There may be advanced bone age (4,12,13).

Skin. Supernumerary nipples are seen in 40% as are coccygeal skin tags. Spotty perioral and palatal pigmentation has been described.

Embryonal neoplasia. There is a higher-than-normal occurrence of Wilms tumor, atypical embryoma, neuroblastoma, hepatoblastoma, rhabdomyoma, and hepatocellular carcinoma (5,8,10,12,18).

Fig. 11–20. *Simpson-Golabi-Behmel syndrome.* (A,B) Coarse facies, wide nasal bridge, wide mouth. (C) Note hypertelorism, short broad upturned nose, and large mouth. (A,B from A Behmel et al, Hum Genet 67:409, 1984. C from M Golabi and L Rosen, Am J Med Genet 17:345, 1984.)



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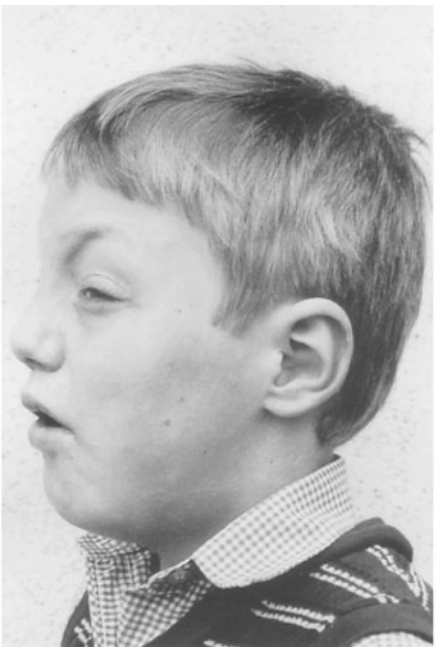

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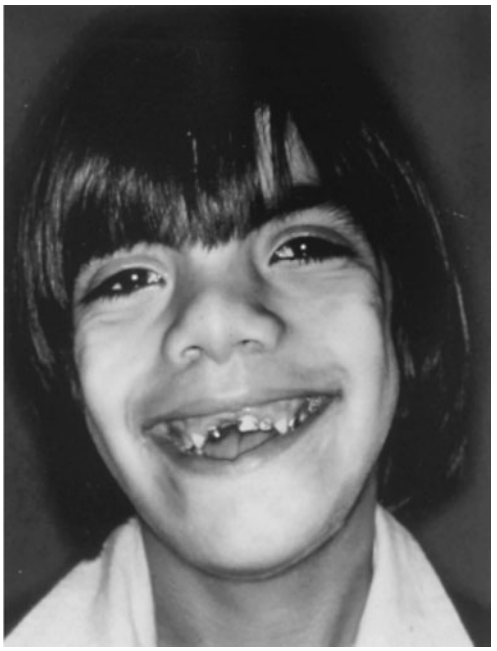

C

Other findings. Various kidney findings have been noted (large kidney, lobulated kidneys, cystic kidneys, duplication of renal pelvis), and hypospadias and cryptorchidism have been seen. Congenital heart anomalies have been cited.

Visceroptosis of the liver, pectus excavatum, and neonatal respiratory distress have been documented.

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Prader-Willi syndrome

Prader-Willi syndrome was initially identified in 1956 by Prader, Labhart, and Willi (104). They described 14 patients with obesity, hypogonadism, cryptorchidism, mental retardation, and hypotonia (Figs. 11–22 to 11–25). Since then, well over 1000 cases have been documented (7,8, 13,14,16,17,22,24,25,27,31,39,40,51,53,60,64,78,79,90,92–94,110,117, 124,133,134). About 1 per 10,000–15,000 individuals are diagnosed with Prader-Willi syndrome (10). Updated reviews are those of Cassidy (25,27) and Nicholls (92,93).

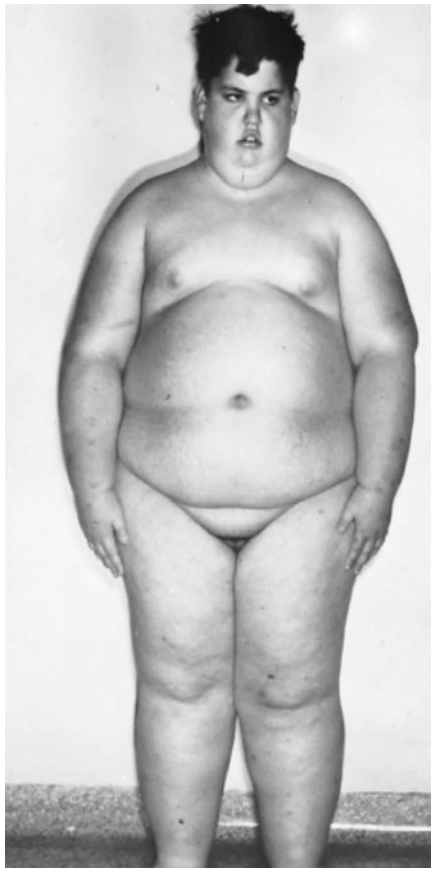


Fig. 11–22. *Prader-Willi syndrome.* Marked obesity, small hands, and hypoplastic genitalia. (From MM Cohen Jr and RJ Gorlin, Am J Dis Child 117:213, 1969.)

Etiology. Cytogenetic and molecular genetic issues have been addressed by numerous authors (3,4,9,12,16,18,28,37,38,41–44,47,54,55, 61, 63, 67,68,73,75,80–82,85,88,90,92–94,96,98,101,103,105–114,118, 124,126,128,132). Of three subgroups of 15q11–q13, the proximal region contains genes that are expressed from the paternally inherited chromosome only. Mosaicism has been detected using FISH technic (112). Multiple molecular genetic mechanisms lead to Prader-Willi syndrome by abrogating one or more genes in this region. Each of these imprinted genes is expressed in the brain. About 70% of patients have a recognizable deletion of 15q11.2. Most other cases involve maternal disomy (86). At least 1% have very small 20–100 kbp deletions, including virtually all families with recurrences (25). Mitotic duplication of the maternal chromosome 15 is another mechanism (42a).

A number of genes in the Prader-Willi region have been described. The promoter elements at SNRPN (small nuclear ribonucleoprotein N) likely play a key role in initiating imprint switching during spermatogenesis. Other genes include ZNF127, IPW, PAR1, and PAR5 (25,27,73, 92,93,96). Another gene, NDN (necdin-encoding gene), is expressed at high levels in the brain and may contribute to abnormal brain development (85). Triplication of the region has been noted (119a).

Ohta et al (96) identified three sporadic cases of Prader-Willi syndrome with an imprinting mutation (IM) but no detectable mutation in the imprinting center (IC). In these cases, the syndrome may arise from developmental or stochastic failure to switch the maternal-to-paternal imprint

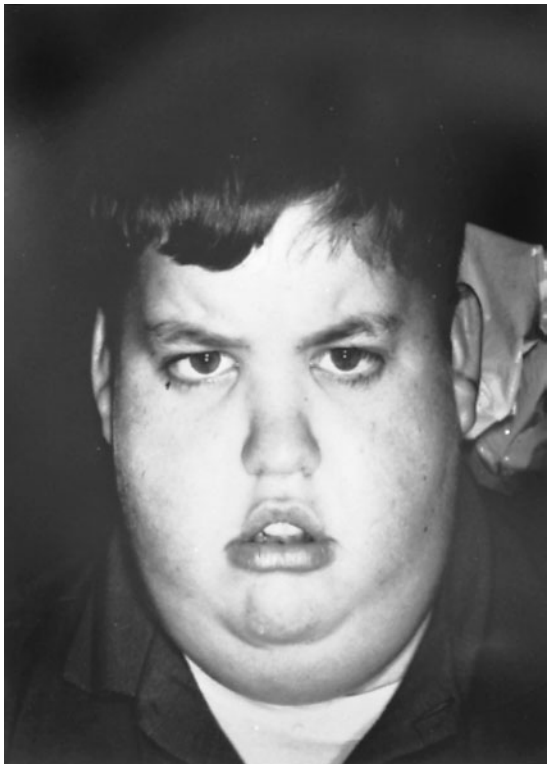


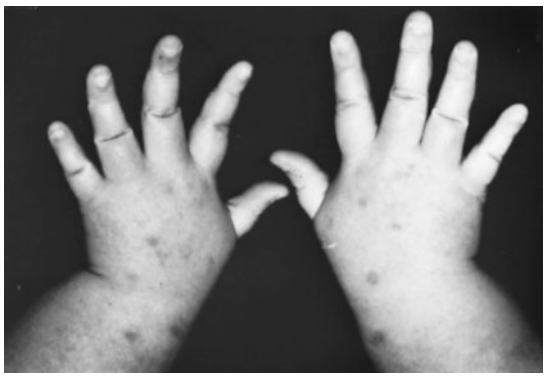
Fig. 11–23. *Prader-Willi syndrome.* Facial obesity, narrow bifrontal diameter, almond-shaped eyes, characteristic mouth. (From MM Cohen Jr and RJ Gorlin, Am J Dis Child 117:213, 1969.)

during spermatogenesis (113a). The *P* gene in the distal region of 15q11–q13 is non-imprinted and codes for tyrosinase positive albinism, and its deletion probably causes the hypopigmentation found in Prader-Willi patients (25,116). First cousins have been reported, one with Prader-Willi syndrome, the other with Angelman syndrome (31).

Familial occurrences and recurrence risk. Familial occurrences of Prader-Willi syndrome have been recorded a number of times (30,35,41,53,55,63,84,98) and concurrence of Prader-Willi and Angelman syndromes has also been noted (50,114). Recurrence risk is less than 1 per 1,000. Kennerknecht (70) estimated an overall recurrence risk of 0.4%, but indicated that if two or more sibs were affected, the risk in the next sib would be 50%.

Genotype–phenotype correlations. Genotype–phenotype correlations have been observed. Lower birth weight has been noted in deletion

Fig. 11–24. *Prader-Willi syndrome.* Disproportionately small hands. (From MM Cohen Jr and RJ Gorlin, Am J Dis Child 117:213, 1969.)



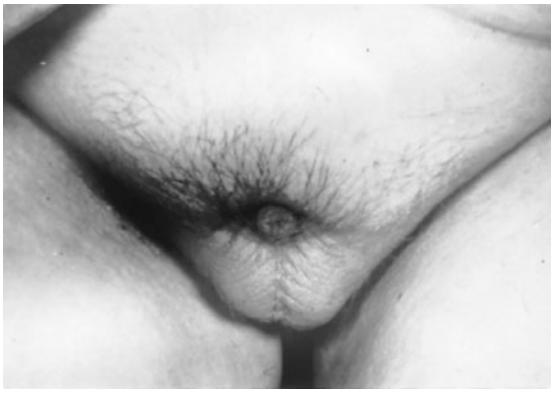


Fig. 11–25. *Prader-Willi syndrome.* Hypoplastic genitalia with penis buried in fat. (From MM Cohen Jr and RJ Gorlin, Am J Dis Child 117:213, 1969.)

patients and shorter birth length in males has been observed in maternal disomy. Cassidy and Schwartz (27) found statistically significant differences with higher frequency in deletion patients of the typical facial appearance, unusual skill with jigsaw puzzles, skin picking, high pain threshold, hypopigmentation, and abnormalities of speech production. Allanson et al (2) found that patients with PWS due to maternal UPD have a longer face, more prominent nose, smaller mouth, and broader and more prominent mandible than those with deletion. Gillessen-Kaesbach et al (46) noted more frequent hypopigmentation and lower birth weight in those with a deletion.

Mitchell et al (90) compared the phenotypes of 43 deletion patients with 79 maternal disomy patients, finding no major clinical differences between the two groups except for more frequent hypopigmentation in the deletion group. Significant sex ratio changes were also observed. The maternal disomy group had a predominance of males (68%). Females with maternal disomy were found to be less severely affected than female deletion patients with respect to length of gavage feeding and later onset of hyperphagia.

Natural history. Individuals with Prader-Willi syndrome have a predictable life scenario. About 7% are premature and 40% are breech deliveries. They have low-normal birth weight, severe hypotonia, and severe feeding difficulties in the newborn period (53). Cryptorchidism and hypogenitalism are noted in males. Otherwise, no significant dysmorphology is found (53). The severe hypotonia requires prolonged and special feeding techniques (22,24,25,27,31,39,40,53,90,91). Hypotonia may be the only finding in infancy (89). Failure to thrive may be a problem during the first 6–12 months (22,24,25,27,58,95). Gradual improvement in muscle tone during the last half of the first year heralds an improved rate of weight gain (7,22,24,25,27,53,133,134). By 3 years, significant weight gain has occurred and delayed milestones are usually recognized (53). Unusual facial appearance, poor linear growth, and small hands and feet are noted at this time (53). Between 3 and 5 years, obesity and mild behavioral problems begin (53). Between mid-childhood and adolescence, obesity becomes more prominent, as do behavioral problems such as stubbornness, temper tantrums, and violent reactions (53,133,134). No signs or few signs of puberty exist (51). During teenage years and young adulthood, severe obesity often causes cardiorespiratory problems (51) and an increased frequency of diabetes mellitus (51,133,134). The teenager and/or adult with Prader-Willi syndrome may become unmanageable, causing much despair in the family (22–25,27,51). Diagnosis at any time, but particularly before 5 years of age, can potentially lead to effective treatment by weight reduction and control with an ameliorating effect on many problems (22,24,25,27). Wharton et al (127) reported six patients with dramatic acute gastric distention. Old age has been discussed by Carpenter (21).

Growth. Low-normal birth weight and failure to thrive are characteristic (53). Proportionate short stature by adulthood is usually in the mild to moderate range (13,51,58). Adult males have an average height

of 61 in., and adult females, 59 in. (8). No consistent hormonal basis for short stature has been identified (8,100).

A number of anthropometric studies have been carried out (13–15, 19,62). Foot length tends to be smaller than hand length, and both hand and foot lengths frequently fall within the normal range before 10 years of age. As the discrepancy between height age and chronological age increases, hand and foot lengths become proportionately smaller. No anthropometric differences have been found between chromosome 15 deletion cases and nondeletion cases.

Central nervous system and performance. Severe congenital hypotonia is a constant feature during the neonatal period and early infancy. Improvement usually begins during the latter half of the first year (53). Hypotonia is clearly associated with poor fetal activity (74%–85%), breech presentation (22%–40%), and severe feeding difficulties (7,22,24,25,53). Early delays in developmental milestones (i.e., sitting up at 1 year, walking alone at 24–30 months) are also probably related (22–25,27,51,53,104,133,134). Mean IQ is about 54 (6). Various studies, including muscle biopsies, nerve conduction times, and electromyelograms, have either been normal, inconsistent, or nonspecific, which suggests that the hypotonia is probably central in origin (8,22,24,25,27).

Sleep disorders are common: daytime somnolence (50%), snoring (45%), restless sleep (40%), cataplexy (15%) (22–25,27). Mental retardation is usually mild (63%) to moderate (31%), but in 3%–8%, intelligence appears to be normal (22–25,27,51,109). Avoidance of obesity through early diagnosis and treatment may improve ultimate intelligence. Seizures occur in 16%–20%, but are usually not a chronic problem (7,53). Febrile convulsions are not unique to Prader-Willi syndrome but can be found in any neurodevelopmentally handicapped individual (131). Speech difficulties are found in almost all children (22,87,133). Visual motor discrimination skills are better than auditory verbal processing skills (34).

It is ironic that Prader-Willi children are known for their severe behavior problems when they are frequently loving, placid, and pleasant to be around. However, it is the behavior problems that cause families the most concern. Large, out-of-control, and not particularly hypotonic adolescents and adults can be very destructive and dangerous to themselves (22,33,51,53,133,134).

Decreased pain sensitivity, particularly of the skin, may explain why ordinary cuts and bruises can be picked at constantly by Prader-Willi individuals without apparent pain (22–25,27,51,53). Chronic sores and scarred skin lesions are found in all children beyond mid-childhood. Nasal bleeding secondary to chronic picking can be a difficult problem (51). Rectal picking with bleeding has been noted (5).

Albinoidism. Some degree of oculocutaneous albinoidism is common (11,32,56,130). Misrouting of retinal-ganglion fibers at the optic chiasm, typically seen in albinos, may be responsible for the strabismus found in Prader-Willi individuals (32). The hypopigmentation is due to deletion of the *P* gene (116).

Obesity. Excessive weight is the major complicating factor in Prader-Willi syndrome (83a). Once severe hypotonia remits, the child begins to gain weight at an excessive rate (53,95). Even before clinical obesity is evident, skinfold thickness indicates excessive adipose tissue (14). Obesity is usually obvious between 3 and 5 years (53) and has a generalized distribution, sparing only the distal finger tips and upper cranium (Figs. 11–22 and 11–24). Voracious appetite or binge eating can be dramatic, but weight gain can occur even on low daily caloric intake (59). Obesity can reach gigantic proportions causing severe cardiorespiratory distress as seen in Pickwickian syndrome (53,79,95,133). Frequent nodding-off or sleeping during normal waking hours and normal activities is typical for older obese individuals with Prader-Willi syndrome (22–25,27,51,79,97). Diabetes mellitus occurs in 4.5%–19% of late-teenage and adult individuals with Prader-Willi syndrome (8,51,79) and seems to be related directly to age and degree of obesity. Insulin is required in about 66%, but with significant weight loss, the need for insulin disappears (51,53). There is some evidence that weight reduction or avoidance of obesity in young Prader-Willi children stabilizes intelligence quotients. Some theorize, and common sense dictates, that effective weight control prolongs life expectancy in individuals with Prader-Willi syndrome (51). Anesthetic risk shows an increased but surprisingly low (2.5%) complication rate considering the obese state of many affected individuals (125).

Sexual development. Cassidy et al (22–25,27) surveyed genital abnormalities and hypogonadism in 105 patients. In general, individuals with Prader-Willi syndrome have few or no signs of pubescence (51). Males have high frequencies of scrotal hypoplasia, cryptorchidism, and micropenis (Fig. 11–25) (51,53,123). When males have any signs of puberty, minimal development of axillary and pubic hair occurs with a slightly higher frequency of demonstrable but scant beard (51).

Hypogonadism, hypogonadotropism, and hypergonadotropic-hypogonadism have been ascribed as causes of faulty sexual development (7,65,66). Testicular abnormalities and oligospermia have also been documented (7,69). Females have similar problems, although usually there is some breast development, and menstrual periods, if they do occur, are usually delayed in onset, irregular, and scant (51). Occasionally, male and female patients have precocious puberty; however, it is almost always incomplete and not true precocious puberty (121). Neither males nor females are fertile (51).

Craniofacial features. Head circumference is usually normal, but the bifrontal diameter is narrow (14,53). These and other measurements have been critically documented (14,15). The eyes are almond shaped (53). Because the medial upper lid hooks sharply downward, the eyes often have a slitlike appearance and an upward slant during infancy (117). Strabismus occurs in 40%–95% (8,53). An open, inverted, V-shaped mouth is usually present in the young child (Fig. 11–23) (22–25, 27,117). Enamel hypoplasia, dental caries, and malocclusion occur with increased frequency (31,38,53,60,75,133). Reduced salivation has been reported (8,22–25,27).

Limbs. The hands and feet are stated to be small (8,13,53) (Fig. 11–24). Although microsomic hands and feet are thought to be present congenitally, they are not usually recognized as such during the first 2 years (53,62). The fingers are short and narrow, but can look wide proximally and tapered distally when obesity becomes significant (22–25, 27,38,53,78,86,104,133). Hudgins and Cassidy (62) found normal-size hands when patients tended to be of normal height.

Skeletal system. Orthopedic and/or osseous problems are common. At birth, talipes (6.4%) and congenital hip dislocation (9.4%) occur with increased frequency (53,133). Later, scoliosis, osteoporosis, and slight increase in fracture rate are often noted (22–25,27,51,53). Delayed bone age can be seen (13,53). Metacarpophalangeal pattern profiles have been used to separate Prader-Willi syndrome from obese non–Prader-Willi controls (13). Skeletal roentgenograms show abnormalities that are both subtle and consistent, but that lack enough specificity to be useful as a major diagnostic tool (75).

Hematologic findings. Three instances of leukemia have been reported (51,52) and one case has been associated with factor XI deficiency (45).

Differential diagnosis. Prader-Willi syndrome should be distinguished from other postnatal-onset obesity syndromes: *Bardet-Biedl syndrome*, *Albright hereditary osteodystrophy, Cohen syndrome,* and Urban-Rogers-Meyer syndrome (120), in which there is a Prader-Willi habitus, with osteopenia, camptodactyly, and mental retardation. The disorder has been described only in males, two of them brothers (99). An X-linked Prader-Willi–like disorder of hypogonadism, gynecomastia, mental retardation, and obesity was reported by Vasquez et al (122). Mental deficiency may be associated with obesity and on occasion with *fragile X* and even with *Angelman syndrome.* Acquired hypothalamic injury from accidents, tumors, or surgical complications may closely mimic Prader-Willi syndrome (25). Syndromal obesity also occurs with paternal dup(7)(q24.3–q27) (115). Other postnatal-onset obesity syndromes have been discussed by Camera et al (20).

Laboratory aids. FISH with probes for 15q11–q13 and a centromeric control probe is the method of choice to detect large deletions or unbalanced translocations in suspected Prader-Willi patients (36,119). Polymorphic marker analysis, using DNA samples from an affected child and a parent, can be used to identify maternal disomy. Differential DNA methylation of maternal and paternal alleles include several genes and DNA markers in 15q11–q13: ZNF127,NDM,PW71, and SNRPN. The most reliable methylation probe is at SNRPN; the maternal allele is completely methylated and the paternal allele is completely unmethylated in all cases. Thus, methylation at SNRPN is the best single diagnostic tool for both Prader-Willi syndrome and Angelman syndrome (3,71,72,92,126).

Pregnancies with diminished fetal activity are candidates for molecular diagnosis by CVS. Other candidates are fetuses in which trisomy 15 or mosaic trisomy 15 have been detected by CVS (28,54,105).

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Cohen syndrome

Cohen syndrome was first reported by Cohen et al (5) in 1973 as an obesity/hypotonia syndrome associated with mental retardation, narrow hands and feet, and characteristic facial appearance consisting of down-slanting palpebral fissures, short philtrum, open mouth, prominent upper central incisors, maxillary hypoplasia, and mild micrognathia (Figs. 11–26 to 11–28). The original report identified male and female sibs and one sporadic instance. To date, well over 100 cases have been recorded (2,3,6–14,16–23,25,27–36,38–43). Some cases have been reported as Cohen-like or resembling Cohen syndrome (1,13,15). In some series, individual cases are suspect, particularly among the sporadically occurring examples (4,10,14,25,27,35). Goecke et al (14) recognized the difficulty in diagnosing sporadic cases because of the wide variability of features among reported patients. Morris et al (24) attempted to divide Cohen syndrome into two separate groups: one with chorioretinal dystrophy, leukopenia, and lack of obesity, the other with classic Cohen syndrome. Norio and Raitta (25) saw no need for such a division and using the criteria of Morris et al (24), case 3 of Cohen et al (5) could not be classified in either category.

The inheritance of Cohen syndrome is autosomal recessive. Affected sibs have been documented frequently (4,5,8–10,13,14,20,24,27,31,35,36), and consanguinity has been noted in a number of instances (20,26,35). Identical female twins were reported by North et al (28). The gene (COH1) has been mapped to 8q22–q23 (18,19,38).

Growth. Newborns have low-normal birth weights, averaging between the 10th and 25th centiles (13,26,35). About 60%–70% ultimately have short stature (26,27), although tall stature has also been documented in a few cases (27,35).

Truncal obesity usually becomes evident between 5 and 12 years of age (Fig. 11–26) (4,5,13). Severe obesity or weight above the 97th centile does not occur, as a rule, and not all patients develop truncal obesity (10,35).

Delayed puberty was first noted by Carey and Hall (4) in 1978. Delayed or absent signs of puberty occur in approximately 80% (27). Precocious puberty was found in the twins reported by North et al (28). About 30% of males are cryptorchid (35).

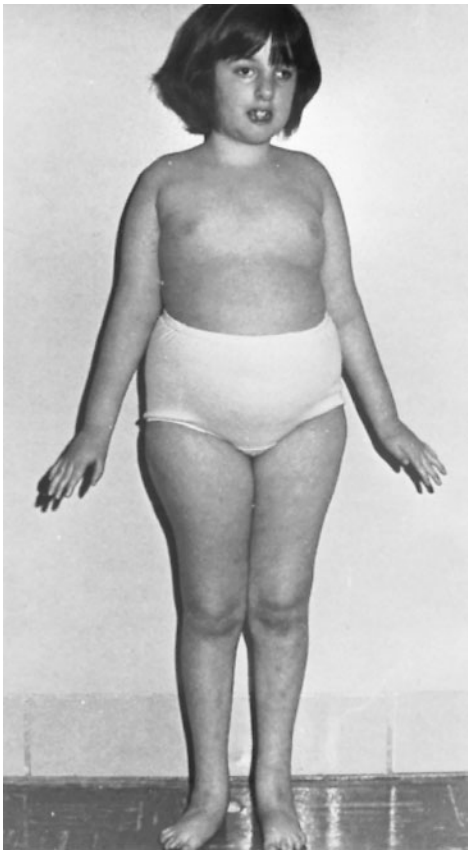

Fig. 11–26. *Cohen syndrome.* Obesity of mid-childhood onset, tapering hands and feet. (From MM Cohen Jr et al, J Pediatr 83:280, 1973.)

Central nervous system and performance. Hypotonia may be present at birth (13). It is usually noticeable in infancy (92%) and may persist into late childhood or early adolescence (4,27). The hypotonia may explain the high frequency of kyphosis and kyphoscoliosis (54%) (35).

Microcephaly is present in 50%–60% (26,27), usually of mild to moderate degree, and may be prenatal or postnatal in onset (14,26). Macrocephaly has been recorded in some patients (10,28). The corpus

Fig. 11–27. *Cohen syndrome.* (A,B) Characteristic facial appearance with mild microcephaly, downslanting palpebral fissures, short philtrum, and open mouth. (From MM Cohen Jr et al, J Pediatr 83:280, 1973.)

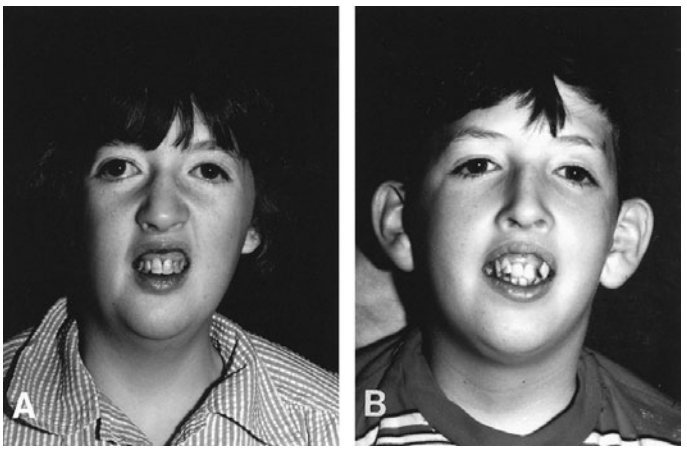

Fig. 11–28. *Cohen syndrome.* Narrow hands and fingers. (From MM Cohen Jr et al, J Pediatr 83:280, 1973.)

callosum is enlarged (17). Autistic behavior may be present up to the age of two years (13). Mental retardation is almost constant, with intelligence quotients ranging from 30 to 80 (26,35). About 6% have minor, nonchronic seizures (27). The demeanor has been noted to be happy, pleasant, and affectionate (5).

Facial features. Open mouth, exposed upper gingiva, and prominent upper central incisors are characteristic (5). The philtrum is short; the upper lip is arched and everted (5,26). Maxillary hypoplasia and mild micrognathia combined with high nasal bridge give the upper two-thirds of the midface a narrow prominence (Fig. 11–27) (5,26,35). The palate is usually high and narrow (97%) (26). The helical rims may be hypoplastic in some cases (26).

Eyes. The palpebral fissures are commonly downslanted (4,5,26,35). Occasionally, iris and/or retinal colobomas may occur with or without microphthalmia (4,5,27). Myopia (46%) and strabismus (52%) are frequent eye findings (27). In one series, 90% had myopia (K. Chandler, personal communication, 2000). Retinal pigmentary abnormalities (or chorioretinopathy) are seen in 80% (4–7,10,27,34,35,39, K. Chandler, personal communication, 2000). ERG is isoelectric and there is peripheral visual loss with some night blindness. The eye findings should never be confused with retinitis pigmentosa; blindness per se has never been noted in Cohen syndrome (26).

Limbs. Cubitus valgus and hyperextensible joints are found in about 50%. Mild syndactyly of the fingers, sometimes of the second and third fingers, occurs in 30%–35% (26,27). Hands are narrow and fingers are thin and long (Fig. 11–28) (4,5,26,27,35). Feet and toes are similarly affected, but less dramatically. Arms and legs are slender, probably secondary to decreased muscle mass (26).

Cardiovascular system. Heart defects have been noted in 10% (35) and may include floppy mitral valve, mitral valve prolapse, pseudotruncus with VSD, and isolated VSD (23,34,35). Norio et al (26) noted significant systolic murmurs in five of six of their cases.

Laboratory findings. Nonsymptomatic congenital neutropenia has been documented in many cases (13,17a,20,26,37). Olivieri et al (30) reported greatly increased neutrophil adhesive capability. Kivitie-Kallio et al (17a) studied 26 patients and found mild-to-moderate granulocytopenia beginning at early age. Massa et al (22) reported a patient with isolated growth hormone deficiency. Okamoto et al (29) found remarkably high levels of urinary hyaluronic acid in three patients and suggested that Cohen syndrome involves a metabolic abnormality in the extracellular matrix. Méhes et al (23) suggested that Cohen syndrome might be a connective tissue disorder. Higgins et al (16) demonstrated pyridoxine responsive hyper-β-alaninemia in one patient. ERG is isoelectric (26).

Differential diagnosis. Cohen syndrome is very distinctive; it is usually easy to separate from other postnatal-onset obesity syndromes. Most cases are not correctly diagnosed until mid-childhood to early adolescence (35). It is important to note that open mouth and prominent upper central incisors often occur in mouth-breathing (or adenoid) facies independently of Cohen syndrome. Furthermore, upper central incisors are prominent in all children from mid-childhood to the onset of adolescence because of the naturally occurring contrast between permanent and deciduous teeth in the mixed dentition. Every patient with mouth-breathing facies and either mental retardation or obesity does not have Cohen syndrome per se, nor does every child with obesity and mental retardation who cannot be diagnosed as having one of the other well-delineated postnatal-onset obesity syndromes.

Cohen syndrome has also been called Pepper syndrome (26) and Mirhosseini-Holmes-Watson syndrome (37); two sibs in the latter category had tapetoretinal degeneration. Norio and Raitta (25) indicated that Mirhosseini-Holmes-Watson syndrome is the same as Cohen syndrome or at least an allelic disorder. Some cases of Cohen syndrome have been misdiagnosed as *Prader-Willi syndrome, Marfan syndrome, Sotos syndrome,* hypothyroidism, minimal brain dysfunction, and most frequently as mental retardation of unknown cause (26). Hyperhyaluronicaciduria is a characteristic finding in *Werner syndrome*.

References (Cohen syndrome)

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Camera-Marugo-Cohen syndrome

A syndrome of neonatal hypotonia, mental retardation, short stature, truncal obesity, gynecomastia, hypogonadism, camptodactyly, clinodactyly, and valgus deformity was first reported in 1979 by Urban et al (3) and Vasquez et al (4). Other examples are those of Camera et al (1) and Lambert et al (2).

The facies is characterized by narrow forehead, hypertelorism, and blepharoptosis.

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Börjeson-Forssman-Lehmann syndrome

Börjeson et al (3), in 1962, reported a syndrome of characteristic facies (Fig. 11–29), mental retardation, obesity, hypotonia, and hypogonadism.

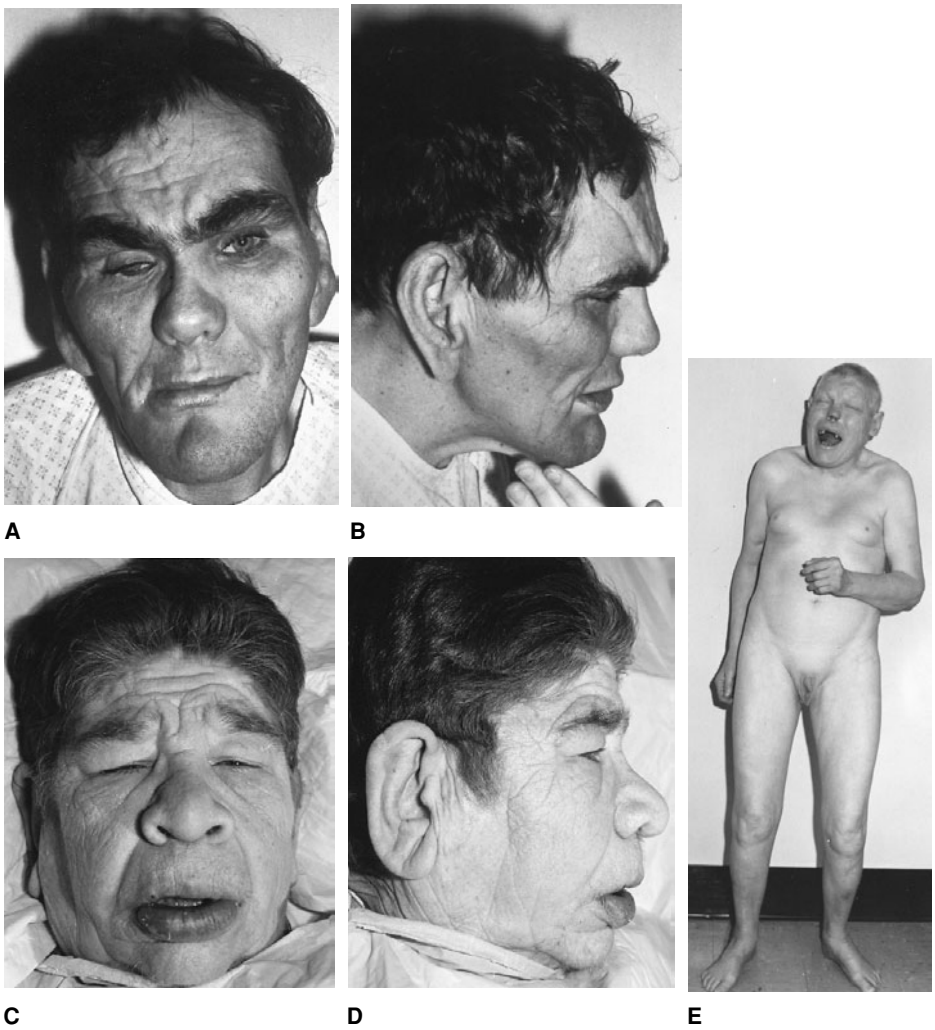

Fig. 11–29. *Börjeson-Forssman-Lehmann syndrome.* (A–D) Characteristic coarse facial appearance with microcephaly, prominent supraorbital ridges, deeply set eyes, nystagmus, ptosis, and large ears. (E) Characteristic facies, gynecomastia, lack of secondary sexual development. (A,B from HH Ardinger, Am J Med Genet 19:653, 1984.)

The syndrome is X-linked with variable expression in female heterozygotes (1,5,7,12,16). The gene map locus is Xq26–q27 (8–11,13). More than 35 cases have been reported (1,3–13,16). Over 80% of affected males are short and at least 60% are obese. These findings may be secondary to hypogonadism.

All affected males have a coarse facial appearance characterized by microcephaly, prominent supraorbital ridges, deep-set eyes, nystagmus, ptosis, and large ears (1,3,12,16) (Fig. 11–29A–D).

Radiographic studies have shown thickened calvaria, narrow cervical spinal canal, Scheuermann-like vertebral changes, mild epiphyseal dysplasia, delayed closure of radial and ulnar epiphyses, and short distal phalanges (1).

Hemizygotes have moderate to severe mental retardation. About 50% exhibit seizures and all have hypotonia. Electroencephalographic study has shown a paucity of alpha rhythms (1). CT scans show mildly dilated lateral ventricles. Female heterozygotes may have somewhat dull intelligence.

Hemizygotes have small atrophic or nonpalpable testes that descend late, small penis, and hypoplastic prostate. Secondary sexual development is poor and puberty is delayed until late in the second decade (1,12). Gynecomastia is frequent (Fig. 11–29E). Robinson et al (12) noted twin female heterozygotes with ovarian dysfunction.

Dermatoglyphic patterns of an affected male included bilateral I4 whorls, double loop hypothenar patterns, Sydney lines, and fibular arch pattern (7).

One case has been insufficiently documented (2) and another case has been erroneously identified (14). Differential diagnosis includes *Prader-Willi syndrome, Coffin-Lowry syndrome,* and *Biedel-Bardet syndrome*. In spite of the severity of their cases, we believe that the patients reported by Verloes et al (15) have Börjeson-Forssman-Lehmann syndrome.

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Chapter 12
Hamartoneoplastic Syndromes

Acanthosis nigricans

Although Pollitzer (62) and Janovsky (44) described acanthosis nigricans (AN) in 1890, it was Pollitzer (63), in 1909, who made the first extensive study of cases previously reported and who emphasized the relationship of the skin disease to abdominal malignancy. During the next 85 years, over 1200 cases have been reported. Several excellent surveys (11,76) have been carried out, probably the greatest contributions being those of Curth and coworkers (19–23).

Acanthosis nigricans is not rare, being seen in at least 7% of children and more often noted in African-American children (13%) (81).

Throughout the years, AN has been classified in various ways, with all classifications being based on the clinical presentation and the association of AN with other conditions. The traditional classification divides AN into benign and malignant forms. It should be emphasized that this division is improper because the skin changes in both the so-called benign and malignant forms are histologically identical, with no cellular evidence of malignancy. The division was established to stress the association of AN with internal malignancy, especially gastrointestinal adenocarcinoma. Presently there is a tendency to divide AN into only two groups, the first associated with an internal malignant neoplasm and the second group composed of several entities that have in common their association with insulin resistance (30,39).

We believe that a division of AN according to clinical presentation can aid in the proper identification of the underlying associated conditions. In reviewing the literature, the following associations of AN have been identified:

A. Neoplastic association
B. Nonneoplastic association
   (1) Insulin-resistant types
      a. Type A syndrome (insulin receptor; includes leprechaunism) (HAIR-AN syndrome)
      b. Type B syndrome (antibodies)
      c. Type C syndrome (postreceptor level)
      d. Obesity
      e. Other endocrinopathies (includes Prader-Willi syndrome)
   (2) Congenital syndromes (Crouzono-dermo-skeletal dysplasia syndrome, Beare-Stevenson syndrome, thanatophoric dysplasia, SADDAN syndrome)
   (3) Autosomal dominant type
   (4) Drug-induced type
   (5) Miscellaneous types (idiopathic or isolated reports of association with other diseases or syndromes)

The nonneoplastic association types occur with greater frequency than the neoplastic association form. The discussion that follows will present, first, the clinical characteristics of AN and then a summary of each of the associated conditions.

Skin. The typical findings are dark-brown, smooth, hyperkeratotic papules, ranging from slight discoloration to cases in which the entire skin can be affected. In approximate order of frequency of pigmentation and papillomatous changes are the axillae, nape and sides of neck, genitalia, groin and inner thighs, umbilicus, perianal area, antecubital and popliteal surfaces, periorbital areas, and areolas (3,55). In addition to these changes, there is exaggeration of normal skin markings. The axillae or neck usually become pigmented before other areas are involved (Fig. 12–1).

The palms may be rugose (tripe palms) (6,16,17,49,65). In binary combination the phenomenon is especially associated with pulmonary carcinoma. When seen in binary combination with gastric carcinoma, acanthosis nigricans is usually present (34,59).

Clinical manifestations also include florid cutaneous papillomatosis and the sign of Leser-Trélat (multiple, rapidly growing seborrheic keratoses) (92). These manifestations may occur individually or in association with each other (2,27,75).

The major histologic changes observed are marked deposition of surface keratin with abnormal stratum corneum. The name acanthosis nigricans is not well chosen, as thickening of the epidermis is variable. In fact, atrophy is not uncommonly seen. The dark color is not related to increased melanocytes but to the proliferation of keratinocytes (30,55,68,73).

Most patients with acanthosis nigricans exhibit insulin resistance (28a,70). This may be due to a defect of the insulin receptor or in the number of receptors (56). This stimulates pancreatic islet B cells to produce excess insulin to compensate for the defect. The insulin binds to insulin receptors or insulinlike growth factor receptors which have tyrosine kinase activity. This induces cellular activity. Both fibroblasts and keratinocytes have insulin receptors and IGF receptors. There is resultant increased glycosaminoglycan deposition in the dermis and focal acanthosis of the epithelium. This results in papillomatosis and hyperkeratosis.

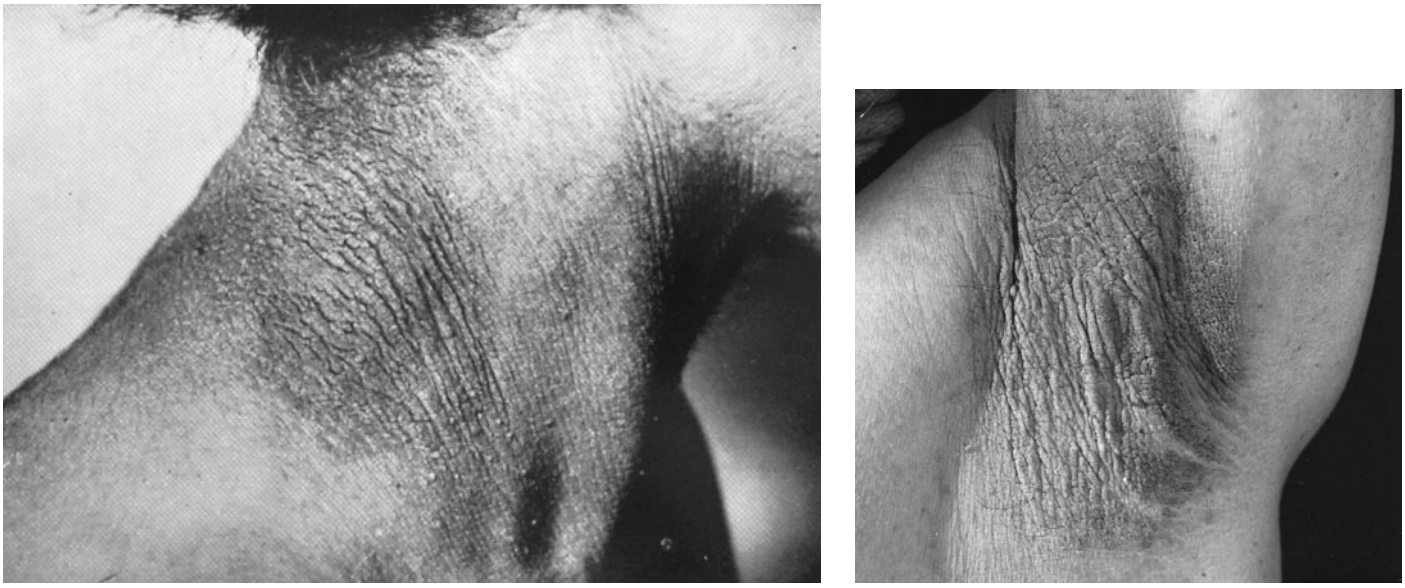
Pathogenesis in the case of malignant tumors is less clear, but it is assumed that growth factors or receptors (EGFR, TGFα) produced by the adenocarcinomas stimulate proliferation and increase resistance to apoptosis in keratinocytes and fibroblasts. These have insulinlike activity at the cell receptor level that effects the same end (4,25,54,76).

Nicotinic acid produces insulin resistance by activity at the cell receptor level (79).

Insulin receptors are found in ovarian stroma. In these cells, insulin is synergistic with luteinizing hormone. It is assumed that during puberty, elevated levels of insulin cause hyperandrogenemia. The more obese these patients, the higher the androgen levels. Hypothyroidism and its association with AN is probably effected through the attendant obesity (60).

Oral manifestations. Possibly the earliest description of oral lesions in AN was made by Pollitzer (63) in 1909. Masson and Montgomery (52) and Fladung and Heite (28) suggested that at least 50% of patients with the neoplastic association form have oral lesions. On the other hand, Sedano and Gorlin (77), on the basis of a survey of over 200 cases of the neoplastic association form, think that a truer value is about 30%–40%. A similar figure was reported by Brown and Winkelmann (11). Unfortunately, the oral mucosa is seldom thoroughly inspected in the course of a general examination.

Of all oral tissues, the tongue and lips are involved most frequently and to the greatest degree (58,85). The dorsum of the tongue, or at times the lateral border, exhibits hypertrophy and elongation of papillae. These give the tongue, marked by deep fissures or furrows, a shaggy or prickly appearance. In addition, one may see papillomatous growths studding its surface (52,63). In contrast to the skin lesions, the growths are rarely pigmented (11).



A B

Fig. 12–1. *Acanthosis nigricans*. (A) Pigmentations and papillomatosis of cervical region associated with gastric adenocarcinoma. (B) Pigmentation and papillomatosis of axillary area associated with gastric adenocarcinoma. (A from HO Curth, New York, New York.)

The lips, especially the upper, may be markedly enlarged and covered by filiform or papillomatous growths. These are especially marked at the angles of the mouth (19,52,63) (Fig. 12–2).

The buccal mucosa is usually less severely involved (2,55,86). There is generally a diffuse unevenness of its surface and a velvety white appearance. Occasionally, single fungiform growths are observed (19,52). The palate may be similarly affected (63). The gingiva, especially the interdental papillae, may become so much enlarged as almost to cover the teeth, resembling idiopathic fibromatosis (2,55,86). The connective tissue in these areas is well vascularized and with elongated papillae. Oral lesions are more deeply pigmented than the normal mucosa.

There is insufficient evidence to suggest the frequency of oral involvement in the nonneoplastic associations of the disease, but it would not appear to be great (11,48,84), Fladung and Heite (28) estimating 15%.

Malignant neoplasia. Curth and coworkers (19,22) and Rigel and Jacobs (71) presented impressive evidence that about 75% of the associated tumors are abdominal adenocarcinomas, of which almost 60% arise in the stomach. Other adenocarcinomas, such as those of uterus (3), pancreas, intestines (86), and, in a smaller percent, bile duct (67), bladder, lung (71), and breast (56), can be associated with AN. These carcinomas have a high degree of malignancy and prognosis is very poor.

Although most patients in this group are middle-aged or older, younger patients have been described (76). The extent of cutaneous and mucosal involvement is greater than in other associations.

The mortality rate is 100%, the average survival period after discovery being less than 2 years. Brown and Winkelmann (11) and Ackerman and Lantis (1) and others (43) argue that, although adenocarcinomas predominate, other tumors such as lymphomas may be part of the neoplasia-associated form (57). Garrott (33) suggested that when AN is associated with osteosarcoma, the distribution of skin lesions is different (extensor surfaces) and it affects young individuals.

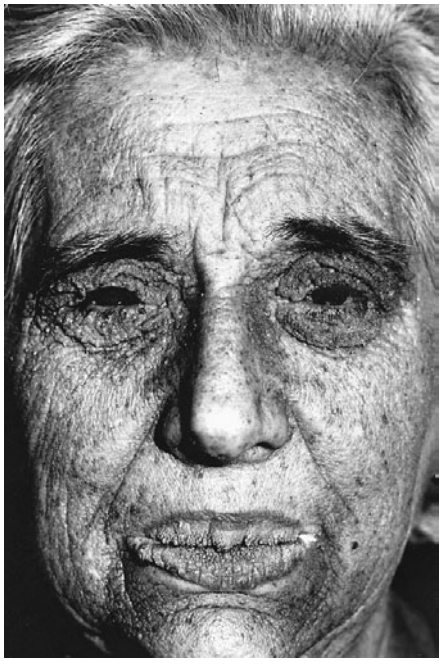
Involvement of the skin may precede, accompany, or follow the detection of the cancer. In about 20%, AN precedes the appearance of the malignancy by up to 16 years. It parallels the cancer in proportion to the degree of spread; it may regress with radiation therapy or surgical removal of the tumor and may reflourish with recurrence of the adenocarcinoma (19,22,46). Generalized skin hyperpigmentation and pruritus occur in about 40% of neoplastic-associated type cases (11,38,55,76).

Other mucosae, such as vaginal, esophageal, conjunctival, laryngeal, and pharyngeal, can also be involved with papillary lesions (76,86).

Insulin-resistant types. This group is composed of conditions associated with AN and characterized by tissue resistance to the action of insulin (5). Patients with insulin resistance have been classified into *type* A (HAIR-AN syndrome). *H*yper*A*ndrogenism, *I*nsulin *R*esistance, and AN characterize this condition, observed mostly in adolescent or young females (5). Virilization, polycystic ovaries, and accelerated early growth with coarse features are part of the clinical findings. Five percent of female patients with hyperandrogenism assessed for hyperinsulinemia when fasting and after oral glucose administration have been found to present this syndrome (31). This variety is due to genetic defects in insulin receptor pathway (30). The vulva is most often (55%) affected by AN in this group, less often the axillae (35%) or neck (30%) (37). Leprechaunism also falls into this type. *Type B* is observed in older females with autoimmune disorders in which insulin resistance is due to circulating autoantibodies directed against the insulin receptor. Recently, a third variety has been described, *type C*. The clinical findings are similar to those found in type A, but in type C the insulin resistance seems to be located at postreceptor levels. The latter has been occasionally observed in men (32). Furthermore, Ritchie et al (72) have reported the association of AN, insulin resistance, hypogonadotrophic hypogonadism, hyperprolactinemia, and multiple organ-specific antibodies in a brother and sister. An excellent review is that of Rendon et al (69).

Seemanová et al (78) reported a 5-year-old boy with protruding eyes, puffy eyelids, ptosis, divergent strabismus, downslanting palpebral fissures, large ears, retrognathia, macrostomia, prominent everted lips, hypotonia, macrosomia, and acromegaloid signs with big hands, feet, ears, and penis. The child also had fasting hypoglycemia, dry and curly scalp hair, and marked AN of skin, neck, axillae, inguinal area and abdomen. Fibroblast cultures showed insulin binding in the normal range but a decreased number of insulin binding sites.

Obesity. This variety is almost always observed in young female patients where receptor and postreceptor mechanisms are responsible for the insulin-resistant state (31,50,51). Hud et al (42) found that 75% of an adult obese population had AN, correlating with the severity of the obesity, especially in African-Americans.



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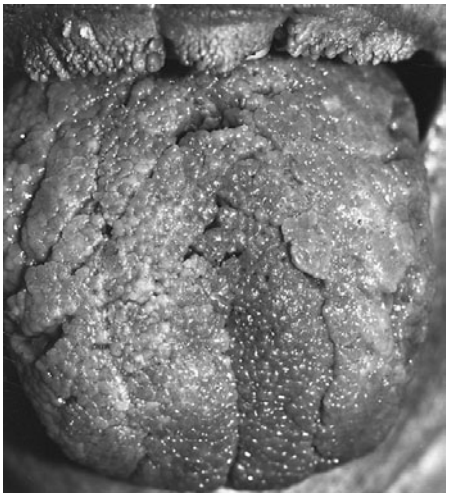

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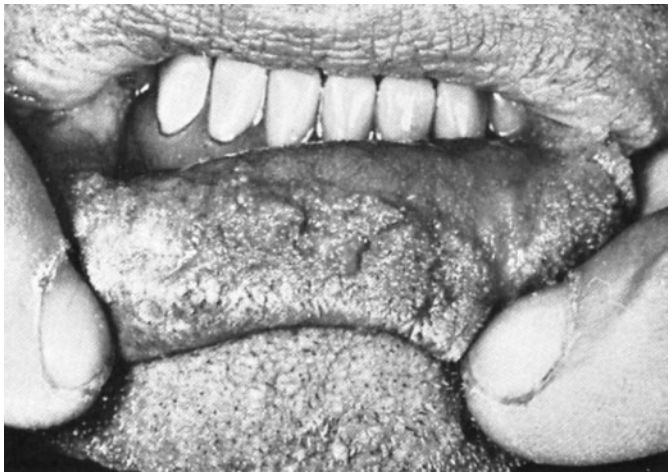

C

Fig. 12–2. *Acanthosis nigricans*. (A) Extensive papillomatosis around eyes and lips. Patient had advanced gastric carcinoma. (B) Matlike thickening of dorsum of tongue. (C) Thickening of labial mucosa and papillomatosis. Pigmentation of oral mucosa is characteristically absent. (A,B courtesy of K Wolff, Vienna, Austria. C courtesy of A Proppe, Kiel, Germany.)

Other endocrinopathies. AN occasionally associated with a variety of other endocrinopathies may reflect the insulin resistance frequently observed in those disorders. The endocrinopathies have included *lipodystrophic diabetes* (13), adrenogenital syndrome (87), Cushing syndrome, acromegaly, Addison disease, Alström syndrome (36), Edmonds syndrome (36), Stein-Leventhal syndrome, *Prader-Willi syndrome* (69), ovarian hyperthecosis, and hyper- or hypothyroidism (11,12,21,30,69). Diabetic patients with insulin resistance may also present AN (7,14).

Mendenhall (53) described two sisters and a brother derived from first-cousin parents. They had unusual facies with marked prognathism, premature aging, precocious eruption of both primary and secondary dentitions with dysplastic teeth, thickened nails, hirsutism, AN, abdominal protuberance, insulin resistance, diabetes mellitus, and phallic enlargement in the male. Pineal hyperplasia was found at necropsy (66). West et al (88,89) reported similar findings in a brother and sister. This is called *Robson-Mendenhall syndrome*. Brown and Winkelmann (11) described two patients with malignant pinealoma and AN.

Congenital syndromes. AN has been observed in patients with *Bloom syndrome, Crouzono-dermo-skeletal dysplasia, thanatophoric dysplasia, and SADDAN syndrome*, among others (20,21,69).

Association of AN and Crouzon-like syndrome was first briefly pointed out by Curth (20) in a dermatology congress without actual case presentation. At least two dozen cases have been published in which this association is fully documented (9,35,41,47,68,82). Meyers et al (54), in 1995, reported that Crouzon-like syndrome and acanthosis nigricans is due to a mutation in the fibroblast growth factor receptor 3 (FGFR3) transmembrane domain mutation, Ala391Glu. The same finding was reported by Wilkes et al (90) in 1996. This is now called *Crouzonodermoskeletal syndrome*.

Beare-Stevenson syndrome is characterized by AN with cutis gyrata, craniosynostosis, cleft palate, hypodontia, and other defects (6,8,80). Przylepa et al (64), in 1996, reported two different mutations in fibroblast growth factor receptor 2 (FGFR2) in patients with the Beare-Stevenson syndrome. In three sporadic cases, a novel missense mutation was found causing an amino acid to be replaced by a cysteine. Two had the identical Tyr375Cys in the transmembrane domain and one had a Ser372Cys mutation in the carboxyl-terminal end of the linker region between the immunoglobulin III-like (Iglll) and transmembrane domains.

Baker et al (4), in 1997, reported an Arg248Cys mutation in the extracellular region of FGFR3 in two long-term-survival patients with

thanatophoric dysplasia type 1 and acanthosis nigricans. The reader is also referred to *SADDAN syndrome*.

Autosomal dominant type. Genetic studies have revealed that in some families a nonneoplastic type of AN exhibits irregular autosomal dominant inheritance (24,28,45,83). This variety manifests as a genodermatosis resembling ichthyosis hystrix, which may be present at birth or may begin later, either in childhood or, more often, at puberty, at which time it becomes more active.

Drug-induced type. The ingestion of diethylstilbestrol or nicotinic acid, or even topical application of nicotinic acid, may occasionally induce the development of AN (26,61,76). About 25% of those on nicotinic acid therapy for hypercholesterolemia for over six years will develop AN (79). AN can appear following corticosteroid therapy (59) or heroin use (79). AN has been seen at the site of insulin injections (29).

Miscellaneous types. A variety of conditions have been sporadically reported associated with AN, such as lupoid hepatitis, pemphigus vulgaris (18), and *hyperphosphatasemia (juvenile Paget's disease of bone)* (74).

Differential diagnosis. Regarding endogenous pigmentation, one should consider Addison's disease, arsenic poisoning, and hemochromatosis, but in none of these conditions is there an associated papillomatosis. Ichthyosis hystrix, *Cowden syndrome*, bromoderma, pemphigus vegetans, *hyalinosis cutis et mucosae*, condyloma acuminatum, and hairy tongue must all be excluded. In Afro-Americans, dermatosis papulosa nigra should be ruled out. Hirschowitz et al (40) described AN in a syndrome of nerve deafness, absent gastric motility, small intestine diverticulitis, and progressive sensory neuropathy. Autosomal recessive inheritance appeared likely. A generalized cutaneous papillomatosis similar to AN, including oral mucosa and palmoplantar surfaces, with no associated internal malignancy and starting at age 63, has been described in an Italian male (93).

Laboratory aids. Abundant deposits of glycosaminoglycans (GAGs) consisting mainly of hyaluronic acid have been found in the papillary dermis of lesions of AN patients with polycystic ovaries and insulin resistance (10). Normal amounts of GAGs were found in nonaffected skin of the same patient (91).

References (Acanthosis nigricans)

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Cowden syndrome (multiple hamartoma and carcinoma syndrome, Lhermitte-Duclos disease)

The syndrome of multiple hamartomas, first described in detail by Lloyd and Dennis (48) in 1963, has its name derived from an affected individual. However, Costello (19), in 1941, reported the skin lesions in a patient who Brownstein et al (12) later documented with the disorder. Another early example is that of Witten and Kopf (89) in 1957. At least 200 cases of the syndrome have been published, emphasizing its hamartomatous character and delineating its principal involvement of the skin, gastrointestinal tract, breasts, and thyroid (Figs. 12–3 to 12–5). There are several excellent reviews (7,23,24,27,38,48,49,53,66,71,75). The frequencies of various abnormalities found in Cowden syndrome are listed in Table 12–1.

Inheritance is autosomal dominant with complete penetrance and variable expressivity (29,65,75). There is an excess of affected females (39). Anticipation was demonstrated with greater severity and earlier onset in each succeeding generation (39). Nelen et al (59) mapped the gene for Cowden syndrome to 10q23.3. Padberg et al (62), in 1991 and Sutphen et al (76), in 1999, showed that Lhermitte-Duclos disease is a component of Cowden syndrome. Liaw et al (46) and Marsh et al (54), in 1997, demonstrated that Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome were allelic, both being due to mutations in PTEN, a tumor suppressor gene (55). One sometimes sees examples of both conditions in one family (64a,92). The PTEN gene is responsible in embryonic development for organizing the relationship among different cell types (46,50,51,60,64). The gene encodes a dual specificity phosphatase that plays a broad role in sporadic human malignancy as well (23). The mutations, although scattered over the entire length of the gene, often involve exon 5 (55), in which a hot spot has been noted (73), but there is no clear cut genotype-phenotype correlation (60a). Diagnostic criteria have been discussed by Eng (23a) (Table 12–2).

Facies. Although head circumference is increased in 45% (39,75), the face is most remarkable for the large number of skin (mostly trichilemmomas) and oral (fibrous hyperplasia) hamartomata (vide infra). Adenoid facies has been present in some patients (20,48).

Skin. Mucocutaneous abnormalities are present in 99% of the cases (23,49,75). Age of onset of the dermatologic lesions is not well documented; however, they are usually noted by the patient at the end of the second or third decade (71). Typical lesions seen in 85% are trichilemmomas. They are lichenoid or papillomatous papules and small

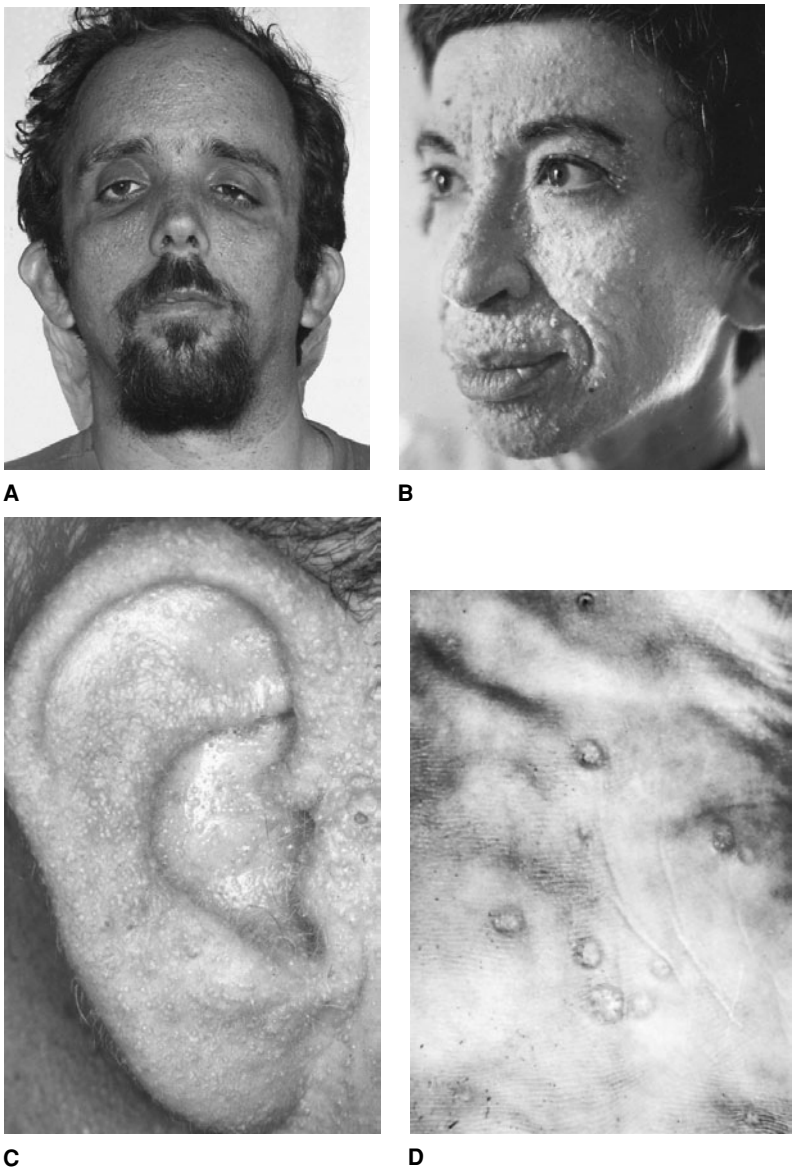

Fig. 12–3. *Cowden syndrome*. (A,B) Flesh-colored keratotic papules, particularly around eyes, nose, and mouth. Compare facies. (C) Ear involvement. (D) Punctate hyperkeratoses of palms. (B courtesy of M Wortzel, Camden, New Jersey. C from WC Gentry et al, Birth Defects 11(4):137, 1975. D from M Rosenbluth, Periodontics 1:81, 1963.)

nodules, located primarily on and around the eyelids, alae nasi, nasolabial folds, mouth, pinnas, lateral neck, glabella (85%), and the dorsa of hands and forearms (70%) (8,29,33,41,48,87) (Fig. 12–3A–C). They are numerous, some individuals having 50 or more. Punctate keratoses are present on the palms and soles (50%) (9,29,33,71) (Fig. 12–3D).

The microscopic features of the skin lesions have been reported in detail by several authors (12,72–74). Hair follicle hamartomas, with most lesions showing the pattern of trichilemmomas, are composed of large, pale glycogen-rich epithelial cells centrally surrounded by a single layer of smaller palisaded cells. A few display features intermediate between those of trichilemmomas and inverted follicular keratoses, whereas others have characteristics intermediate between trichilemmoma and tumor of the follicular infundibulum. Some specimens show nonspecific verrucous acanthomas or were not diagnostic. Any patient with two or more trichilemmomas should be considered to have Cowden syndrome (64). Trichilemmomal carcinoma has been described in one case (61). Dermal fibromas (acrochordons) are also found, characterized by interwoven collagen bundles with a laminated or tortuous appearance, embedded in abundant mucin (75).

Subcutaneous lipomas (9,11,29,40,68,70,71,85) have been noted in 25% and cutaneous hemangiomas (3,6,40,68,71,84,85) in 35%.

Squamous cell carcinoma of the skin of the nose (9) and basal cell carcinomas of the skin of the face (5) and perianal skin (15) have been reported.

Breasts. About 75% of females have fibrocystic disease or fibroadenomas, while another 25% have breast cancer, bilateral in about 35% (6,13,32,39,80). Specific references include: fibroadenomas (13), virginal hypertrophy (48,71), fibrocystic disease (4,48,70,71), ductal papillomas (71) and intraductal adenocarcinomas (6,13,29,48,52,65,71,77, 84,85,88). About 65% have nodal metastases. Adenocarcinoma of breast in males has been reported (28,55). Both carried germline PTEN mutations. Gynecomastia and fibrocystic disease have been noted in males.

Brain. Macrocephaly, ataxia, seizures, tremors, increased intracranial pressure, diadochokinesia, and dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease), a rare disorder of the cerebellum, is characterized by global hypertrophy of the folds, thickening of the molecular layer, enlargement of the Purkinje cells, and granular layers with astrogliosis (61,70,81). A number of examples have clearly been associated with Cowden syndrome (1,42,47,57,80,82,87). Padberg et al (58), Albrecht et al (1), Eng et al (26), and Wells et al (87) demonstrated that Lhermitte-Duclos disease was part of Cowden syndrome. See Albright et al (1) for survey of cases. There may be massive enlargement of the cerebellum and displacement and compression of the brainstem anteriorly resulting in hydrocephalus.

Meningiomas have been reported (22,33,47,52,76,85) as has astrocytoma (82) and medulloblastoma (6).

Mental retardation was documented in 10% (39).

Fig. 12–4. *Cowden syndrome*. Note thyroid enlargement. (From KM Lloyd and M Dennis, Ann Intern Med 58:136, 1963.)

Thyroid. Benign thyroid gland abnormalities, noted in about 60%–65% (39,71), include "goiter" (13,21,65,70,71,85,86) and adenoma (4,15,31,33,35,48,52,56,66,68,70,73). Follicular adenocarcinoma (13,39,85) is found in about 7% (Fig. 12–4). Hashimoto thyroiditis (85) and myasthenia gravis (90) have also been reported. Thyroid tumors have been noted in both males and females (28,55).

Gastrointestinal tract. The frequency of gastrointestinal neoplasms is not known, since all reported patients have not received complete gastrointestinal examinations. However, Carlson et al (16) and Chen et al (17) noted that 70% of those who had undergone lower gastrointestinal examinations had hamartomatous colonic polyposis. Hanssen et al (39) suggested that 40% have benign neoplasms, while 3% have colon cancer, a figure no different from that of the normal population. Chen et al (17) reported involvement of the entire alimentary tract. Polyps are found in descending order in the colon, stomach, small intestine, and esophagus. Polyps have been reported as early as 5 years of age (85) and have been found in all parts of the intestinal tract: esophagus (33,40,41,45,68,71,85,86), stomach (31,37,86), small intestine (31,37,86), and large intestine (31,32,74,86). On microscopic examination, polyps may be ganglioneuromatous (45), hyperplastic (32,40), benign lymphoid (40,71), hamartomatous (13,16,32,44,80), lipomatous (40,44), leiomyomatous (16), juvenile (40), and adenomatous (45,85). Esophageal polyps have been diagnosed on microscopic examination as exhibiting glycogenic acanthosis (40,45).

Gorensek et al (32) reported one patient with many hyperplastic polyps and adenocarcinoma of the descending colon. Burnett et al (13) reported adenocarcinoma of the cecum and Walton et al (84) described metastatic colon carcinoma; neither report noted preceding polyposis. We do not believe that malignant degeneration of colonic polyps is characteristic of the syndrome (69,79).

Other neoplasms. Many other neoplasms have been noted: cerebral gangliocytoma (71), meningioma (33,52,86), medulloblastoma (6), dural arteriovenous malformation (71), hemangioma (9,11,40,68, 71,84,85), parotid hamartomas (79), neurofibroma (21), granular cell tumor (71), xanthoma (10), salivary gland carcinoma (68), neuroma of Auerbach's plexus (13), lipomas (13,16,29,39,67,68,70,71,85), cystic hygroma (87), angiolipoma (29,86), angiomyomas of the extremities (29), liposarcoma (11,71), acute myelogenous leukemia (20), non-Hodgkin

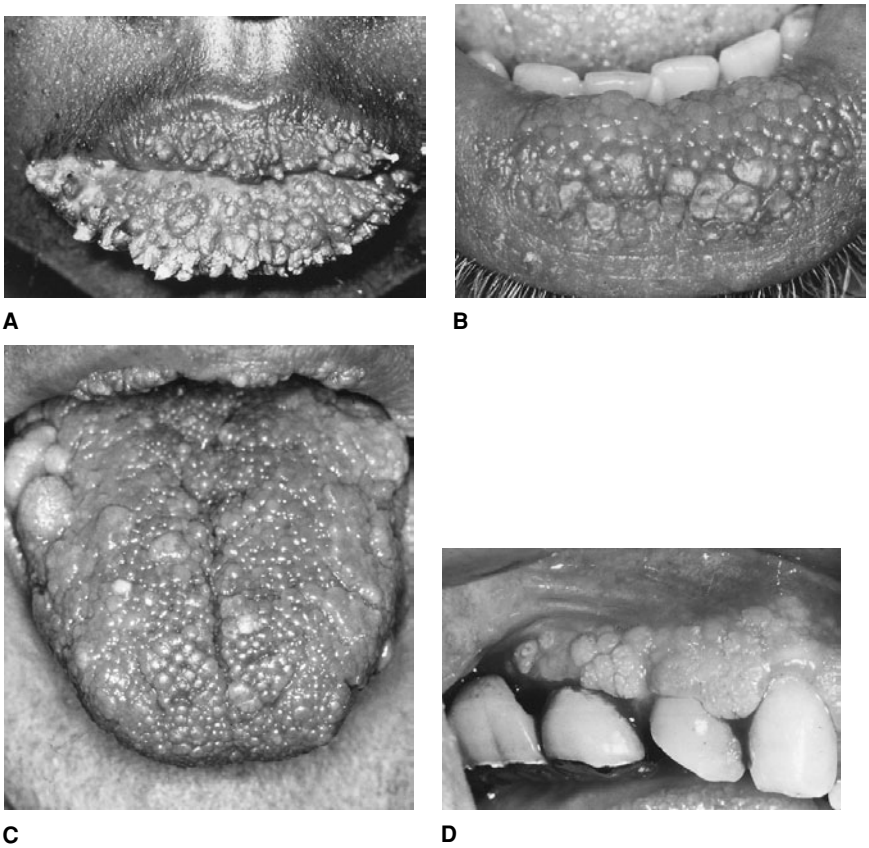

Fig. 12–5. *Cowden syndrome*. Oral involvement. (A,B) Papillomatous lesions of lips. (B) Close-up of lower lip involvement. (C) Papillomatous tongue. (D) Gingival involvement. (A from BS Allen et al, J Am Acad Dermatol 2:303, 1980. C from P Fritsch et al, Hautarzt 32:285, 1981.)

Table 12–1. Abnormalities associated with Cowden syndrome (n = 100; M = 37; F = 63)

Abnormalities	Percent
Mucocutaneous	
Multiple facial papules	85
Acral keratoses	73
Palmoplantar keratoses	54
Multiple oral papillomas	85
Dermal fibromas	24
Multiple skin tags	16
Oral fibromas	86
Scrotal tongue	20
Lipomas	31
Vascular malformations	18
Cutaneous and oral malignancies	8
Thyroid gland	
Goiter, adenoma	68
Hyperthyroidism	2
Hypothyroidism	3
Thyroiditis	3
Thyroglossal duct cyst	2
Follicular adenocarcinoma	3
Female breast	
Fibrocystic disease	52
Anatomic abnormalities	8
Virginal hypertrophy	6
Ductal adenocarcinoma	28
Ductal papilloma	14
Male breast	
Benign gynecomastia	7
Female genitourinary system	
Menstrual irregularities	20
Ovarian abnormalities (mainly cysts)	19
Leiomyomas	5
Vaginal and vulvar cysts	6
Adenocarcinoma of uterus	6
Carcinoma of uterine cervix	3
Carcinoma of ovary	2
Transitional cell carcinoma of renal pelvis	2
Male genitourinary system	
Hydrocele, varicocele	3
Transitional cell carcinoma of bladder	3
Gastrointestinal tract	
Polyps of upper GI tract	22
Polyps of colon and rectosigmoid	29
Diverticula of colon and sigmoid	2
Ganglioneuromas and neuromas	4
Epithelioid leiomyoma of rectosigmoid	1
Hepatic hamartoma	1
Adenocarcinoma of cecum	2
Adenocarcinoma of colon	1
Facial dysmorphism and skeletal abnormalities	
High head circumference	21
Adenoid facies	8
Highly arched palate	14
Kyphosis, kyphoscoliosis	14
Hand and foot abnormalities	6
Pectus excavatum	6
Bone cysts	4
Nervous system	
Neuromas of cutaneous nerves	5
Neurofibroma	3
Meningioma	3
Hearing loss	2
Eye	
Cataracts	3
Angioid streaks	2
Congenital blood vessel anomaly	1
Myopia	3

Adapted from TM Starink et al, Clin Genet 29:222, 1986.

Table 12–2. *Cowden syndrome*—diagnostic criteria

Major criteria	
Cutaneous facial papules	
Oral mucosal papillomatosis	
Minor criteria	
Acral keratoses	
Palmoplantar keratoses	
Diagnostic requirements	
two major criteria or	
one major and one minor criterion or	
one major and family history or	
two minor and family history.	

From OS Salem and WD Steck. J Am Acad Dermatol 8:686, 1983.

lymphoma (20), melanoma (16,34,43,67,80), endometrial carcinoma (5), transitional cell carcinoma of bladder (40,46,55), renal cell carcinoma (36), and Merkel cell carcinoma of skin (36).

Skeletal abnormalities. Large head circumference was found in 80% by Starink et al (74). Lordosis (9), kyphosis (71), scoliosis (13,20), kyphoscoliosis (48), pectus (20), and bone cyst (28,48) have been documented.

Genitourinary abnormalities. About 50% of female patients have genitourinary anomalies. Menstrual irregularities (20%) and ovarian cysts (20%) have been documented (11,13,83,84). Other tumors have included: transitional cell carcinoma of the bladder, renal cell carcinoma, uterine cervical cancer, and uterine leiomyomas (36). These may be aleatory. There is increased incidence of miscarriage (11,85).

Other findings. Angioid streaks of the retina have been reported (2,3). Laryngeal polyps that interfere with phonation have also been noted (32,85,86). Pulmonary changes have been discussed by Solli et al (70a).

Oral manifestations. Papular and verrucous lesions of the lips, tongue, gingivae, alveolar ridges, buccal mucosa, palate, and tonsils have been seen in 85% (2,6,9,14,18,21,29,30,33,35,46,77) (Fig. 12–5). These lesions may coalesce and produce a cobblestone appearance (35, 65,78). The light microscopic appearance of oral lesions is consistent with the diagnosis of fibroma according to some investigators (11–13, 30,37,85). Others have described epithelial hyperplasia and papillomatosis (48,72,77). Squamous cell carcinoma of the tongue has been reported (15). We suspect that this association was fortuitous.

Differential diagnosis. A patient reported by Byars and Jurkiewicz (14) exhibited giant fibroadenomas of the breast, secondary kyphosis, hypertrichosis, and gingival fibromatosis. This condition (Byars-Jurkiewicz syndrome) may represent a disorder distinct from Cowden syndrome.

On clinical examination, cutaneous lesions in Cowden syndrome resemble those of warts, acrokeratosis, epidermodysplasia verruciformis, Darier disease, Torre-Muir syndrome, *lipoid proteinosis*, and *tuberous sclerosis*. However, the microscopic features and associated abnormalities serve to distinguish among these disorders. The intraoral lesions of focal epithelial hyperplasia and *multiple endocrine neoplasia syndrome, type 2B* are somewhat similar to those of Cowden syndrome, but differ on microscopic examination. The lesions at the oral commissures simulate those of *acanthosis nigricans* and oral lesions resemble those of Heck disease.

Polyps of the colon are found in a number of disorders (for discussion, see *Gardner syndrome)*. Ganglioneuromatous proliferation of the bowel may also be associated with *multiple endocrine neoplasia type 2b syndrome, neurofibromatosis*, and with juvenile polyposis of the colon (64) that does not exhibit PTEN mutations (25).

A Proteus-like syndrome has been shown to be due to PTEN mutations (91).

Laboratory aids. Biopsy of cutaneous and mucosal lesions should aid in differential diagnosis. T lymphocyte deficiency (37) has been reported but the significance is moot.

Germline mutation testing for PTEN can establish the diagnosis of Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome (9a,25,55).

References [Cowden syndrome (multiple hamartoma and carcinoma syndrome, Lhermitte-Duclos disease)]

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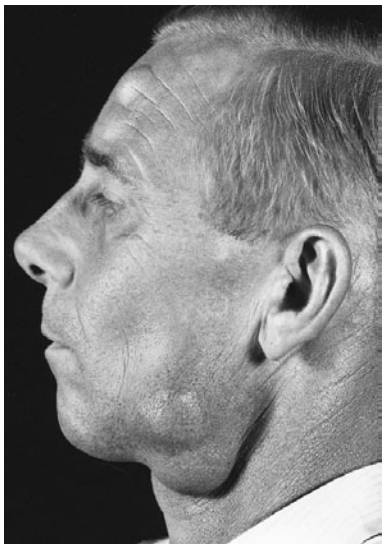
Gardner syndrome

During 1950–1953, Gardner and coworkers (48,49) recognized and reported a syndrome of multiple adenomatous polyposis of the large intestines, multiple osteomas of facial bones, cutaneous epidermoid cysts, and desmoid tumors and fibrous hyperplasia of the skin and mesentery. Similar cases had been documented earlier (18,38,46,47), but Gardner was the first to recognize the hereditary pattern.

Gardner syndrome (GS) was initially thought to be an entity separate from familial adenomatous polyposis (FAP). However, with accumulation of data, many investigators have demonstrated that it represents one tail of the spectrum of that disorder (36,131,132). Cohen (28) found that about 50% of those with FAP had no extracolonic manifestations.

Inheritance is autosomal dominant with complete penetrance, and markedly variable expressivity (11,17,48,116). The FAP-GS gene has been mapped to 5q21–q22, but there is probable genetic heterogeneity (13,105,114,138,147,149). The syndrome has been found in individuals with interstitial deletion of 5q22.1–q31.1 (85,97). Linked DNA markers or direct detection can be used for presymptomatic diagnosis (40,115,147). The severity of the disease depends upon which codon is mutated (35,41). GS has been reported in 28-year-old monozygous

Fig. 12–6. *Gardner syndrome*. (A) Osteomas of forehead, zygomatic area, and mandible. (B) Radiograph showing numerous osteomas scattered throughout jaws and skull. (C) Histologic appearance of bony mass of mandible. (A courtesy of EL Jones, Washington, DC. C from K Ooya et al, J Oral Pathol 5:305, 1976.)



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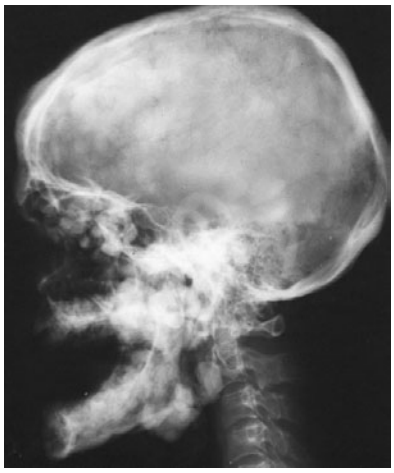

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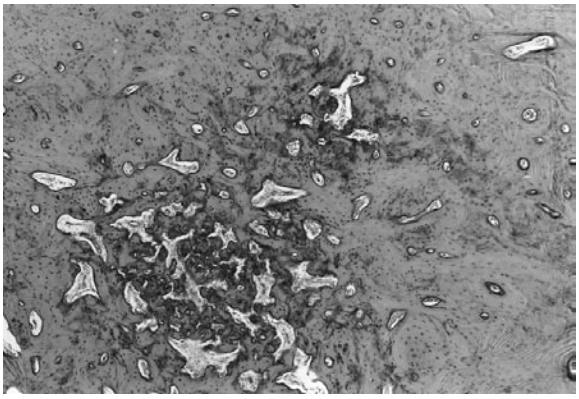

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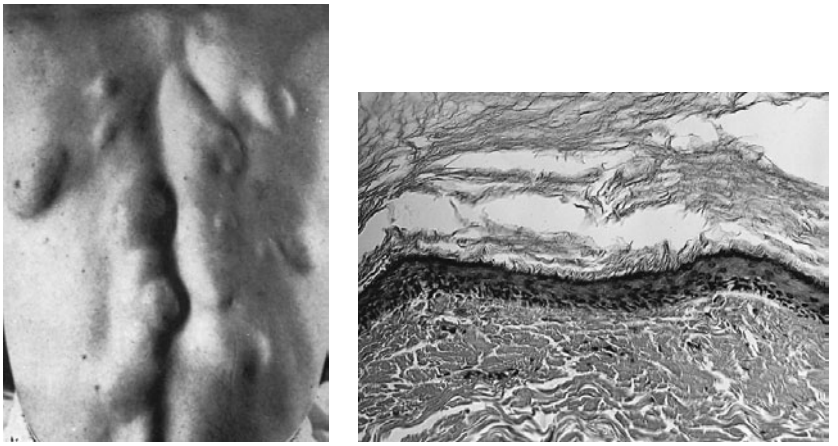


A B

Fig. 12–7. *Gardner syndrome*. (A) Multiple epidermoid inclusion cysts over dorsal region. (B) Histologic section of epidermoid inclusion cyst. (A from MC Oldfields, Br J Surg 41:534, 1954).

twins (51). One had complete expression of the disorder; the other had only osteomas of the jaws. The frequency of FAP-GS has been estimated to be between 1 in 12,000 (11,156) and 1 in 1400 (116). New mutations account for about 25% (98). The mutation rate of 5×10^{-6} mutations per gene per generation is on the same order of magnitude as other human mutations (11).

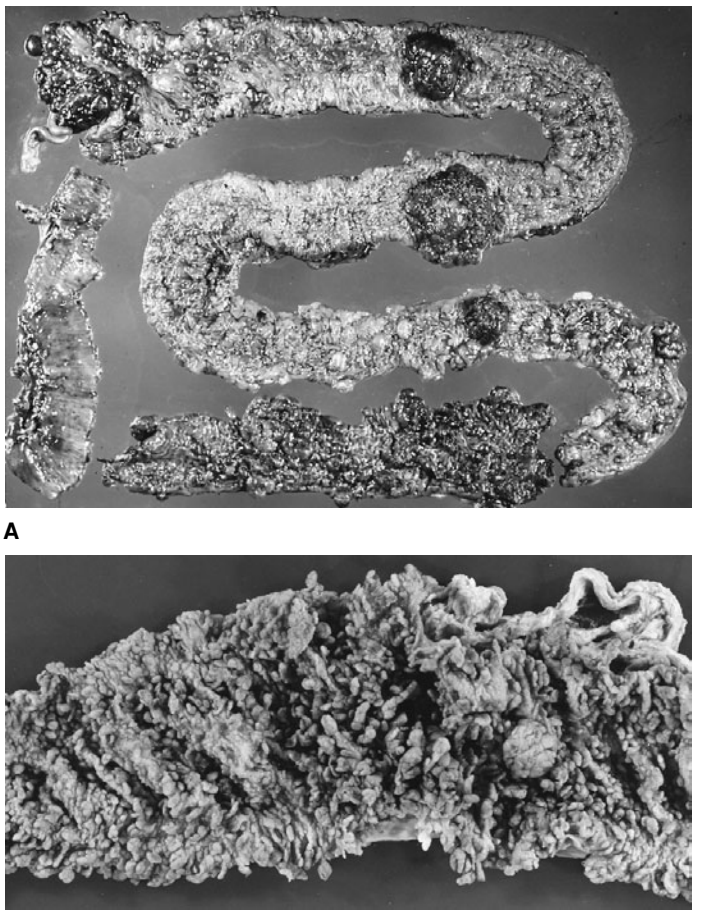
Osteomas. The osteomas associated with FAP, and particularly those associated with GS, are of various sizes and have limited growth potential. The radiopacity and microscopy are similar to those of mature compact bone and they have well-developed Haversian systems (5,72). The osteomas can be found in any bone, but most often are seen throughout the calvaria, frontal and ethmoidal sinuses, maxilla, and mandible (Fig. 12–6) (25,78,122). The tooth-bearing areas of the mandible and even of the maxilla are commonly involved (72). Those in the mandible often become confluent and enlarge (5,72,143,154). In a Japanese study, 50% had skeletal involvement (153), and 46% had three or more osteomas of the jaws (72), whereas 81%–93% had one or more (72,153,154). The osteomas may protrude (exostoses), but in most cases they appear as enostoses without palpable swelling (25,72,154). Bülow et al (14) studied individuals at risk for FAP and found that 76% had mandibular densities, contrasting sharply with 4% in the normal population. Long tubular bones, most often the radius, ulna, and metacarpals, may be sites of small osteomas, but involvement—in contrast to that of the facial skeleton—is minimal, and usually manifests as rather diffuse radiologic subperiosteal cortical thickening. In a few cases, however, these osteomas presented as small, well-defined exostoses (25,78). Osteomas may be found in members of families with FAP who do not have manifest polyposis (52) and may precede the appearance of intestinal symptoms (51,122). Woods et al (161), however, found significant bone lesions in only 15%.

Epidermoid cysts. Cysts of the skin occur in about 50%–60% of all cases of GS, but have been present in some families in nearly all of those affected (91,158). In one study of 74 patients with the syndrome, over 50% had cysts and all those with cysts had or subsequently developed colonic polyposis (91). The number of cysts has ranged from 1 to 20, with an average of 4 per patient. They occur most often on the legs, face, scalp, and arms, the trunk being seldomly affected (Fig. 12–7A) (91). Although the cysts may appear at any time from birth to 35 years, they most often become manifest around puberty, prior to the appearance of colorectal polyposis (48,52,91,93). New cysts appear periodically (52,158). The early appearance of the cysts can be used as a guide to indicate which members of a family are at risk for developing polyposis (30,39).

The histologic picture of the cyst shows the characteristic features of epidermoid cysts (Fig. 12–7B) (91), although they are often referred to as sebaceous cysts. It has been pointed out that about 50% of the cysts have shadow cells, resembling pilomatrixoma (31,93,120,127).

Gastrointestinal system. Multiple intestinal polyposis of the colon and rectum with a marked tendency to malignant degeneration is characteristic (Fig. 12–8A,B). Although the polyps may appear before puberty (30,39,116), the chance for malignant transformation at this age is less than 5%. The mean age for diagnosis of the polyps is 23–31 years (92). The mean age for diagnosis of the intestinal cancer is 37 years (116). By 30 years, about 50% of the patients exhibit malignant degeneration,

Fig. 12–8. *Gardner syndrome*. (A) Multiple polyps of colon undergoing malignant transformation to adenocarcinoma. (B) Close-up of multiple colonic polyps. (B from K Ooya et al, J Oral Pathol 5:305, 1976.)



A

B

but the frequency of malignancy with advanced age is probably near 100%. The origin of the polyps is multiclonal (70). The age of presentation and the degree of malignancy depend on the specific mutation (23,24).

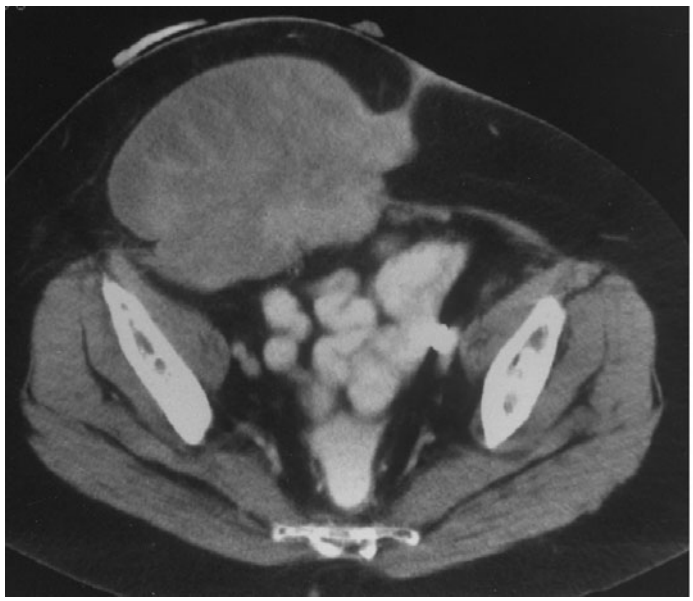
Polyposis of the stomach and small intestines has rarely been reported (52,59,66,82,155,163), and malignant degeneration of small bowel polyps appears to be relatively low (2%–3%) (16). The reader is referred to a good summary of these and other cases (131).

The association of periampullary adenocarcinoma (carcinoma of the ampulla of Vater, duodenum, or pancreas) has been established (18,79). It may develop in the absence of other extracolonic adenomatous polyps. The frequency has been estimated as high as 12% among patients with FAP but in only 2%–3% among patients with GS (12). Lymphoid hyperplasia of the terminal ileum has also been noted (131).

Desmoid tumors. Both abdominal and extraabdominal desmoids exhibiting diffuse fibrous infiltration have been seen in 15%–30% of patients with GS (22,26a,42,78), but in only 6% of those with FAP (84,136) (Fig. 12–9). The tumors usually arise 1–3 years following abdominal surgery. Their removal may be followed by further desmoid formation, although desmoids, fibromas, and fibrosarcomas of the skin have been noted without prior surgery (108,136). It should be noted that among patients who exhibit both FAP and desmoids, about half will show other stigmata of GS (101,134). Desmoid tumor development depends upon which codons are mutated (23,24). Mesenteric and retroperitoneal fibromatosis has been reported in patients with no stigmata other than FAP (52,101,124,134). Occasionally, the fibroblastic tumors may precede the discovery of the colonic polyposis (101,131).

Other neoplasms. There appears to be a distinct proclivity for those with FAP to develop a variety of neoplasms. The extracolonic neoplasms may be diagnosed a long time prior to the symptoms of intestinal polyposis (10,46,109). Various tumors of the central nervous system (glioma, medulloblastoma) have been reported (4,19,20,28,33,94,113,136,162). This has created confusion with Turcot syndrome, which has been confused with GS (see *Differential diagnosis*). Papillary carcinoma of the thyroid been found in at least 35 cases and is 100 times more frequent in the syndrome than in the normal population (102). See Delamarrre (37) for tabulation of cases. Other examples are offered (4,8,28,29,82,137). At least 90% of these patients are female. Many of these patients also had medulloblastoma.

A wide variety of other neoplasms has been reported: adrenal adenoma (38,106), adrenal adenocarcinoma (99), hepatocellular carcinoma (164), hepatoblastoma (50,55,71,83,88,96,142), retroperitoneal leiomyoma (28,55,108), neurofibroma (12), rhabdomyosarcoma (6), osteosarcoma (65,157), osteochondroma (56), chondrosarcoma (54), lipoma



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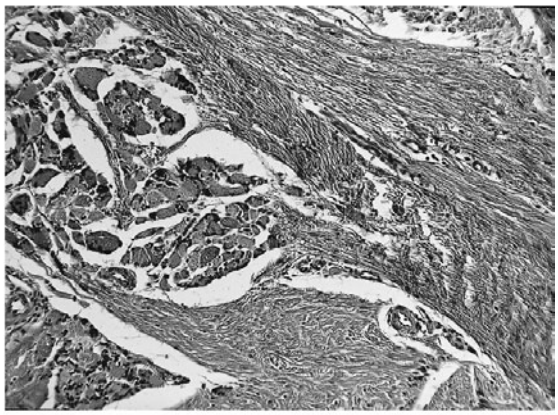

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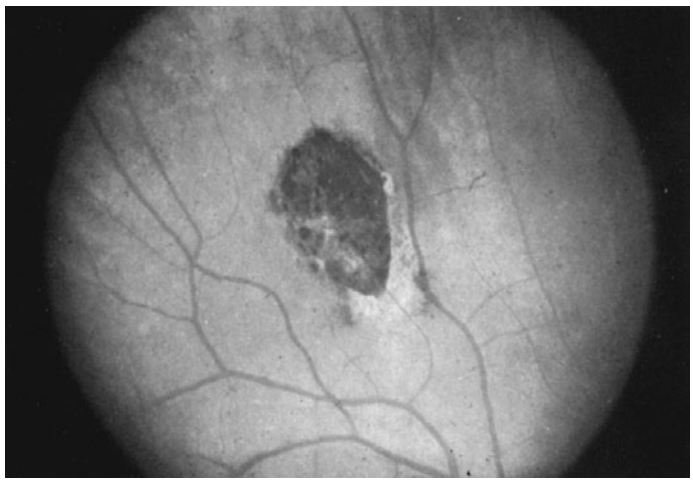

C

Fig. 12–9. *Gardner syndrome*. (A) Desmoid tumor. Note desmoid tumor bulging abdominal wall. (B) Benign-appearing fibrous connective tissue involving abdominal musculature (to the left). (C) Congenital hypertrophic retinal pigment epithelium (CHRPE). (A from D Einstein et al, AJR Am J Roentgenol 157:275, 1991.)

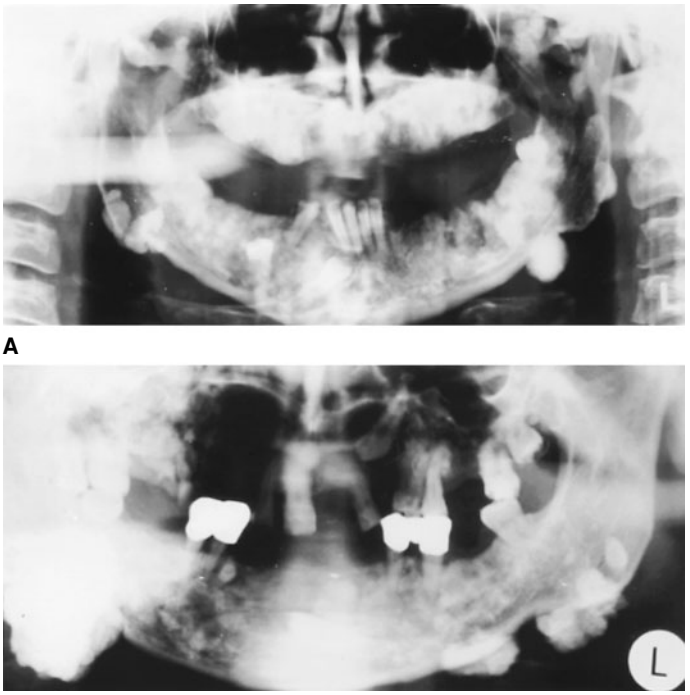

Fig. 12–10. *Gardner syndrome*. (A,B) Panorex of jaws showing osteomas and odontomas. (A from J Wolf et al, Br J Oral Maxillofac Surg 24:410, 1986. B From F Sitzman and H Bruning, Dtsch Zahnarztl Z 32:781, 1977.)

(28,89), fibroma of the breast (56,134), basal cell carcinoma (28,95,103), and a host of other tumors (28,63,131,132,157).

Eye findings. Over 60% of patients with GS have one oral patch of congenital hypertrophic retinal pigment epithelium (CHRPE) (Fig. 12–9). The ocular fundal lesions are bilateral in over 75% (64,88, 104,117,140,150,151). However, Shields et al (133) found no such correlation and Houlston et al (68) cautioned using its presence as a marker. It has been demonstrated that whether CHRPE is present depends upon which codons are mutated (19,23,24,110).

Skin. Increased skin pigmentation has been noted (159).

Oral manifestations. Fitzgerald (46) appears to be the first to have described multiple odontomas in the syndrome—he did so in 1943. In 1962, Fader et al (45) added supernumerary teeth (Fig. 12–10). These findings have been supported by many other investigators (25,78,123, 135).

In 97 patients with FAP, 17% had dental abnormalities; 11% had supernumerary teeth and/or osteomas, and 9% had impacted permanent teeth (139). Utsunomiya and Nakamura (154) found impacted teeth in about 35% of patients with intestinal polyposis. Söndergaard et al (139) noted supernumerary teeth in 10% and impacted teeth in 9%. Ida et al (72), in a study of 52 patients with polyposis coli, reported embedded teeth (27%), supernumerary teeth (21%), and compound odontomas (11%). One or more osteomas of the jaws were found in over 80%. Occult radiopaque lesions of the jaws are common (21,109,112,143,160). Thakker et al (144), using a weighted scoring system, found almost 70% to have significant bony changes.

Various incidental findings have included hypercementosis (165), root resorption, ankylosis (5), and persistent primary teeth (2).

Differential diagnosis. Multiple polyps of the intestine have been described in a number of disorders (Table 12–3). The reader is referred to several excellent reviews (17,36,57,61,126).

Juvenile polyposis of the colon. Juvenile polyps of the colon may have autosomal dominant inheritance (141). The polyps are hamartomatous and not precancerous. They are composed of an excess of lamina propria in which epithelium-lined tubules are embedded with or without cystic dilatation and secondary inflammation.

Turcot syndrome. In 1959, Turcot et al (152) reported sibs with multiple intestinal polyposis and brain tumors. Several authors (7,74, 81,86,103,107,146,152) subsequently reported sibs with glioblastoma multiforme and multiple polyposis. Astrocytoma, spongioblastoma, and glioma have also been reported (75,146). Multiple café-au-lait spots and axillary freckling, similar to that seen in neurofibromatosis, may be seen (44,75,145). Parental consanguinity and sib involvement clearly indicate autosomal recessive inheritance (7,32,44,76,103, 107,121,146,152). Tops et al (148) have shown that Turcot syndrome is not allelic to FAP. However, there have been both numerous examples of nonfamilial occurrence of brain tumors with colonic polyposis and several examples of brain tumors in typical FAP (GS) that have dominant inheritance. These cases have been reviewed elsewhere (74,75,87, 96,121,146). The brain tumors in these cases are far more often medulloblastoma (60,100,104). Colonic polyps in Turcot syndrome are presumably smaller in number, larger in size, and earlier to undergo malignant degeneration than those in FAP.

Peutz-Jeghers syndrome. This autosomal dominant syndrome, characterized by generalized gastrointestinal hamartomatous polyps and macular pigmentation of the face, lips, and oral mucosa, is described in detail later in this chapter. The typical polyp contains muscularis mucosa. The epithelial element is related to the smooth muscle in the same manner as in normal mucous membrane.

Cronkhite-Canada syndrome. Generalized gastrointestinal polyposis in middle-aged to elderly individuals may be associated with edema, malabsorption, diarrhea, protein-losing enteropathy, generalized alopecia, and nail dystrophy. Brownish skin pigmentation may be diffuse over the face, neck, and hands, including palmar creases (34,77,80). The disorder is not hereditary. Most cases have been reported from Japan.

Muir-Torre syndrome. This autosomal dominant syndrome includes multiple sebaceous neoplasms (generally benign), keratoacanthomas, and adenocarcinomas, most often of the colon, endometrium, and ovary (1,27,58,62). Over 135 cases have been published (62). It has been shown to be due to an underlying DNA mismatch-repair defect and to be allelic to dominant nonpolyposis colorectal cancer (88).

Perifollicular fibromas and intestinal polyposis (Birt-Hogg-Dubé syndrome, Hornstein-Knickenberg syndrome). Hornstein (67) reported autosomal dominant perifollicular fibromas and skin tags of the face, neck, and trunk associated with adenomatous colorectal polyposis as an entity separate from Gardner syndrome. The association of skin tags and intestinal polyps has been discussed by several authors (2,26,125,130). Ishii et al (73) reported sibs with congenital atrichia, pigmented and papular cutaneous lesions in the 20s, and gastrointestinal polyposis in the 30s.

Other multiple intestinal syndromes. Polyps of the large intestine may be seen in *Cowden syndrome*. There are several inherited examples of associated polyposis of stomach and colon, familial polyposis of the entire gastrointestinal tract, and several cases of solitary polyps of the colon and rectum apparently inherited as an autosomal dominant trait (66). However, it is possible that these are merely examples of the variability of familial colonic polyposis (17,36).

Howel-Evans syndrome refers to the occurrence of gastrointestinal adenocarcinoma and punctate keratosis of the palms and soles (9).

Bannayan-Riley-Ruvalcaba syndrome consists of macrocephaly, intestinal polyposis, and pigmentary spotting of the genitalia; inheritance is autosomal dominant. *Infantile Cronkhite-Canada syndrome* consists

Table 12–3. Syndromes with polyposis

Syndrome	Characteristics	References
Cowden syndrome	Facial papules, acral keratoses, oral papillomas, thyroid adenoma, fibrocystic disease of the breast, menstrual irregularities, gastrointestinal polyposis, ductal adenocarcinoma of the breast, autosomal dominant	See pages 432–437.
Familial colorectal polyposis (FCP)/Gardner syndrome (GS)	FCP and GS represent a spectrum; FCP-GS mapping to 5q22; autosomal dominant; osteomas of frontal bone, maxilla, and mandible; epidermoid cysts; intestinal polyposis with high predisposition to malignancy, desmoids, odontomas, supernumerary teeth	See pages 437–443.
Juvenile polyposis of the colon	Hamartomatous polyps (nonprecancerous), autosomal dominant	(138)
Peutz-Jeghers syndrome	Gastrointestinal polyposis, macular pigmentation of face and lips, predisposition to malignancies (gastrointestinal, nongastrointestinal, ovarian), autosomal dominant	See pages 476–480.
Turcot syndrome	Multiple intestinal polyposis; glioblastoma, medulloblastoma, or astrocytoma; autosomal recessive inheritance	(7,74,81,86,103,107,146,152)
Cronkhite-Canada syndrome	Generalized gastrointestinal polyposis, edema, malabsorption, protein-losing enteropathy, generalized alopecia, nail dystrophy, middle-to-old age, sporadic occurrence	(34,77,80)
Infantile Cronkhite-Canada syndrome	Macrocephaly, gastrointestinal polyposis, hypotonia, hepatosplenomegaly, anemia, portein-losing enteropathy, alopecia, nail dystrophy, clubbing of fingers and toes, sporadic occurrence	(90,128)
Torre-Muir syndrome	Multiple sebaceous tumors; keratoacanthomas; adenocarcinomas of colon, endometrium, and ovary; sporadic occurrence	(27,58,62)
Perifollicular fibromas and intestinal polyposis	Perifollicular fibromas; skin tags of the face, neck, and trunk; adenomatous colorectal polyposis; autosomal dominant	(3,26,67,125,130)
Bannayan-Riley-Ruvalcaba syndrome	Macrocephaly, intestinal polyposis of distal ileum and colon, pigmentary spotting of the penis, hypotonia, mild to moderate mental deficiency, infantile overgrowth	See pages 410–413.

of diffuse gastrointestinal polyposis, macrocephaly, alopecia, nail dystrophy, clubbing of fingers and toes, hypotonia, hepatosplenomegaly, anemia, and protein-losing enteropathy (90,128,129). Most examples undoubtedly represent *Bannayan-Riley-Ruvalcaba syndrome*.

Juvenile polyposis has been associated with arteriovenous malformations and hypertrophic osteoarthropathy [see Gorlin et al (53) for review of earlier cases]. Additional examples have been described by Prieto et al (119) and Erkul et al (43). Germline mutations in SMAD4 that map to 18q21.1 account for some cases of juvenile polyposis (68). Some germline PTEN mutations have been found as well (111).

Diagnosis. The presence of multiple epidermoid inclusion cysts, desmoids, or bony growths, especially of the facial skeleton, should lead to a complete search for the intestinal component. Recording of these incidental findings should be just as mandatory as radiographic search for additional intestinal polyps if a single rectal polyp is detected. The discovery of multiple polyps, or of any other component, also places the onus of responsibility upon the investigator to search other relatives thoroughly for stigmata. Since a negative report does not mean that polyps or other components will not appear in future years, periodic reexamination of all persons with a parent or sib who had one or more signs is necessary.

Prenatal or presymptomatic diagnosis can be carried out by the use of closely linked DNA markers (40).

Laboratory aids. Radiographic survey, especially of the facial skeleton, and barium studies of the large and small intestines are mandatory. Prenatal and postnatal diagnosis can be carried out by molecular methods (98,115,118,147).

References (Gardner syndrome)

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Gorlin (nevoid basal cell carcinoma) syndrome

Nevoid basal cell carcinoma syndrome (NBCCS) is characterized by numerous basal cell cancers and epidermal cysts of the skin, odontogenic keratocysts of the jaws, palmar and plantar pits, calcified dural folds, various neoplasms or hamartomas (ovarian fibromas, medulloblastoma, lymphomesenteric cysts, fetal rhabdomyomas, etc.), and various stigmata of maldevelopment (rib and vertebral abnormalities, cleft lip and/or palate, cortical defects of bones, etc.) (Figs. 12–11 to 12–15).

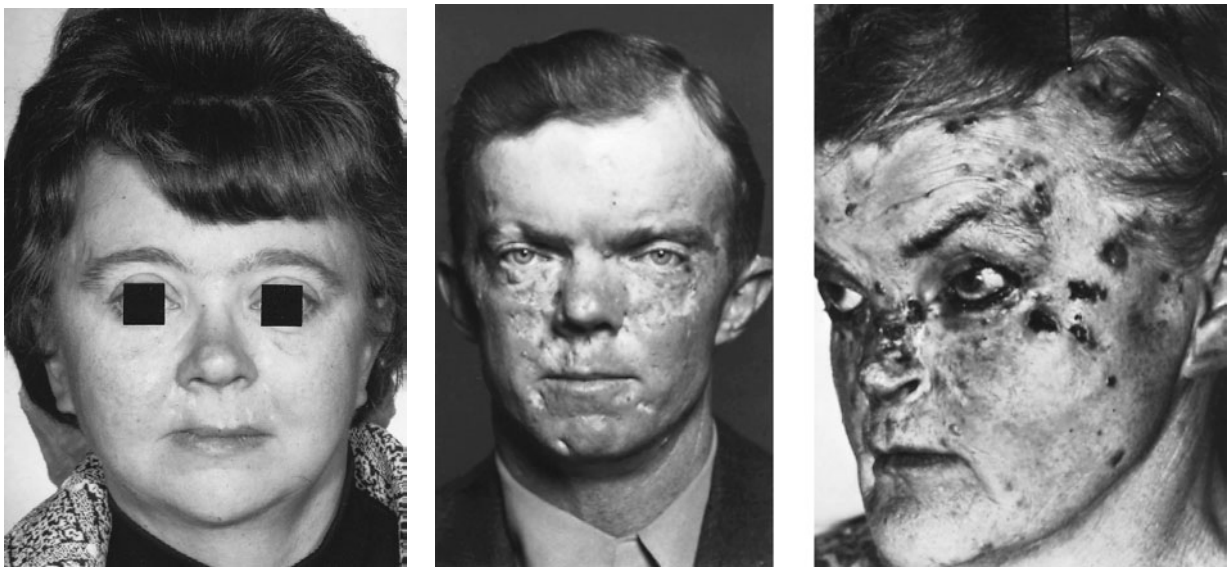
The condition, first described independently by Jarisch (95) and White (211) in 1894, probably existed during dynastic Egyptian times (175). It has been variously known as basal cell nevus syndrome, Gorlin-Goltz syndrome, Gorlin syndrome, and nevoid basal cell carcinoma syndrome. Admittedly, none is satisfactory, as selection of only one facet (and in blacks a relatively uncommon one) is highly biasing. The term *nevus* does not project the truly cancerous nature of the skin lesions—although only a small number of basal cell carcinomas become aggressive. Eponyms imply priority of description (and are often wrong, frequently chauvinistic, and say nothing about the disorder). They serve to plague residents who are required to memorize them.

Early American reports are those of Binkley and Johnson (18), Howell and Caro (91), and Gorlin and Goltz (70). Comprehensive systematic surveys (52,67,68,106,125,181) and historic reviews (67,90) of the syndrome are available.

The frequency of NBCCS has been variously estimated. Maddox (128) found the syndrome in about 0.4% of all cases of basal cell carcinomas. Rahbari and Mehregan (158) calculated that 2% of those younger than 45 years of age with basal cell carcinomas have NBCCS, in contrast to 22% of those younger than 19 years. Evans et al (50) suggested that the minimal prevalence was 1 per 57,000. A similar prevalence can be calculated from the data of Pratt and Jackson (157). Chevenix-Trench et al (29) found a minimal prevalence of 1 per 164,000.

NBCCS has autosomal dominant inheritance with complete penetrance and quite variable expressivity. There is no sex predilection. About 35%–50% represent new mutations (132). The gene has been mapped to chromosome 9q22.3 (29,34,53,54,58,165,203,212). It consists of 23 exons with 12 transmembrane spanning domains and two large extracellular loops (117). There have been a few examples of deletion of this area of chromosome 9 in patients with the syndrome (7,17,184). These patients have been mentally retarded. Widespread developmental anomalies as well as other neoplasms and overgrowth and loss of heterozygosity at this site suggested mutation of a tumor suppressor gene (37,58). Tumor suppressor genes are recessive oncogenes (anti-oncogenes), homozygous inactivation being a requisite for their carcinogenic expression (37,119). The gene *PTCH*, which modifies the Hedgehog signaling pathway, is mutated not only in the syndrome but in ordinary basal cell carcinomas (3,30,45,57,59,75,100,149,186,202,205a,217). *Patched*, a transmembrane gene in the absence of its ligand, sonic hedgehog, acts as a cell cycle regulator, normally inhibiting expression of downstream genes (*smoothened*, among others) which control cell fates, patterning, and growth (185). In accordance with the Knudson two-hit hypothesis, the gene of one homolog results from inherited point (germline) mutation with loss of the second homolog by mitotic nondisjunction, deletion, or mitotic recombination, i.e., random somatic events (119). In NBCCS, tumors (basal cell carcinomas, keratocysts, meningiomas, ovarian fibromas, odontogenic keratocysts) exhibit loss of heterozygosity (116,177).

Fig. 12–11. *Gorlin syndrome*. (A) Typical facies of patient with nevoid basal cell carcinoma syndrome. Note increased head circumference, mild hypertelorism, and several scars from removed basal cell carcinomas. (B) Frontal and temporoparietal bossing, numerous basal cell carcinomas. (C) Extensive basal cell carcinomas. (B from WD Maddox, Thesis, University of Minnesota, 1963. C from U Berendes, Hautarzt 22:261, 1971.)



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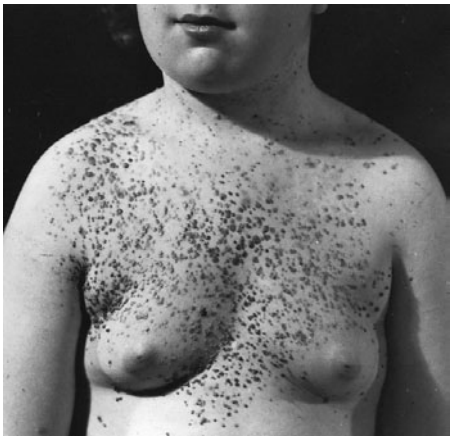

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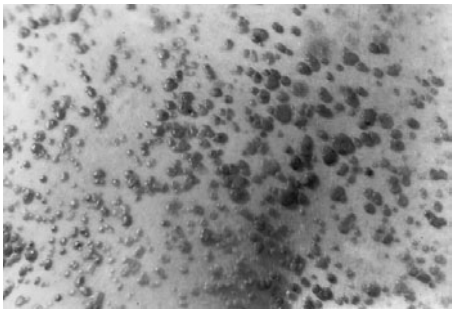

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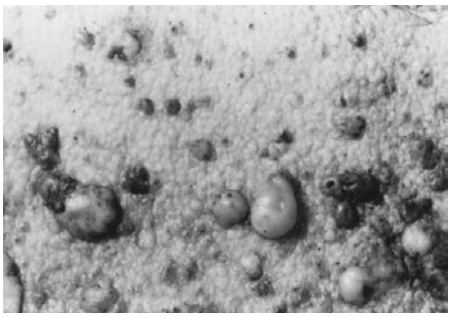

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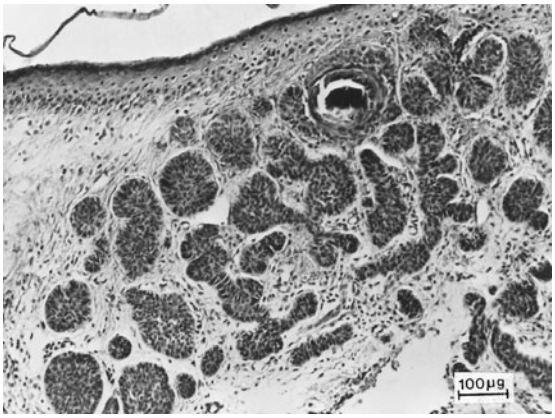

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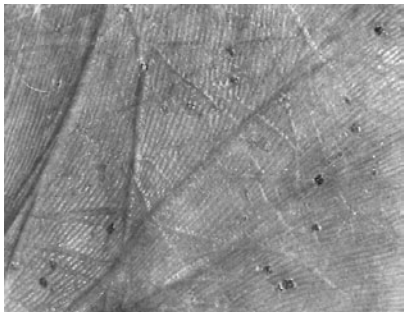

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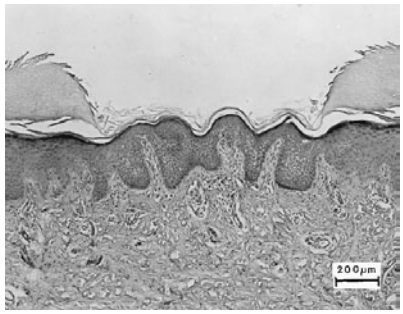

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Fig. 12–12. *Gorlin syndrome*. (A) Multiple nevoid basal cell carcinomas scattered over chest. (B) Close-up of lesions shown in A. (C) Multiple basal cell carcinomas. Note differences in size and pigmentation. (D) Photomicrograph of nevoid basal cell carcinoma. Note ectopic calcification (100×, H and E). (E) Palmar pits. Pits are usually a few millimeters deep, more evident in those performing manual labor; relatively rare in children. (F) Photomicrograph of palmar pit. Note mild acantholysis of epithelium at bottom of pit. (A from JB Howell and MR Caro, Arch Dermatol 79:67, 1959. B,F courtesy of JB Howell, Dallas, Texas. C courtesy of RA Cawson, London, England.)

Various physical anomalies (bifid rib, macrocephaly, cleft lip, etc.) apparently need but one-hit. The reader is referred to several excellent reviews of the molecular aspects of NBCCS (8,20,146,184). There is no genotype–phenotype correlation (117,213). Two patients have been reported with associated Turner syndrome (1a,107a). It is interesting that the gene for Ferguson-Smith syndrome (multiple self-healing squamous cell carcinomas or keratoacanthomas) maps to the same site on chromosome 9q22.3, possibly representing different mutations within the same gene (71,167). There is a second *Patched* gene at 1p32–p34 that may play a similar role (33,186,187). Farther down the hedgehog pathway, Gli2 overexpressed causes basal cell carcinoma in mice (71a).

Craniofacial features. The head appears large (>60 cm in adults). Relative macrocephaly (occipitofrontal circumference greater than 95th centile for height) is found in 50% (106). Although one-third of probands have an occipitofrontal circumference less than the 50th centile for height, i.e., when head size is adjusted for height, most do not have true macrocephaly (8). Only rarely is hydrocephalus reported (126). Frontal bossing, noted in 25%, may cause the eyes to appear sunken. Mild true hypertelorism is seen in only about 5%. The eyebrows are highly arched in about 40% (181). Median age of onset is 25 years. In about 35% in both whites (67) and blacks (65), mild mandibular prognathism, noted as "pouting lower lip," is seen. Facial milia are scattered among the basal cell carcinomas in at least 50%–60%, especially around the eyes, eyelids, nose, malar region and upper lip (vide infra). The palate tends to be high (Fig. 12–11).

Eyes. Various ocular problems occur with a frequency (10%–25%) far greater than in the normal population. These include congenital cataract (5%), microphthalmia, orbital cyst, coloboma of iris, choroid and optic nerve, strabismus (15%), and nystagmus (52,67,130,176,200). Small keratin-filled cysts (milia) are found intermixed with basal cell carcinomas in 30%–50% (29) on the palpebral conjunctiva, where they are transitory.

Skin. Basal cell carcinomas, which may appear as early as 2 years of age, especially on the nape, most often proliferate between puberty and 35 years (181). Median age of onset is 25 years. Of those over 30 years, only about 10% have none (164). There appears to be a relationship to increased sun exposure, because only about 40% of blacks with the syndrome manifest basal cell cancers, and then usually have only a few lesions in contrast to the numerous basal cell carcinomas evident in whites (ca. 90%) (65,109). It should be emphasized that the melanotic skin pigmentation does not protect against ionizing radiation (109).

The basal cell cancers, which vary in number from a few to literally thousands, range in size from 1–10 mm in diameter. They are pearly to flesh colored to pale brown and may be mistaken for skin tags, nevi, hemangioma, or molluscum contagiosum. Most often the basal cell carcinomas involve the face, back, and chest (Fig. 12–12). Only rarely is one found below the waist or on the extremities. New lesions appear from time to time, but most remain static in growth. It is only after puberty that the basal cell carcinomas can become aggressive and invade locally. It must be emphasized that only a small fraction of the lesions become

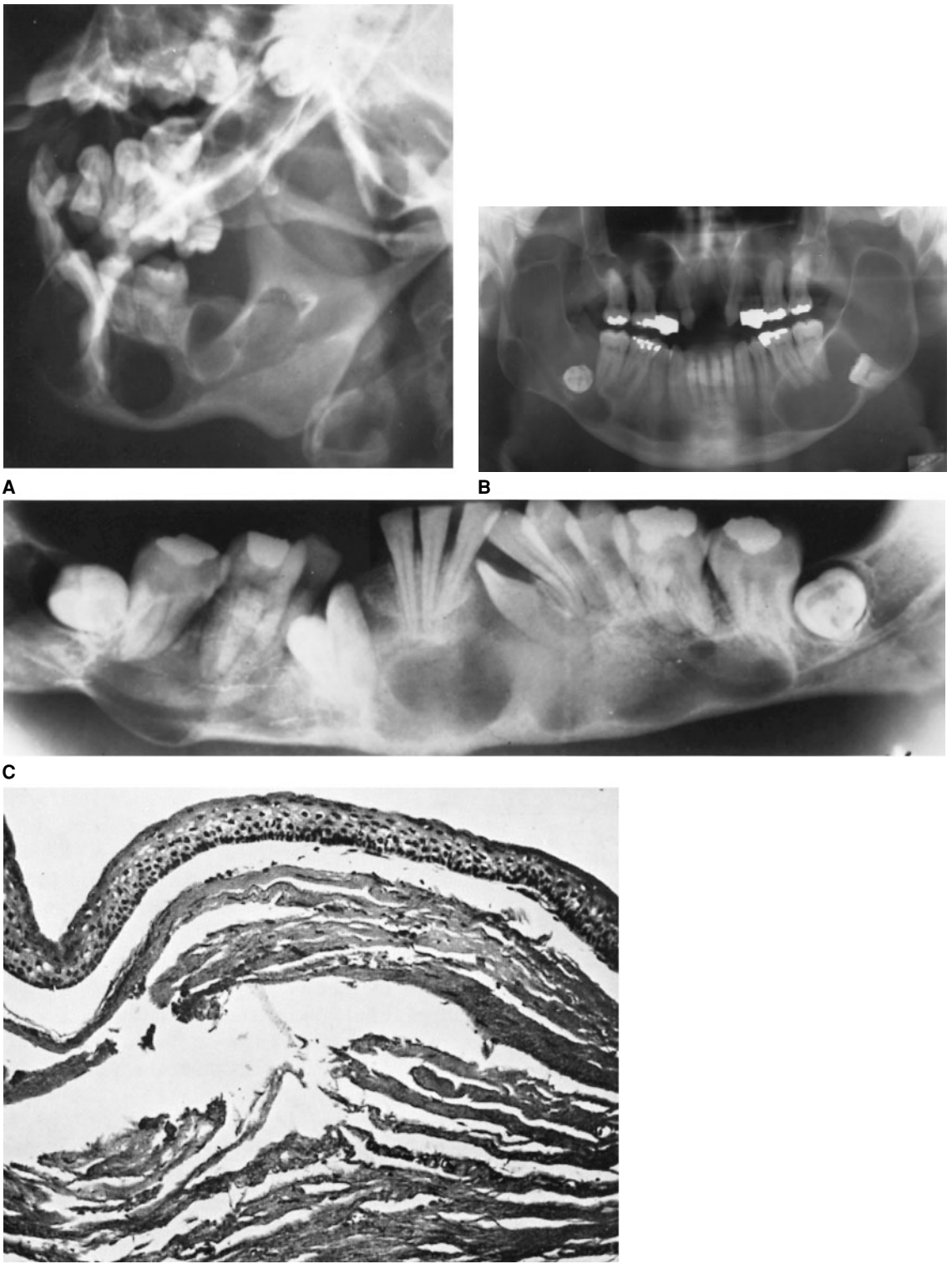

Fig. 12–13. *Gorlin syndrome*. (A) Multiple cysts scattered throughout both jaws. (B) Panorex showing multiple odontogenic keratocysts. Note displaced molars. (C) Extensive involvement of mandible with multiple cysts. (D) Photomicrograph of odontogenic keratocysts from 40-year-old female. (A from RJ Gorlin et al, Cancer 18:89, 1965. C from J Mills and J Foulkes, Br J Radiol 40:366, 1967.)

invasive. Increase in size, ulceration, bleeding, or crusting indicates invasion. Radiation therapy causes proliferation of basal cell carcinomas and invasion several years later (67,208). Death has resulted in the very rare instance from invasion of the brain or lung. Even less often has metastasis been documented (10,14,63,140,215).

Several examples of unilateral or even quadrant involvement with basal cell carcinomas likely represent postzygotic somatic mutation (25,26,74,89,183,216,222).

Multiple basaloid follicular hamartomata have been noted by Gartmann et al (61) in a family with the syndrome. The relationship of

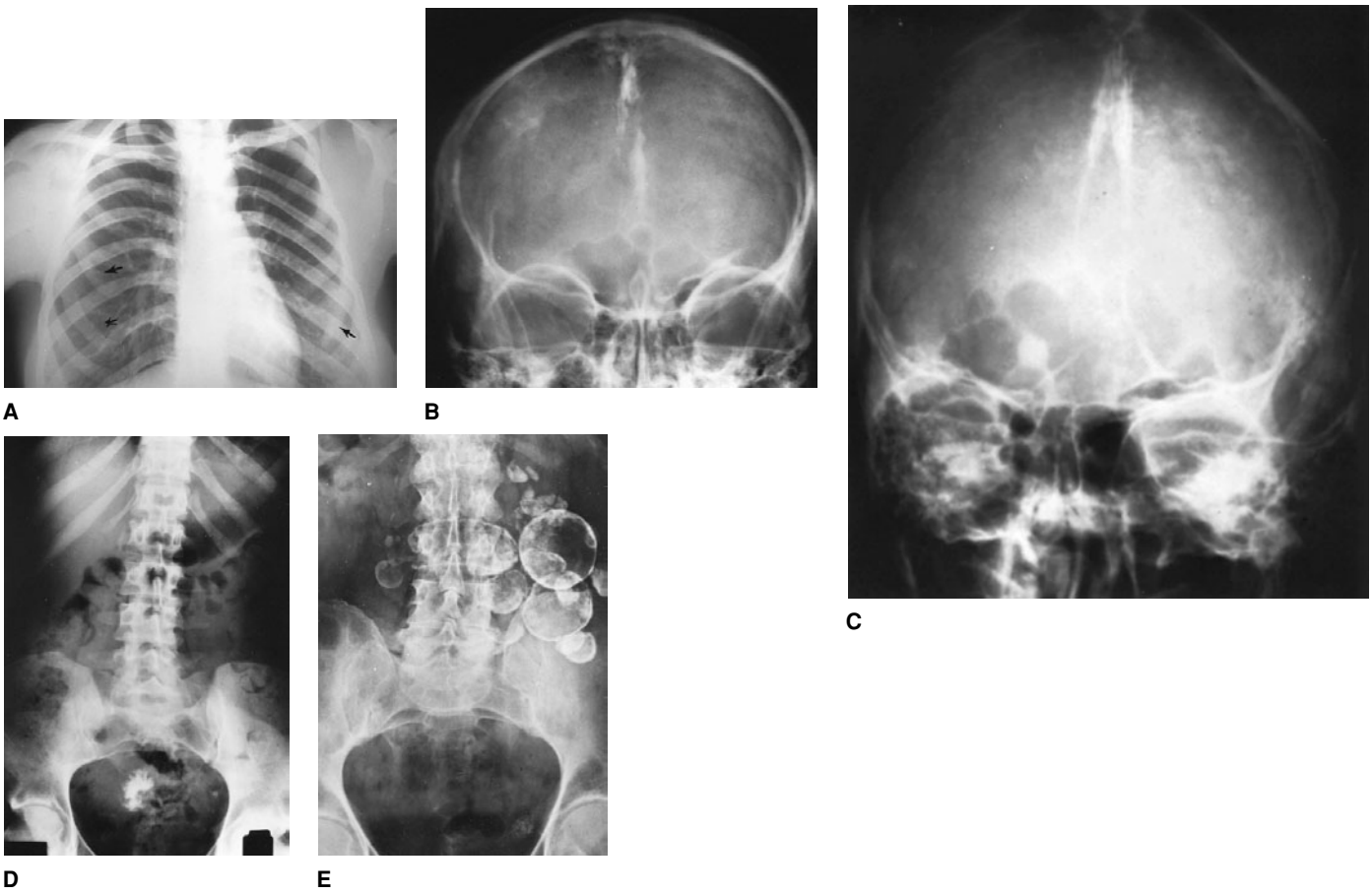

Fig. 12–14. *Gorlin syndrome*. Radiographs. (A) Bifid ribs (arrows) and scoliosis. (B) Calcified falx cerebri. (C) Lamellar calcification of falx cerebri. (D) Calcified ovarian fibromas. Most often mistaken for calcified uterine myomas. Usually bilateral, they often overlap in the midline. (E) Multiple lymphomesenteric (chylous) cysts.

Fig. 12–15. *Gorlin syndrome*. (A) Note meningioma. (B) Fibroma of ventricle of heart. (A from PJW Stoelinga et al, Oral Surg 36:686, 1973. B courtesy of C Reiter, Vienna, Austria.)

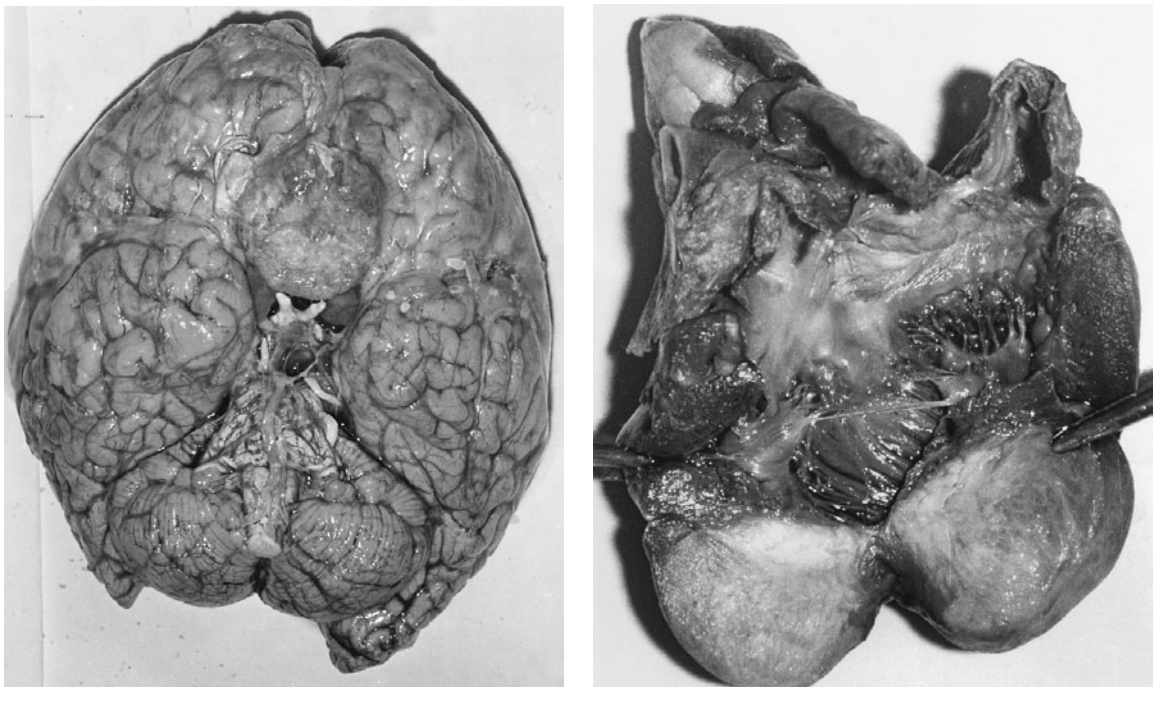

Table 12–4. *Nevoid basal cell carcinoma syndrome*—diagnostic findings in adults

50% or greater frequency
Enlarged occipitofrontal circumference (macrocephaly, frontoparietal bossing)
Multiple basal cell carcinomas
Odontogenic keratocysts of jaws
Epidermal cysts of skin
High-arched palate
Palmar and/or plantar pits
Rib anomalies (splayed, fused, partially missing, bifid, etc.)
Spina bifida occulta of cervical or thoracic vertebrae
Calcified falx cerebri
Calcified diaphragma sellae (bridged sella, fused clinoids)
Hyperpneumatization of paranasal sinuses
15%–49% frequency
Brain ventricle asymmetry
Calcification of tentorium cerebelli and petroclinoid ligament
Calcified ovarian fibromas
Short fourth metacarpals
Kyphoscoliosis or other vertebral anomalies
Lumbarization of sacrum
Narrow sloping shoulders
Prognathism
Pectus excavatum or carinatum
Pseudocystic lytic lesion of bones (hamartomas)
Strabismus (exotropia)
Syndactyly
Synophrys
14% or less but not random
Medulloblastoma
True ocular hypertelorism
Meningioma
Lymphomesenteric cysts
Cardiac fibromas
Fetal rhabdomyoma
Ovarian fibrosarcoma
Marfanoid build
Anosmia
Agenesis of corpus callosum
Cyst of septum pellucidum
Cleft lip and/or palate
Low-pitched female voice
Polydactyly, postaxial—hands or feet
Sprengel deformity of scapula
Vertebral body fusion
Congenital cataract, glaucoma, coloboma of iris, retina, optic nerve, medullated retinal nerve fibers
Subcutaneous calcifications of skin (possibly underestimated frequency)
Minor kidney malformations
Hypogonadism in males
Mental retardation

Modified from RJ Gorlin et al, Dermatol Clin 13:113, 1995.

multiple basaloid follicular hamartomata to nevoid basal cell carcinomas has been hotly debated (98,207).

Barr et al (11) suggested that these were analogous to the odontogenic keratocysts (vide infra). Larger, often multiple, epidermal cysts arise on the limbs and trunk in about 50% of whites (12,29,143,181). About 35% of blacks have these cysts (65). Transitory multiple cysts located on the palpebral conjunctiva (120) have been noted in 40%.

Palmar and, somewhat less often, plantar pits (1–2 mm) are asymmetrically present in 65%–80% (29,52,181). Palmar pits are as frequent in blacks as in whites (65). They are better visualized if the patient wets the hands in warm water for 10 minutes before examination. Individuals whose occupations involve manual labor may have more obvious pits because of ingrained dirt or grease. They may be present in children, but a careful age-related study is lacking. Rarely, basal cell carcinomas have arisen in these pits (198). Such cases have been cited by Gorlin (67). An additional example is that of Golitz et al (66) (Tables 12–4 and 12–5).

Table 12–5. *Nevoid basal cell carcinoma syndrome*—diagnostic criteria (diagnosis based on two major or one major and two minor criteria)

Major criteria
1. More than 2 BCCs or one under age of 20 yr
2. Odontogenic keratocyst
3. Three or more palmar pits
4. Bilamellar calcification of falx cerebri
5. Bifid, fused, or splayed ribs
6. First-degree relative with NBCCS
Minor criteria
1. Macrocephaly adjusted for height
2. Fontal bossing, cleft lip/palate, hypertelorism
3. Sprengel deformity, pectus, syndactyly of digits
4. Bridging of sella turcica, hemivertebrae, flame-shaped radiolucencies
5. Ovarian fibroma
6. Medulloblastoma

Adapted from VE Kimonis et al, Am J Med Genet 69:299–308, 1997.

Odontogenic keratocysts. Characteristically, multiple (average: 6; range: 1–30) cysts of both the upper and lower jaws appear after the seventh year of life. Median age of appearance is about 15 years. Mandibular cysts are three times as common as maxillary examples (Fig. 12–13). Evans et al (52), in a population-based study, found odontogenic keratocysts in 90% of those over 40 years and in 80% of those over 20 years, with an overall frequency of over 65%. They peak during the second and third decades but continue to appear during the life of the patient (29,182). In one patient they did not present until the sixth decade (164). There is no racial predilection (65). The cysts may be extremely large but rarely cause symptoms. They effect marked tooth displacement but only rarely cause fracture (190). About one-third do not produce significant symptoms. Approximately 50% present with swelling, 25% with mild pain, and 15% with unusual taste following rupture of a cyst (29). Rarely they perforate the cortex and extend into soft tissues. In the maxilla, the sinuses may be invaded; in the mandible, the cysts may extend throughout the molar–ramus area to the coronoid process. They may cross the midline (67).

There is marked tendency (over 60%) for these cysts to recur following surgery (47). This appears to result from several causes: incomplete removal, retention of epithelial islands and/or satellite microcysts which occur with great frequency in the connective tissue capsule, and from proliferation of the basal layer of the epithelium (39,45,103,219).

There have been very few reports of ameloblastoma arising in the odontogenic keratocysts (28,31,76,96,129,178). The brief article of Jensen (97), in spite of its title, suggests only odontogenic rests. Squamous cell carcinoma has arisen from a cyst wall in a few examples (79,138,159).

Odontogenic keratocysts present as multilocular or invaginated cysts (along with microdaughter cysts or epithelial rests in 25%–50% of the cases), with parakeratinized or, rarely, orthokeratinized (4%), stratified squamous epithelium consisting of five to eight rows of cells having a regularly oriented, well-defined basal epithelial cell layer, palisaded nuclei, but no rete ridges (67). Some of the larger keratocysts expand in size to include tooth follicles.

In some cases, the epithelial rests proliferate to produce a picture like that of squamous odontogenic tumor. The mitotic index is comparable to that of the dental lamina. Budding of the epithelium into the connective tissue and suprabasilar splitting are noted in at least 50%. Inflammatory cells rarely are found in the underlying connective tissue. The cyst capsule is thin (103). Some cysts exhibit foci of calcification in the walls (35).

Woolgar et al (219) and Dominiguez et al (46) found significant differences between syndrome keratocysts and single keratocysts. Syndrome keratocysts were found to have a markedly increased number of satellite cysts, solid islands of epithelial proliferation, odontogenic rests within the capsule, and mitotic figures in the epithelial lining of the main cavity. There are immunochemical differences between syndromal and solitary keratocysts (121). Woolgar et al (219) noted that syndrome keratocysts tend to occur at a much earlier age than single keratocysts. Most authors believe that odontogenic keratocysts arise from the dental lamina (13,181).

Cleft lip and/or palate have been found in 3%–8% (41,52,67,106,114, 171,181,189,196).

Musculoskeletal and radiographic findings. Mean height in males is 183 cm, 174 cm in females (8). About 15% of patients are extremely tall (190,191). The calvaria tends to be large (80%) with frontal and biparietal bossing, but this appears to be correlated with height (8). The interorbital distance is only mildly increased (39) (Fig. 12–14).

Lamellar calcification of the falx cerebri is found in 55%–95% (normal: 5%) (29,163). Calcification of the tentorium cerebelli has been noted in 20%–40%, the petroclinoid ligament in 20%, and the diaphragma sellae in 60%–80%. Radiographically this appears as if the sella turcica is bridged—i.e., as if there were fusion of the anterior and posterior clinoid processes (29,48). Agenesis of the corpus callosum with or without lipoma has been noted as well as empty sella syndrome (196a).

Fused, splayed, hypoplastic, or bifid ribs have been documented in 45%–60% (162). Kyphoscoliosis with or without pectus is found in 25%–40% with spina bifida occulta of the cervical or thoracic vertebrae in 60% (162). The latter was noted in only 20% of a series by Kimonis et al (106). Sprengel deformity and/or unusual narrow sloping shoulders has been described in 10%–40% (29,106,157,164). Other anomalies seen in about 40% include cervical or upper thoracic vertebral fusion, hemivertebra, and lumbarization of the sacrum. Pectus occurs in about 15%–25% (106).

Various other bony anomalies have been reported in about 5%: pre- or postaxial polydactyly of hands or feet, hallux valgus, syndactyly of fingers 2–3. These examples have been cited by Gorlin (67). Shanley et al (181) found syndactyly in 3% and polydactyly in 4%. Although the fourth metacarpal has been alleged to be short, this is a "poor sign" because about 10% of the normal populations has a positive sign (29,67).

Small pseudocystic bone lesions (flame-shaped lucencies) have been identified in the phalanges, metapodial bones, carpal and tarsal bones, long bones, pelvis, and calvaria in 30% (19,42,48,106,145). Calvarial involvement may give the impression that medulloblastoma has spread to bone (80). Histologically, the flamelike lesions are hamartomas consisting of fibrous connective tissue, nerves, and blood vessels (136). Subcutaneous calcification of fingers and scalp has also been reported (140). Sclerotic bone lesions have been reported occasionally (19,83,220). A radiolucency of the upper humerus has been documented (40).

Kidney anomalies. Minor kidney anomalies, found in roughly 5%, have included horseshoe kidney, L-shaped kidney, unilateral renal agenesis, renal cysts, and duplication of renal pelvis and ureters (32,67,173). Because most of these findings have been diagnosed on laparoscopy or at autopsy, their frequency is probably higher.

Hypogonadism in males. Perhaps 5%–10% of males exhibit such signs of hypogonadotrophic hypogonadism as anosmia, cryptorchidism, female pubic escutcheon, gynecomastia, and/or scanty facial or body hair (67,206). Gorlin (67) cited numerous examples. Shanley et al (181), in their survey, noted 10% with anosmia.

Medulloblastoma, other brain tumors, and seizures. The association of NBCCS with medulloblastoma was first pointed out by Herzberg and Wiskemann (85) in 1963. The tumor characteristically presents during the first 2 years of life in NBCCS, as opposed to 7–8 years in the general population. Cases reported prior to 1986 can be found tabulated in the 1987 summary of Gorlin (67). The incidence of medulloblastoma in NBCCS was determined by Evans et al (50) to be 1%–2% in 173 consecutive cases of the tumor. Conversely, a population study of NBCCS determined 3%–5% had medulloblastoma. There appears to be male sex predilection: male to female, 3:1 (112). Because medulloblastoma presents early (mean 2.5 years) in patients with NBCCS, children who present with the tumor especially those less than 5 years, should be carefully examined for signs of the syndrome (106). An especially malignant medulloblastoma was reported by Albrecht et al (1).

Radiation therapy of medulloblastoma results in profuse numbers of invasive basal cell carcinomas appearing in the radiation field (from nape to base of spine) (51,67,208). Clinically, a "rash" appears from 6 months to 3 years after radiation therapy. The rash represents activated basal cell carcinomas, which often become markedly invasive in another 10 years. It should be pointed out that numerous small radiolucencies of bone that are really hamartoses may be confused with intracalvarial spread of medulloblastoma (67).

Other brain tumors are infrequent. The next most common appears to be meningioma (67,139,197) (Fig. 12–15A), but other tumors have included: astrocytoma (27,52,84), craniopharyngioma (197), and oligodendroglioma (107). These tumors may well be secondary to radiation therapy (106,148).

Cysts of the brain have been reported: colloid cyst of the third ventricle (188), "median ventricular cyst" (38); arachnoid cyst (152,196a); intraparenchymal cyst (199; Chevenix-Trench, personal communication, 1992), cysts of the septum pellucidum (38,115,123). Empty sella syndrome has been found (196a).

Seizures have been occasionally noted (64,141,142) unassociated with brain tumors, possibly due to focal neuronal heterotopia (87).

Cardiac fibroma. Cardiac fibromas occur in NBCCS with far higher frequency than that of chance. In general, primary cardiac tumors are rare in infancy and childhood, estimates ranging from 0.03%–0.08%, with cardiac fibromas being the second most frequently found, most often in the anterior left ventricular wall (36). They are discrete, well circumscribed, non-encapsulated, firm, gray-white, 3–4 cm in diameter and may upon occasion exhibit central calcification. When they project into the chamber, the hemodynamics of the left ventricle is impeded. Conduction defects (arrhythmias) can eventuate from involvement of the intraventricular septum (88). About 5% of those with cardiac fibromas have NBCCS (Fig. 12–15B).

Approximately 20 examples of cardiac fibroma have been reported in NBCCS (4,23,24,32,36,41,49,52,55,67,78,82,86,94,113,122,124,150, 166,196a). Evans et al (52), in a population-based study, estimated that the frequency of cardiac fibroma in the syndrome is about 3%. The tumor is composed of fibroblasts embedded in dense matrix of collagen and elastic fibers. Because of the variability of microscopic appearance, the same tumor has been stated to be a cardiac fibroma in one report (94) and a fibrous histiocytoma in a second report (101). A possible case is that of Grubben et al (72).

Cardiac fibromas in NBCCS have been quite similar to those occurring as solitary examples. Most have arisen in the left ventricle. Presentation time has varied from birth to 60 years (HA Heggtveit, Hamilton, Ontario, Canada: Personal communication, 1992), but some have been recognized due to cardiomegaly. Most, having caused no symptoms, have been found incidentally.

Mesenteric cysts. Single or multiple chylous (lymphatic) mesenteric cysts have been documented. As most of these examples have not produced symptoms, the majority have been found at laparotomy and hence are underestimated. Gorlin (67) cited at least 10 examples.

The cysts are thin-walled and measure 2–14 cm in diameter. The contents are chylous but may contain hemorrhagic turbid fluid. Microscopically, the wall is composed of hyaline fibrous connective tissue and smooth muscle. Islands of lymphocytic cells may be located beneath the endothelial lining.

A true enterogenous cyst was reported by MacSweeney et al (127).

Ovarian fibromas and fibrosarcomas. Ovarian fibromas are rare, accounting for only 4% of all ovarian tumors. Less than 10% are found in women less than 30 years, and their occurrence in prepubertal females is truly unusual (99). It is difficult to know the true frequency of ovarian fibromas in NBCCS, as they do not present unless they become large and calcified and twist on their pedicles. A population-based study carried out in 1992 suggested that a figure of 25% might be reliable (52). Shanley et al (181) and Kimonis et al (106) found ovarian fibromas on ultrasound in 15%. Ovarian fibromas associated with NBCCS are most often bilateral (75%), often overlapping medially. A number of such cases have been erroneously diagnosed as calcified uterine

leiomyomas. In contrast, the ovarian fibroma not associated with the syndrome is unilateral and calcified only 10% of the time (180). Cases reported prior to 1986 are cited by Gorlin (67). Additional examples have been noted (21,56,191,221). The tumor may rarely be virilizing (92) or renin-secreting (56,221).

Histopathologically, they are composed of mature fibroblasts separated by collagenic connective tissue in which extensive calcified foci may be seen.

Ovarian fibrosarcoma has also been described (93,110,123,169, 172,194) as well as other ovarian tumors (15,169,193).

Fetal rhabdomyoma. Schweisguth et al (179), in 1968, was the first to report fetal rhabdomyoma in a newborn with NBCCS. Originally thought to be an intercostal rhabdomyosarcoma, immunochemical reexamination in April 1986 (67) showed its true nature. Dahl et al (39) described examples on the thigh and chest wall in a newborn child with NBCCS. In 1975, R. Gorlin (unpublished, 1975) had occasion to see an adult male with NBCCS who had a fetal rhabdomyoma of intercostal muscles. Klijanienko et al (108) reported a presternal example in a 1-year-old. Subsequently, additional fetal rhabdomyomas appeared at the angle of the mandible at 6 years and in the cervical area at 26 years. DiSanto et al (44) reported a 6-year-old female child with fetal rhabdomyoma of the posterior mediastinum and retroperitoneum. Hardisson et al (77) described a retroperitoneal example in a 15-year-old male.

Miscellaneous other tumors. There appears to be an increased incidence of several other neoplasms or hamartomas: leiomyomas of the bowel and mesentery (81,102,199), leiomyosarcoma (60), lymphangiomyoma (170), melanoma (9,104,195), mesenchymoma (176,218), Hodgkin's disease (142,156,224), rhabdomyosarcoma (13), nasal dermoid (154), seminoma (223), paratesticular pseudotumor (209), schwannoma (108), pleomorphic adenoma of parotid (81), adrenal cortical adenoma (199), and a host of other neoplasms cited by Gundlach and Kiehn (73), Gorlin (67), and Stieler et al (193). Cyst of the lung was noted by Totten (201).

Chromosome instability and cellular radiation sensitivity. Carefully controlled studies by Sarto et al (174) and Bale et al (5) have not supported chromosomal instability or increased rates of sister chromatid exchange. Studies of cellular radiation sensitivity have also resulted in conflicting results [for complete discussion, see (68)]. Dezawa et al (43) found an increased number of nucleoli in fibroblasts of patients with the syndrome.

Differential diagnosis. Basaloid follicular hamartomas have been reported with alopecia and myasthenia gravis on several occasions (22,111,131,133,137,168,192,210). Bazex syndrome consists of basal cell carcinomas (especially of the face) (40%), follicular atrophoderma (especially of hands, feet, and elbows) (85%), hypotrichosis (85%), milia (65%), and generalized hypohidrosis or anhidrosis of face and head (25%), (62,105,147,155,160,204). [The reader should note that there is another Bazex syndrome (acrokeratosis paraneoplastica), a quite unrelated disorder.] It has X-linked dominant inheritance (111), the gene mapping to Xq24–q27 (205). Follicular atrophoderma also occurs in *chondrodysplasia punctata*. Rombo syndrome, named after a family, resembles Bazex syndrome, but there is neither follicular atrophoderma nor sweating abnormality, and it has autosomal dominant inheritance (2,135). Rasmussen syndrome consists of trichoepitheliomas, milia, and cylindromas (161). The binary combination of congenital hypotrichosis and milia has been documented in a few instances (151,160). Mehregan and Hardin (134) described tricholemmal cysts, palmar pits, and cicatricial alopecia. The sebaceous nevus has been found to have deletions in PTCH (219a).

Laboratory diagnosis. Prenatal, presymptomatic and possible preimplantation diagnosis has been accomplished in at-risk infants by ultrasonography and molecular techniques (6,16,88,153).

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Klippel-Trenaunay syndrome, Parkes Weber syndrome, and Sturge-Weber syndrome

This section considers Klippel-Trenaunay syndrome, Parkes Weber syndrome, and Sturge-Weber syndrome together because all three have various types of vascular malformations. However, it is shown that they

should be considered separate clinical entities that almost always occur sporadically. In this connection, it is essential to discuss vascular tumors vs. vascular malformations and also the Kasabach-Merritt phenomenon. The analysis here is based on Cohen (11).

Klippel-Trenaunay syndrome. Klippel-Trenaunay syndrome consists of (a) combined vascular malformations of the capillary, venous, and lymphatic types, (b) varicosities of unusual distribution, in particular the lateral venous anomaly (vide infra), observed during infancy or childhood, and (c) limb enlargement. Males and females are equally affected. The lower limb is involved in almost 95% of patients, the upper limb accounting for almost 5% of patients. Approximately 15% have combined upper and lower limb involvement. Uncommonly, patients may have trunk involvement only (29,46,49,58).

The original paper of Klippel and Trenaunay (24) shows that "Trenaunay" and not "Trénaunay" is correct; there is no accented *e* although many articles have added the accent (see 17 for review). Well over 1500 cases have been recorded (29,36,46,49,58). Servelle (49) alone documented 768 operated patients.

Conventional wisdom about Klippel-Trenaunay syndrome includes the following: (a) addition of arteriovenous fistulas and renaming the disorder Klippel-Trenaunay-Weber syndrome (3,19,22,25–27,39,48); (b) overlap with Sturge-Weber syndrome (6,15,18,21,44,52); (c) the presence of a bleeding diathesis of the Kasabach-Merritt type (46); and (d) familial aggregation (1,8,12,25,28,29,38) with various genetic interpretations. This conventional thinking can be seriously challenged.

Etiologic considerations. Koch (25) cited a number of familial cases from the literature. Relatives of probands had isolated varicosities or birth marks of the posterior neck. Some examples of neurofibromatosis were also included.

Lian and Alhomme (28) reported congenital varicose veins in three generations of a family in which the propositus had Klippel-Trenaunay syndrome. Norwood and Everett (38) noted an affected propositus whose brother and mother had macular stains scattered over the face and trunk. Lindenauer (29) observed a brother and sister with well-documented Klippel-Trenaunay syndrome. Craven and Wright (12) described a patient with Klippel-Trenaunay syndrome whose grandmother was also said to be affected. Ceballos-Quintal et al (8) observed a 3-year-old girl with Klippel-Trenaunay syndrome; the mother had a capillary malformation on her back and developed varicose veins in both legs. The maternal grandmother also had varicosities but no vascular malformation.

Aelvoet et al (1) sent a questionnaire to 114 patients with Klippel-Trenaunay syndrome; results were based on 91 respondents. Klippel-Trenaunay syndrome patients were said to have been found in both a propositus and a second-degree relative in two different families. "Naevi flammei" and "angiomatous naevi" were noted in some relatives of Klippel-Trenaunay syndrome patients. Varicosities were also found in some families. Aelvoet et al (1) indicated that familial occurrence of Klippel-Trenaunay syndrome was found once in 880 cases. There appears to be increased parental age and increased number of pregnancies (29a).

Happle (20), in reviewing the data provided by Aelvoet et al (1), suggested that paradominant inheritance could be an explanation of (a) why Klippel-Trenaunay syndrome occurs sporadically, (b) why the lesions of Klippel-Trenaunay syndrome are arranged in mosaic fashion, (c) why relatives with Klippel-Trenaunay syndrome are so rare, and, when recorded, do not exhibit Mendelian inheritance, and (d) why "naevi flammei" show an increased incidence in relatives of Klippel-Trenaunay syndrome patients.

Assuming paradominant inheritance, Klippel-Trenaunay syndrome would be caused by a single gene defect. Heterozygous individuals would almost always be normal and thus the allele would be transmitted imperceptibly. The trait would only become expressed if a somatic mutation occurred early during embryonic life. The resultant loss of heterozygosity would result in either homozygosity or hemizygosity for the Klippel-Trenaunay syndrome mutation (20).

Whelan et al (55) reported a case of Klippel-Trenaunay syndrome associated with a 5:11 balanced translocation. Wexler et al (54) noted a case with chromosomal mosaicism for a 1:20 translocation.

Careful scrutiny of published "familial cases" indicates one or more of the following problems: (a) inadequate documentation of cases; (b) overinterpretation of minor manifestations in relatives, including "nevus flammeus," hemangiomas, and varicosities,[1] all of which occur commonly in the general population; and (c) defining Klippel-Trenaunay syndrome as a capillary malformation *with or without* "hemihypertrophy" with no mention of lymphatic malformations, lateral venous anomaly, lymphatic vesicles or venous flares within the capillary malformation, or macrodactyly; thus, it is uncertain whether these cases represent Klippel-Trenaunay syndrome. Only the affected brother and sister described by Lindenauer (29) are *well-documented* examples of Klippel-Trenaunay syndrome within a family.

It is possible that when the basic molecular defect becomes known, it may be the same or similar to those of Parkes Weber syndrome and Sturge-Weber syndrome. It is only claimed here that it is useful to distinguish them because their clinical implications are so different. Also, it is not claimed that there is no genetic basis, only that future documentation of families must be much more thorough to prove this.

Capillary malformations. Capillary malformations of the skin are bluish to purplish in color. No large surgical series of Klippel-Trenaunay syndrome patients includes patients with capillary malformations involving the face (29,36,46,58). Capillary malformations may be studded with lymphatic vesicles and venous flares (vide infra) (Fig. 12–16).

Varicosities. Varicosities in Klippel-Trenaunay syndrome differ from commonly occurring varicose veins in two ways. The distribution is different, being more extensive, and the age of onset is different, first being manifest during infancy or childhood. The classic lesion is the lateral venous anomaly, which occurs in about 80% of patients. The malformation begins as a plexus of veins on the dorsum and lateral side of the foot and extends superiorly for various distances (Fig. 12–17). Termination occurs in the popliteal vein in 11% of patients, superficial femoral vein in 17%, deep femoral vein in 19%, and external iliac vein in 6%; full leg-length distribution is found in 33% of patients (46,58).

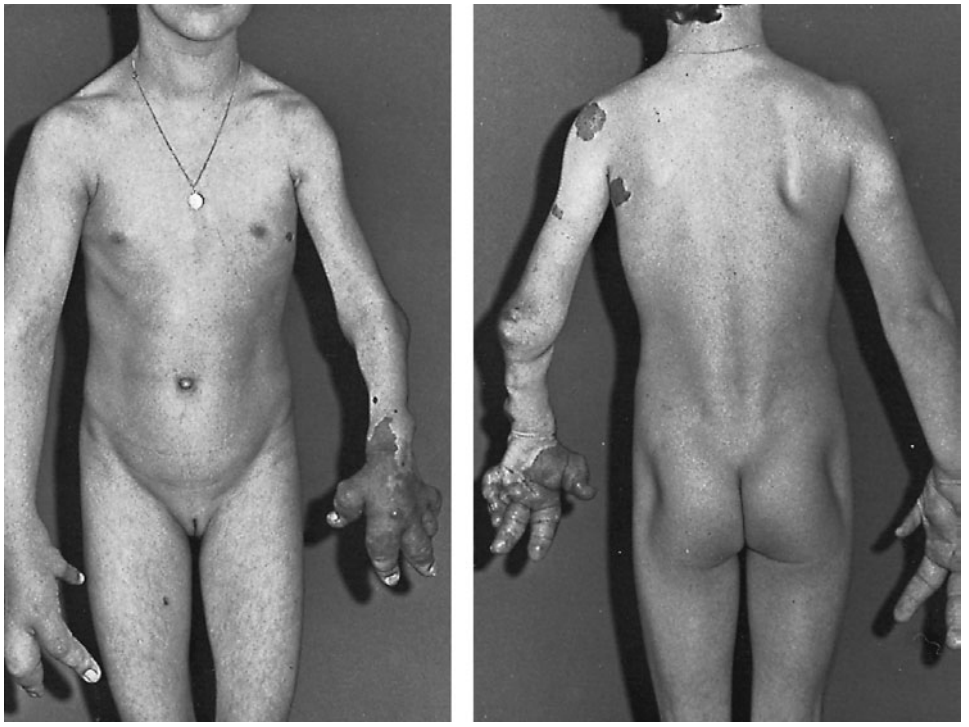
Veins may have valves or may be valveless. Ectatic veins may appear as studded venous flares in capillary malformations of the skin. These result from reflex of venous blood secondary to hypertension in the main venous anomaly (58). Intermittent episodes of thrombophlebitis in the affected limb have been reported in about 50% of children ($n = 47$), often associated with pain. Phleboliths result from past thromboses. Pulmonary embolism is found in about 10% of children ($n = 47$) (46) and may be higher in adults (5). The risk is particularly increased postoperatively.

Abnormalities of the deep veins are common in some series but not in others. Defects may include agenesis, atresia, hypoplasia, valvular incompetence, or aneurysmal dilatation (5,29,46,58). Resection of varicosities in patients with Klippel-Trenaunay syndrome is controversial. Severe vascular reflux and the presence of deep venous anomalies in some cases probably contraindicate excision. Graded elastic compression should be the first line of treatment, with surgical resection being reserved for significant incapacitating problems (46).

Significant arteriovenous communications of the type found in Parkes Weber syndrome are never found in Klippel-Trenaunay syndrome; in many large surgical series (29,46,49,58), clinically significant arteriovenous malformations are *not* reported (see Parkes Weber syndrome below). In Klippel-Trenaunay syndrome, there are *physiologic arteriovenous connections that are always trivial and never clinically important* (5,57).

Lymphatic malformations. Lymphatic abnormalities are very common and are found in more than 70% of patients with Klippel-Trenaunay syndrome (23,58). Cutaneous capillary malformations may be studded with lymphatic vesicles that leak lymph. Lymphedema of the lower limb is particularly common (Fig. 12–17). When the trunk is involved, lymphatic malformation of the intestine may be associated with a

[1] Varicosities in Klippel-Trenaunay syndrome have early onset in infancy or childhood, with more extensive distribution than classic varicose veins in the general population.



A B

Fig. 12–16. *Klippel-Trenaunay syndrome*. (A,B) Extreme enlargement of hands, disparity in size of arms, fixation of left elbow joint. (From E Nöh and R Steckenmesser, Z Orthopad 112:243, 1974.)

protein-losing enteropathy. Micro- and macrocystic lymphatic malformations often involve the groin, genitalia, and retroperitoneum.

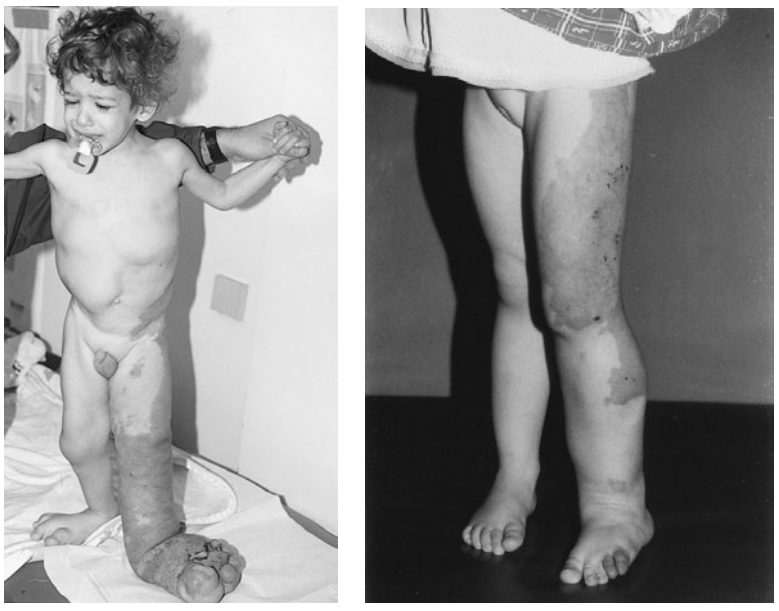
Limb enlargement. Lower limb enlargement is found in almost all cases. The affected limb may be thicker and longer. Thickness results from soft-tissue enlargement and is especially pronounced with lymphatic involvement. Increased adiposity is found in some patients. When the long bones are involved, the affected limb is increased in length and bone thickness is also increased. With leg-length discrepancy, compensatory scoliosis may result.

Macrodactyly may involve toes on the affected foot but may be present on both feet. Other abnormalities are associated with some cases. Cutaneous syndactyly rarely involves more than two toes. Miscellaneous defects may include polydactyly, clinodactyly, talipes equinovarus, talipes calcaneovarus, and metatarsus varus (33).

Secondary cutaneous manifestations. These may include eczema, hyperhidrosis, atrophy, ulceration, and cellulitis (16).

Other. Cerebral hemihyperplasia has been found in 18% (52a).

Parkes Weber syndrome. Parkes Weber syndrome, considered a separate entity here, is commonly designated with a hyphen—Parkes-Weber syndrome. In Parkes Weber's own papers (41–43), no hyphen is used. He described patients with enlarged arteries and veins, capillary or venous malformations, and enlargement of a limb. Although Parkes



A B

Fig. 12–17. *Klippel-Trenaunay syndrome*. (A,B) Combined capillary, lymphatic, and venous malformation. Involvement of left leg with extension to buttock and perineum. Note increased girth and axial overgrowth. The cutaneous capillary malformation is studded with lymphatic vesicles. (Courtesy of JB Mulliken, Boston, Massachusetts.)

Table 12–6. Comparison between Klippel-Trenaunay syndrome and Parkes Weber syndrome

	Klippel-Trenaunay syndrome	Parkes Weber syndrome
Color of cutaneous vascular malformation	Tends to be bluish to purplish	Usually pink and more diffuse
Arteriovenous fistulas	Insignificant	Significant
Lateral venous anomaly	Very common	—
Limb affected		
Upper	5%	23%
Lower	95%	77%
Limb enlargement	Usually disproportionate, involving soft tissue and bone; macrodactyly, particularly of toes, common	Arm- or leg-length discrepancy
Prognosis	Usually good; pulmonary embolism encountered occasionally	More problematic, particularly in those that develop bradycardia, which may lead to cardiac enlargement or limb amputation

Data from AE Young, Hemangiomas and malformations. In: Vascular Birthmarks, JB Mulliken and AE Young (eds), W.B. Saunders Company, Philadelphia, 1988, and DJ Robertson, Ann R Coll Surg Engl 18:73, 1956.

Weber syndrome and Klippel-Trenaunay syndrome are similar, slow-flow venous malformations are predominant in Klippel-Trenaunay syndrome, but arteriovenous (AV) fistulas are always found in Parkes Weber syndrome. Large series of patients are those of Robertson (45) and Young (58). All cases have been sporadic.

The involved limb is warm. The color of the cutaneous vascular malformation is usually more diffuse and pinker than that observed in Klippel-Trenaunay syndrome. Lymphatic malformations do not occur and no lymphatic vesicles are found in the discolored skin. The prognosis in Parkes Weber syndrome is more problematic; cardiac failure may lead to cardiac enlargement and cutaneous ischemia, requiring limb amputation (45,58). Klippel-Trenaunay syndrome and Parkes Weber syndrome are contrasted in Table 12–6.

Sturge-Weber syndrome. Sturge-Weber syndrome, a sporadically occurring disorder, is defined as a capillary malformation of the leptomeninges with or without choroid and facial V1 or V1–V2 involvement (Table 12–7). The syndrome can be explained by an embryonic defect with secondary consequences. During the sixth week of development, a vascular plexus forms around the cephalic portion of the neural tube and beneath the ectoderm destined to become facial skin. Normally, this vascular plexus regresses during the ninth week, but in Sturge-Weber syndrome, it persists, resulting in a capillary malformation of the leptomeninges overlying the cerebral cortex together with a facial "port-wine" stain on the ipsilateral side. Variation in the persistence or regression of the vascular plexus accounts for cases with unilateral or bilateral involvement and also for cases with capillary malformation of the leptomeninges with absence of facial involvement (2,10,51) (Figs. 12–18 and 12–19).

Capillary malformations of the skin may extend below the head and neck and appear anywhere on the body, including the upper and lower limbs. Limb involvement is different from that found in Klippel-Trenaunay syndrome. The latter has lymphatic malformations, lateral venous anomaly, lymphatic vesicles and venous flares within the capillary malformation, limb enlargement, and macrodactyly—*which do not occur in Sturge-Weber syndrome*. Only capillary malformations are found in Sturge-Weber syndrome. Hemiparesis, present in some patients, may result in a *hypotrophic limb*.

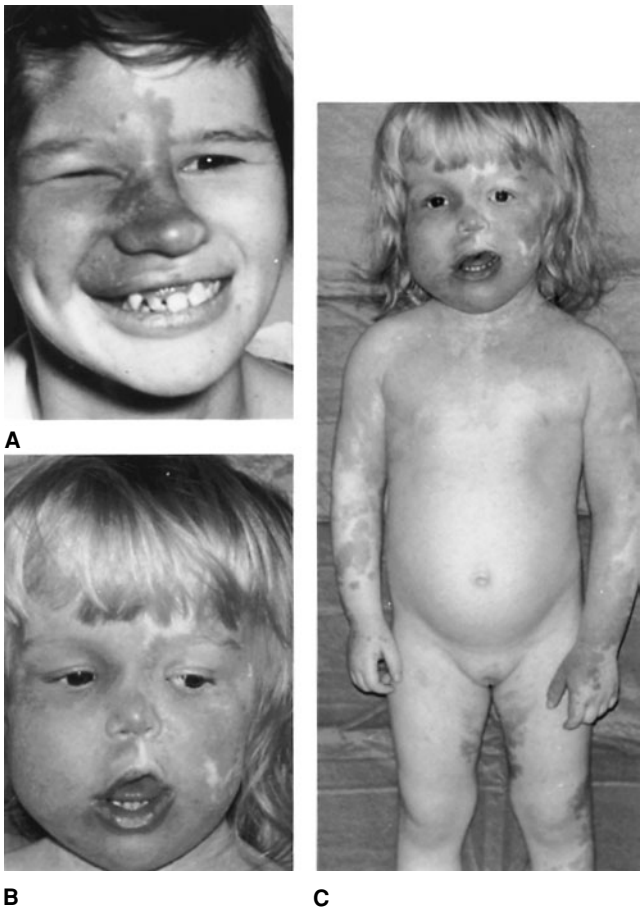
Table 12–7. *Sturge-Weber syndrome*—manifestations (n = 52)

Manifestation	%
Craniofacial capillary malformation	98
Unilateral	46
Bilateral	54
V_1	100
V_2	76
V_3	60
Extracephalic capillary malformation	52
Seizures	83
Neurologic deficits	65
Headaches	62
Glaucoma	60
Lower-limb hemihypoplasia	48

Data from E Sujansky and S Conradi, Am J Med Genet 57:35, 1995.

Overgrowth may occur in Sturge-Weber syndrome, but it tends to be minor and is always secondary to the vascular anomaly. Overgrowth of the bony maxilla is common. When the capillary malformation involves the ear, its length may be greater than that of the contralateral ear. Rarely, a digit may be enlarged. In contrast, overgrowth in Klippel-Trenaunay syndrome is striking and macrodactyly may occur in the "uninvolved" limb.

Fig. 12–18. *Sturge-Weber syndrome*. (A) Note facial distribution of angiomatosis. (B) Note bilateral involvement. (C) Same patient as observed in B. Note angiomatosis on body and enlargement of left arm and hand. This patient represents an example of Sturge-Weber syndrome as part of Klippel-Trenaunay syndrome). (B,C from MM Cohen Jr, Dysmorphic syndromes with craniofacial manifestations. In: Orofacial Genetics, Stewart RE, Prescott GH (eds), Mosby, St. Louis, 1976.)



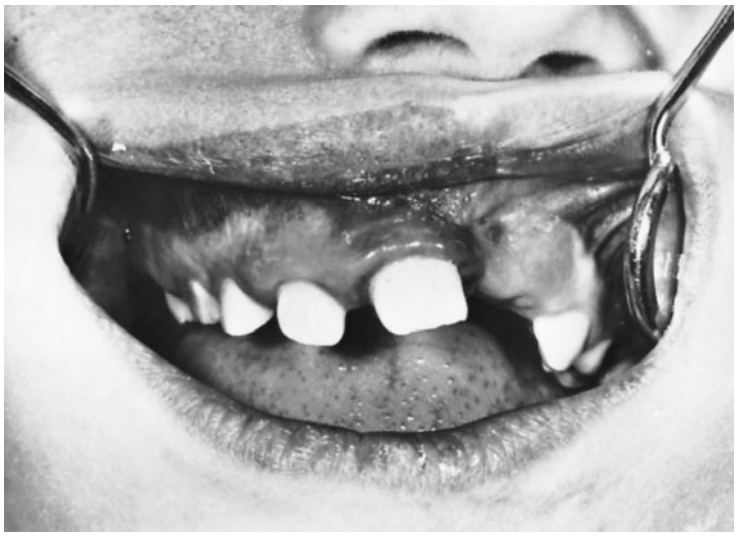


Fig. 12–19. *Sturge-Weber syndrome*. Gingival enlargement and angiomatosis. Eruption of teeth on affected side is more advanced than on unaffected side.

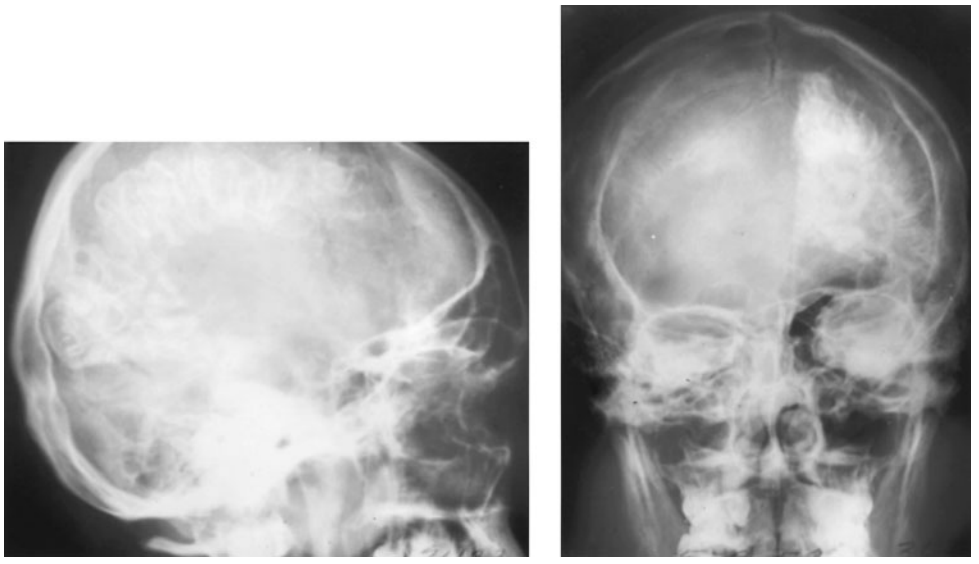
Seizures occur in about 83% of the cases (Table 12–7). These can begin during infancy; seizures are contralateral to the leptomeningeal capillary malformation. Most often seizures are local, but generalized seizures may also occur. Hemiparesis is less frequent (2,51).

CT and MRI may demonstrate subtle early leptomeningeal abnormalities. Using SPECT with xenon-133 to evaluate cerebral blood flow, 75% of infants studied prior to the onset of seizures had *increased* cerebral blood flow in the involved cortex. Patients who had already developed seizures had *hypoperfusion* of the damaged hemisphere. Thus, rapid cerebral impairment follows seizures in patients with Sturge-Weber syndrome (4,9,13).

Seizures and cognitive disability. An alteration in the vascular dynamics of leptomeningeal malformation results in precipitation of calcium deposits in the cerebral cortex underlying the vascular malformation (Fig. 12–20), producing the double contoured ("railroad track") phenomenon. Seizures and mental deficiency may be secondary to this process. Several other possibilities have been suggested. First, documented microgyria might account for intractable seizures and cognitive deterioration. Second, arterial or venous thrombosis might also explain neurological and neuropsychological deterioration. Third, high seizure rates of discharge from the involved hemisphere might interfere with the function of the normal hemisphere or with its vascular control. Focal hyperperfusion for voluntary and cognitive acts might then be impaired. Fourth, abnormal venous circulation with reduced capacity for venous return might result in venous hypertension and chronic progressive ischemia. Failure to increase cerebral blood flow during seizures might then compromise an already ischemic cortex, resulting in further deficit and more seizures (2,4,30–32,40,50,53).

Vascular tumors and vascular malformations. Mulliken and Glowacki (37) and Mulliken (34) made a distinction between hemangiomas and vascular malformations based on cellular kinetics and clinical behavior. Hemangiomas have endothelial hyperplasia with rapid postnatal growth followed by slow involution. In contrast, vascular malformations are characterized by flat endothelium, growth of the lesion being commensurate with growth of the child. In vascular malformations, a single type of channel anomaly may predominate, or combined channel anomalies of various types may occur (Table 12–8).

Mulliken (34) noted that the "standard" terminology used for vascular lesions had led to confusion, improper diagnosis, illogical treatment, and misdirected research efforts. The Mulliken classification, which is based on research and clinical behavior of vascular lesions, is now considered state-of-the-art in plastic surgery. Significant inroads are also being made in dermatology and pathology.



A B

Fig. 12–20. *Sturge-Weber syndrome*. Radiographs. (A,B) Typical double contoured calcification. Note unilateral distribution.

Table 12–8. Biological classification of vascular malformations

Single channel
Arterial (AM)
Capillary (CM)
Lymphatic (LM)
Venous (VM)
Complex/combined
CLM
CVM
CLVM
LVM

Adapted from JB Mulliken, Semin Vasc Surg 6:204, 1993.

Burns et al (7) indicated that by clinical and cellular criteria, vascular birthmarks can be classified as hemangiomas, malformations, or macular stains. Because hemangiomas occur in 10%–12% of normal infants by one year of age and macular stains are found in about 40% of normal newborns, the authors queried whether either of these are *pathogenetically related* in the syndromes in which they have been described. True hemangiomas occur only rarely in malformation syndromes, but vascular malformations are common. Clinical conditions of concern in this chapter—Klippel-Trenaunay syndrome, Parkes Weber syndrome, and Sturge-Weber syndrome—have vascular malformations, not hemangiomas.

Kasabach-Merritt phenomenon. "Kasabach-Merritt syndrome" is better designated "Kasabach-Merritt phenomenon" because it is likely to be pathogenetically variable, as thrombocytopenia occurs in various types of vascular neoplasms and has variable therapeutic response (47).

Understanding the Kasabach-Merritt phenomenon is important for understanding Klippel-Trenaunay syndrome, in which it does *not* occur. The term "Kasabach-Merritt syndrome" is frequently applied incorrectly to patients with extensive venous or lymphaticovenous malformations who develop a localized intravascular coagulopathy (chronic consumptive coagulopathy) in which the platelet count is minimally depressed, varying from 50,000 to 150,000/mm^3. In contrast, with true Kasabach-Merritt phenomenon, thrombocytopenia is profound, varying from 3,000 to 60,000 mm^3 with an average of less than 25,000/mm^3 (47). The distinction has important treatment implications. For example, heparinization might be indicated in consumptive coagulopathy, particularly with thrombotic complications, but would be contraindicated with Kasabach-Merritt thrombocytopenia (47).

It has been demonstrated that the Kasabach-Merritt phenomenon occurs only with Kaposiform hemangioendothelioma and tufted angioma, *not* with common hemangioma (47). The differences between Kaposiform hemangioendothelioma and hemangioma are contrasted in Table 12–9. Tufted angioma is composed of discrete vascular tufts in the dermis and hypodermis together with peripheral crescentlike slits (13,14,56). Neither Kaposiform hemangioendothelioma nor tufted angioma occurs with Klippel-Trenaunay syndrome, and therefore the Kasabach-Merritt phenomenon does not occur with Klippel-Trenaunay syndrome either; Klippel-Trenaunay syndrome is associated with vascular malformations. Klippel-Trenaunay syndrome patients with extensive lymphaticovenous malformations may develop chronic consumptive coagulopathy, in which the platelet count is minimally depressed (50,000–150,000/mm^3).

Diagnosis. Klippel-Trenaunay syndrome should be separated clinically from Parkes Weber syndrome, because the prognosis is much more problematic in the latter disorder with its associated AV communications (Table 12–10). Although geneticists, dermatologists, and many other clinicians have merged the two conditions as "Klippel-Trenaunay-Weber syndrome," surgeons who deal with *large numbers* of Klippel-Trenaunay syndrome patients *all* separate the two disorders (29,36,46,49,58).

Presumed cases of merged Klippel-Trenaunay syndrome and Sturge-Weber syndrome simply represent Sturge-Weber syndrome with capillary malformations below the head and neck (Table 12–10). None of these presumed "combined cases" have essential manifestations of Klippel-Trenaunay syndrome such as lymphatic malformations, lateral venous anomaly, lymphatic vesicles and venous flares within the cutaneous capillary malformation, limb enlargement, or macrodactyly.

Table 12–9. Hemangioma and kaposiform hemangioendothelioma—a comparison.

	Hemangioma	Kaposiform hemangioendothelioma
Female:male ratio	3:1 (higher in some series)	~1:1
Time of appearance	Nascent at birth or appears within first 2 weeks; if deep or visceral, as late as 2–3 months	Present at birth, neonatal period, or later during infancy (2–12 months)
Location	~66% cervicofacial; ~20% multifocal (particularly intrahepatic); rare on trunk or retroperitoneum	Predilection for trunk, extremities, or retroperitoneum; never multifocal
Clinical appearance	If superficial: soft, red, raised; if deeper: bluish and slightly raised; if very deep or visceral: normal skin	Red to purple; centrifugally, advancing rim of ecchymosis with poorly defined margins; warm and indurated (edematous) on palpation; after widespread petechiae of thrombocytes < 10,000/mm^3
	Hemangioma	Kaposiform hemangioendothelioma
Histopathology	Proliferative phase: rapidly dividing endothelial cells. Early involuting phase: mast cells macrophages, fibroblasts. Involuted phase: fibrous tissue	Infiltrative growth pattern; spindle-shaped endothelial cells; microthrombi; hemosiderin
Kasabach-Merritt phenomenon	No	Yes
Complications	~20% (e.g., major ulcerations, destruction, distortion of involved tissue or obstruction of vital structures); ~1% life-threatening complications	12%–24% mortality rate (hemorrhage, sepsis, and/or inversion of vital structures)

Derived from JB Mulliken, Semin Vasc Surg 6:204, 1993 and M Sarkar et al, Plast Reconstr Surg 100:1377, 1997. Table from MM Cohen Jr, Am J Med Genet 93:171, 2000.

Differential diagnosis. Vascular malformations may also occur in *Maffucci syndrome*, *Bannayan-Riley-Ruvalcaba syndrome*, *Proteus syndrome*, and *macrocephaly–cutis marmorata syndrome*. Increased limb girth and macrodactyly may be found in *hemihyperplasia*.

Table 12–10. Criteria for distinctions between Klippel-Trenaunay, Parkes Weber, and Sturge-Weber syndromes

Klippel-Trenaunay syndrome	Slow flow, combined vascular (capillary, lymphatic, and venous) involving limb(s) and/or trunk
Parkes Weber syndrome	Fast flow, combined vascular (capillary, arterial, and venous) involving upper/lower limbs
Sturge-Weber syndrome	Capillary malformation of leptomeninges with or without choroid and facial V_1 or V_1–V_2 involvement. Capillary malformations can occur elsewhere on body.

Adapted from MM Cohen, Jr, Am J Med Genet 93:171, 2000.

Laboratory aids. Documenting the manifestations of Klippel-Trenaunay syndrome more thoroughly is essential in the future. Included should be an MRI with gadolinium to distinguish lymphatic from venous malformations. When this is done, perhaps all or most patients with true Klippel-Trenaunay syndrome will be found to have a lymphatic component. Careful study (magnetic resonance venogram or phlebography/venography) should also document the lateral venous anomaly and any abnormalities that may be present in the deep veins of the leg.

MRI is the most informative modality for studying various vascular malformations and can demonstrate flow characteristics and the extent of involvement within tissue planes. MRI can demonstrate the arteriovenous malformations of Parkes Weber syndrome. Cranial CT and MRI with contrast enhancement can demonstrate early leptomeningeal abnormalities in Sturge-Weber syndrome. Additional single-photon emission CT (SPECT) with xenon-133 to evaluate cerebral blood flow is a highly reliable method for diagnosing the CNS abnormalities in Sturge-Weber syndrome. In various conditions, CT may be used to demonstrate intraosseous vascular malformations and also secondary bone changes (13,34,35).

References (Klippel-Trenaunay syndrome, Parkes Weber syndrome, and Sturge-Weber syndrome)

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Maffucci syndrome (enchondromatosis and vascular malformations)

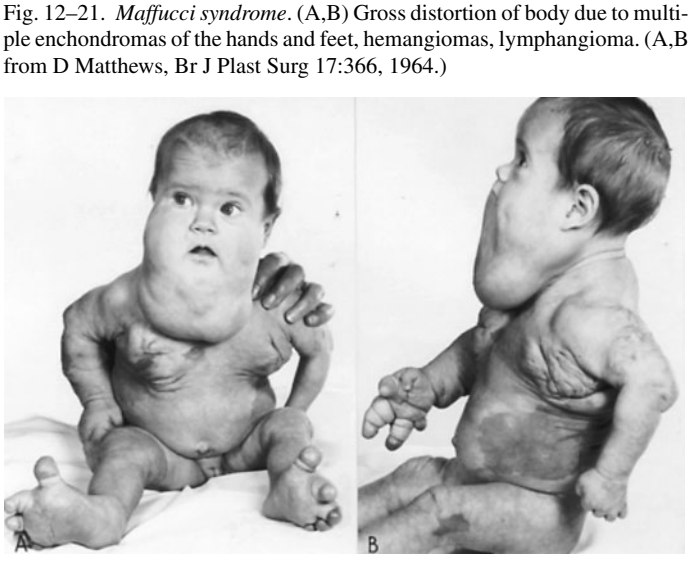
This syndrome is characterized by enchondromatosis, bone abnormalities, vascular malformations, and phlebolithiasis. The condition was described by Maffucci (40) in 1881 and by Kast and von Recklinghausen (32) in 1889. There are a number of excellent reviews (2,8,9,13,31,36). About 225 cases have been described, about 40% of these during the past 25 years. The etiology is unknown. All reported cases have been sporadic and there is neither racial nor sex predilection (2,36).

Skeletal system. Enchondromas are usually diagnosed between 1 and 5 years of age (38,44). These cartilaginous tumors are most numerous in the phalanges of the hands and feet, but may involve any bone preformed in cartilage (12,14,36,43,49). They have been unilateral in approximately 40% (2), but are frequently bilateral, although asymmetric. Skeletal abnormalities may become so severe as to produce gross bone deformity (Figs. 12–21 and 12–22) (10,14,27,36,43,49). Limb-length discrepancy (2,4,15,16,30,34,41), scoliosis (4,9,30,34,35,52), and bowing of limbs (4,28,34,38,41) may also occur. Short stature is not uncommon (30,34,44). Fractures have been reported (4,9,12,24,25,27,34,41,49,52).

Vascular abnormalities. Vascular malformations are often venous, but capillary malformations have also been recorded (1,2,11,12,14,16, 18,36,39,45,46,49). They occur most commonly on the skin, and the hand is frequently involved. Internal sites have also been noted, including the meninges (18), pharynx (37,38,52), tonsil (55), esophagus, ileum, and anal mucosa (25,27,35a,46). Phlebectasia has been reported in approximately 25% (2,46) and phlebolithiasis is common (6,7,10,28,34,36,41,44,50). Lymphatic malformations also occur (4,34,37,41,51).

Neoplasms. Chondrosarcomas may develop in enchondromas (7,16,18,24,26,36,49,50,54). The incidence of malignant transformation has been estimated as 17.8% and also as 30% (2,8,17,24,36). These figures are clearly inflated because of reporting bias. A variety of other tumors have been noted, including carotid body tumor (3), angiosarcoma (8,19,33), pancreatic carcinoma (50), hepatic adenocarcinoma (50), ovarian teratoma (34), ovarian cystadenocarcinoma (38), malignant ovarian tumor of mesenchymal origin, otherwise unspecified (36), glioma (13,18), astrocytoma (18), pituitary adenoma (42, also see 47), and unspecified brain tumor (50).

Fig. 12–21. *Maffucci syndrome*. (A,B) Gross distortion of body due to multiple enchondromas of the hands and feet, hemangiomas, lymphangioma. (A,B from D Matthews, Br J Plast Surg 17:366, 1964.)



Oral manifestations. Vascular malformations, seen in 5%–10%, have been frequently noted on the tongue (34,35,35a,37,39,41), although the buccal mucosa (5,34,37), lips (56), gingiva (56), and palate (39,46,49,53) have been documented sites.

Differential diagnosis. The syndrome should not be confused with Ollier disease (enchondromatosis without vascular malformations). Occasionally, difficulty may be encountered in distinguishing Maffucci syndrome from blue rubber bleb nevus syndrome, in which capillary malformations are found on the skin but multiple enchondromas are not present. Gallione et al (22) suggested that familial venous malformation syndrome that maps to 9p is identical to blue rubber bleb nevus syndrome. Sakurane et al (46) described a patient with Maffucci syndrome and the blue rubber bleb nevus syndrome who probably really had Maffucci syndrome. Schnall and Genuth (47) reported a patient with enchondromas, vascular malformations, pituitary adenoma, parathyroid adenoma, and neurilemoma of the nerve roots at the level of the sixth thoracic vertebra, which may represent a disorder different from Maffucci syndrome. Patients with the *Klippel-Trenaunay syndrome* and blue rubber bleb syndrome (23) also have cutaneous capillary malformations but lack enchondromatosis. *Proteus syndrome* should be excluded. Various other forms of enchondromatosis have been discussed elsewhere (20,21,24,29,48).

Laboratory aids. Use of CT scans has been advocated to distinguish enchondromas from chondrosarcomas (54).

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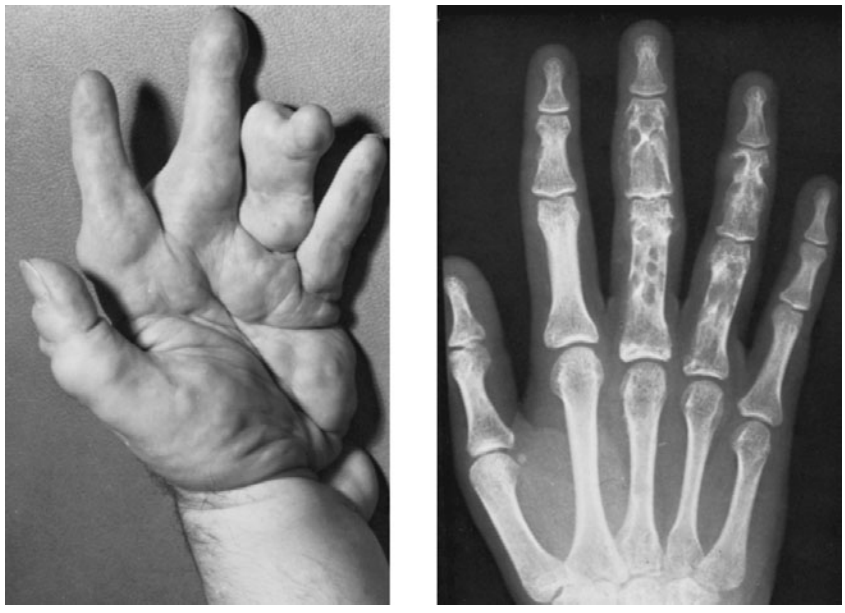
A B



C D

Fig. 12–22. *Maffucci syndrome*. (A) Hemangiomatous and enchondromatous involvement. (B) More severe involvement. (C) Distortion from multiple enchondromas. (D) Radiograph showing enchondromas of several phalanges. (A from GFY Ma and PC Leung, Br J Plast Surg 37:615, 1984. B from DA Tilsley and PW Burden, Br J Dermatol 105:331, 1981. C from WB Bean, Arch Intern Med 95:767, 1955. D from WG Cauble and HS Bowman, Arch Surg 97:678, 1968.)

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Multiple endocrine neoplasia, type 2B (multiple mucosal neuroma syndrome, MEN type 3)

Initially described in part by Wagenmann (90) and by Froboese (36) in 1922–1923, the syndrome of multiple mucosal neuromas, pheochromocytoma, medullary carcinoma of the thyroid, and asthenic body build with muscle wasting of the extremities (marfanoid habitus) was delineated in considerable detail by a number of authors (16–23,37,40–42,46,53,59,94). About 150 patients have been described.

The syndrome has autosomal dominant inheritance with high penetrance and variable expression. About 50% represent new mutations (20). The gene maps to 10q11.2 (67). The syndrome can be explained by hyperplasia and/or neoplasia of neural crest derivatives (6,86,93,94). MEN 2B is due to two different missense mutations in the receptor tyrosine kinase of the RET protooncogene (9,15,32,49). Over 95% are caused by a single methionine to threonine (M918T) substitution in the intracellular tyrosine kinase domain (32,65). The mutation is of paternal origin (14). The other 4% are due to an A883F mutation.

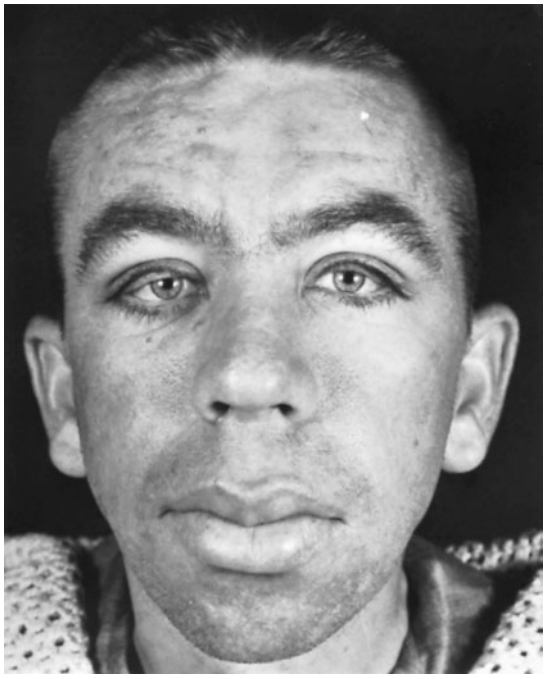


Fig. 12–23. *Multiple endocrine neoplasia, type 2B*. Facies is characterized by coarse features, large nodular lips, eversion of upper eyelids. (From RN Schimke et al, N Engl J Med 279:1, 1968.)

Facies. In infancy, there is often a history of profound difficulty in feeding with failure to thrive. The distinct facies is elongated and characterized by a wide-eyed expression, broad-based nose, and large nodular lips with submucosal nodules on the vermilion border. The tarsal plates are visibly thickened resulting in eversion of the upper eyelids. Surgical reduction of the lips reveals enormous enlargement of the diameter of the peripheral nerves (69). The lower face appears long (Fig. 12–23). The characteristic facies is not always present (77). Circumoral and/or midfacial lentiginosis has been occasionally seen (6,12,26).

Ophthalmologic manifestations. The upper eyelid margins are thickened and often everted (10,24,43,53,62). Pedunculated neuromas are present on the palpebral conjunctiva, eyelid margins, or, rarely, the cornea in about 60%.

The cornea is the site of thickened prominent white medullated nerve fibers (5,10,36,53,64,79,82) that can easily be seen under slit lamp examination. They extend into the pupillary area, where they anastomose (Fig. 12–24).

It is the personal experience of one of us (RJG) that there are insufficient tears in about 40%. This has rarely been noted (66).

Otolaryngologic manifestations. Nasal, laryngeal, and bronchial mucosa may also be the site of neuromas (5,10,41,53,54,64,79). Perinasal skin may rarely be affected (77,85). Hyperplasia of neurenteric ganglion cells has been found in the bronchi.

Thyroid gland. Medullary carcinoma of the thyroid has been found in more than 90% (53,70). With predictive testing, most patients have been about 10 years of age at time of initial diagnosis of the thyroid cancer but about 75% have metastasis at the time of diagnosis. However, patients

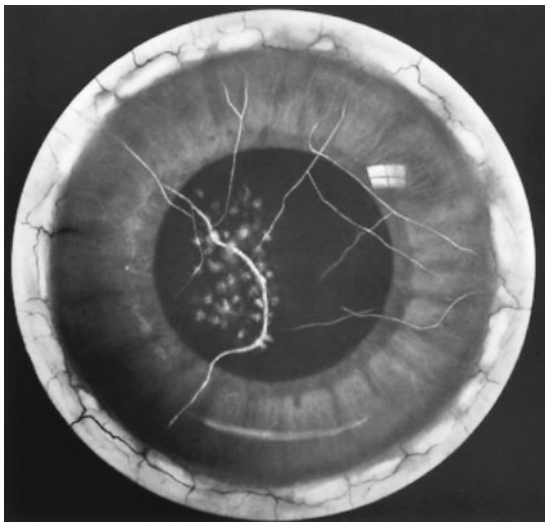


Fig. 12–24. *Multiple endocrine neoplasia, type 2B*. White medullated corneal nerve fibers which anastomose in pupillary area. [From DL Knox, Birth Defects 7(3):161, 1971.]

in the first decade of life, including one as young as 6 months (83,84), have been reported to have already developed this neoplasm (53,64,70). Prophylactic thyroidectomy should be done as soon as diagnosis is made. Prospective surveillance should begin at birth and continue to the age of about 40 years. The carcinoma occurs with equal frequency in both sexes and may be present without symptoms or palpable nodules in the thyroid gland (35,83). Several tumors often develop multifocally within the same or within different lobes of the thyroid gland (35,61,64). In over 90% this neoplasm spreads through lymphatic vessels to cervical lymph nodes and mediastinum. Metastasis to regional lymph nodes is frequently found at initial thyroid surgery (Fig. 12–25A) (24,25,41,52,70,79). The average age at death from this neoplasm is 21 years (75).

Medullary carcinoma of the thyroid arises from parafollicular cells (C cells) that have their origin in the embryonic ultimobranchial body, which in turn is derived at least in part from the neural crest (41,48,58,95). It is the only thyroid tumor that contains amyloid (Fig. 12–25B), which is seen interspersed among the cells and fibrous septa. The amyloid frequently calcifies. The C cells on electron microscopy exhibit characteristic secretory granules (Fig. 12–25C). C-cell hyperplasia is frequently found adjacent to areas of carcinoma; occasionally, in young patients, only C-cell hyperplasia is present, indicating that it is a precursor of medullary carcinoma (27,88). In addition to elaborating calcitonin, medullary thyroid carcinoma may also produce amyloid, serotonin, cytokeratin, chromogranin, bombesin, carcinoembryonic antigen, 5-hydroxyindole acetic acid, histaminase, bradykinin, various prostaglandins, DOPA decarboxylase, somatostatin, and an ACTH-like peptide (11,41,79).

Adrenal gland. Pheochromocytoma has been diagnosed in about 50%. It increases in frequency with age, probably being present in 90% of older patients. It most often presents during the second and third decades of life, especially when provoked during investigation of the thyroid neoplasm. About 10% of patients die from a cardiovascular crisis just before or after surgery; the average age at death in those with pheochromocytoma is 21 years (75). Although rare, extra-adrenal lesions have been reported (63). The presence of pheochromocytomas due to catecholamine secretion is often heralded by paroxysmal weakness, flushing, pounding headache, nausea, hypertension, dyspnea, palpitation, flatulence, paresthesia, blanching of the extremities, profuse sweating, and intractable diarrhea. Abdominal discomfort or cramping is frequently experienced.

Pheochromocytomas arise from cells derived from the neural crest. The tumors are multiple and bilateral in 70% when associated with medullary carcinoma of the thyroid (Fig. 12–26) (5,60,63,79,92,94,96). When bilateral, one of the tumors may precede the other by decades. They range in size from a few millimeters to several centimeters in diameter. Malignant change is uncommon before the tumor exceeds 4 cm in diameter (80). Adrenal medullary hyperplasia is a precursor to pheochromocytoma (20,92).

Gastrointestinal tract. Gastrointestinal abnormalities may be present shortly after birth. Abdominal distension is common. At least 30% have some intestinal complaint: megacolon (Fig. 12–27A), diverticulosis, and chronic constipation alternating with watery diarrhea (16,19,28,29,61,64). Achalasia has also been reported (26). These abnormalities are in part related to a vasoactive intestinal peptide (90) and in response to the secretory products of the medullary carcinoma of the thyroid (61). Histopathologic study has revealed diffuse intestinal ganglioneuromatosis (Fig. 12–27B), which may involve the entire gut as well as the liver, gallbladder, and pancreas (16,19,94,96). Esophageal dysmotility has also been shown (28). Rectal carcinoid (30) and adenomatous polyposis coli have been found (72).

Musculoskeletal alterations. At least 60% have an asthenic or Marfanoid habitus with severe muscular wasting (56). Weakness especially of the proximal muscles of the extremities seen in 15% simulates a myopathic state (Fig. 12–28) (10,20,23,25,29,41,62,64,69,79). Various skeletal alterations include: pectus excavatum, talipes equinovarus, pes cavus (25%), slipped femoral epiphysis (10%), aseptic necrosis of lumbar spine, kyphoscoliosis (25%), lordosis, and increased joint laxity (12%). These findings have been extensively reviewed elsewhere (34,41,69).

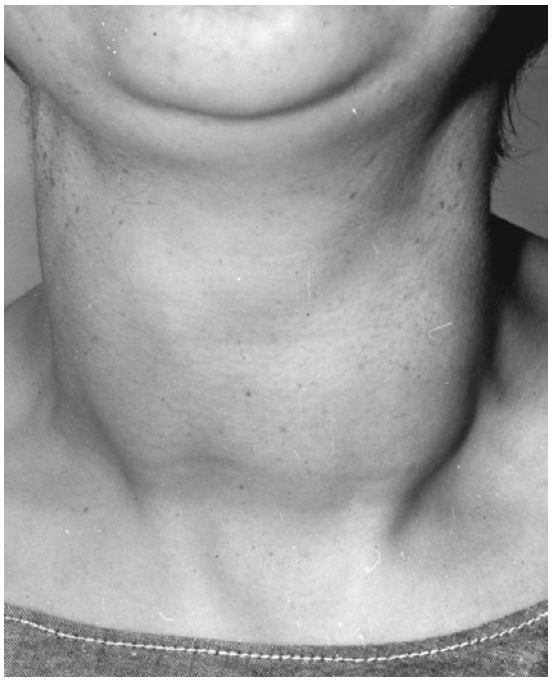
Other findings. Melanotic skin pigmentation has been reported, possibly reflecting elaboration of an MSH-like peptide by the medullary carcinoma of the thyroid (25). Hypertrophy of peripheral nerves has been found (51,68,97). Dyck et al (31) found involvement of autonomic nerves as well as of somatic motor and sensory neurons; these investigators postulated that neurologic symptoms in this disease could be attributed to neuroma formation. The cutaneous nerves are enlarged (22). Pubertal delay has been reported (59,93).

Oral manifestations. Oral and labial involvement is the first component of the syndrome to bring attention to the disorder, almost always in the first decade of life (51). In possibly 50%, these lesions are congenital or noticed in early infancy (16,19,41–43,51,64). The oral lesions consist of mucosal neuromas that principally involve the lips and tongue, although the buccal mucosa, gingiva, and palatal mucosa may be affected (20,41–43) (Fig. 12–29A,B). Both lips are extensively enlarged and nodular and have been described as blubbery. The lingual lesions are most commonly found on the anterior dorsal surface of the tongue and appear as pink pedunculated nodules; they have also been reported on the ventral tongue surface (56).

On light and electron microscopy, the mucosal nodules are plexiform neuromas (18,24,42,97)—that is, unencapsulated masses of convoluted myelinated and unmyelinated nerves surrounded by a thickened perineurium (Fig. 12–29C) which elaborate calcitonin (79). Histochemical investigation demonstrates absence of both specific and nonspecific cholinesterase activity, in contrast to neurofibroma, which rarely contains axons but is cholinesterase positive (42). Mucosal neuromas are epithelial membrane antigen positive and S-100 negative (13).

Cephalometric studies report high palatal vault, posterior crossbite, steep mandibular plane, and mandibular retrognathism (73). The mandibular canal and mental foramen are widened (Fig. 12–29D) (2). Mandibular prognathism has been noted in several patients (29,53).

Differential diagnosis. Pheochromocytoma may occur as an isolated tumor or as an autosomal dominant trait (87). It is also found in about 1% of cases of neurofibromatosis. Pheochromocytoma may also be seen with von Hippel–Lindau syndrome (4) and with brain tumors, including cerebellar hemangioblastoma, ependymoma, astrocytoma, meningioma, and spongioblastoma. Medullary carcinoma of the thyroid has been reported to occur without other abnormalities or as an autosomal dominant



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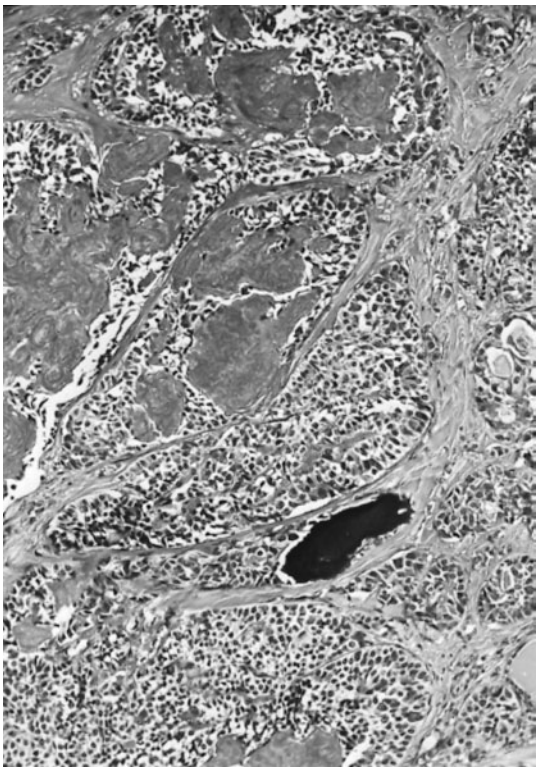

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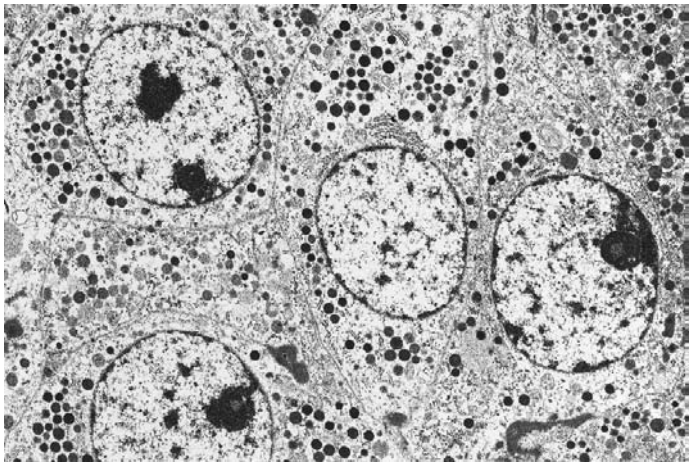
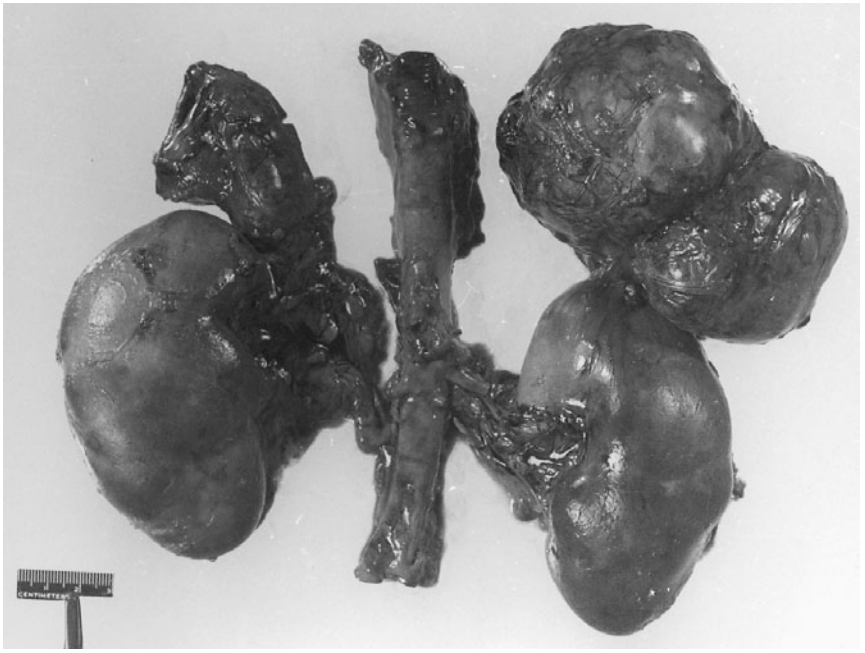


C

Fig. 12–25. *Multiple endocrine neoplasia, type 2B*. Multiple endocrine neoplasia. (A) Presentation of medullary carcinoma of the thyroid. (B) Photomicrograph showing sheets of round to spindle-shaped cells among which are masses of amyloid. (C) Medullary carcinoma of thyroid (original mag. × 6500). The C cells containing multiple secretory granules are easily visualized. (B from GH Friedell, Cancer 15:241, 1962. C courtesy of GM Dodd and B Mackay, MD Anderson Hospital and Turner Institute, Houston, Texas.)

trait (45). Pheochromocytoma-medullary thyroid carcinoma-parathyroid adenoma (MEN 2A, Sipple syndrome), an autosomal dominant disorder also mapping to 10q11.2, results from missense mutations, i.e., replacement of one of several cysteine residues in the *extracellular* domain of the RET proto-oncogene molecule. As indicated earlier, patients with MEN 2B have a mutation in the intracellular catalytic domain of the molecule (32). MEN 2A is about six times as common as MEN 2B. Importantly and in contradistinction to MEN 2B patients, most of those with MEN 2A have hyperparathyroidism secondary to hyperplasia or adenomas of the parathyroids due to excess calcitonin (88). The corneal nerves may be somewhat enlarged in MEN 2A (55). Hyperparathyroidism may rarely have autosomal dominant inheritance or exhibit central giant cell granulomas or fibro-osseous lesions of the jaws (74,91). Carney et al (21) reported three families in which pancreatic islet cell tumors and pheochromocytomas had autosomal dominant inheritance. Griffiths et al (45) described the association of pheochromocytoma, neurofibromatosis, and duodenal carcinoid. Other overlapping syndromes have been reviewed by Schimke (76). Ganglioneuromatous polyps and juvenile or adenomatous polyposis of the large bowel have been reported. Intestinal ganglioneuromatosis as an isolated finding may have autosomal dominant inheritance (3). In a small series of apparently isolated intestinal ganglioneuromatosis cases, occult germline RET M918T mutations were found. Ultimately they were found to have MEN2B (33). Multiple systematized neuromas of the skin and mucosa have been reported in the absence of the syndrome (1).

Laboratory aids. It should be emphasized that DNA analysis permits the unambiguous identification of MEN 2B carriers (60,81). Germline RET testing should be done from cord blood or during the neonatal period. As indicated earlier, 95% have the M918T mutation, the other 4% being due to an A883F mutation (68). Before molecular technology was available, elevated calcitonin levels were expected if medullary carcinoma of the thyroid was present (7) even if the tumor was not clinically apparent. Screening was begun at birth and continued at regular



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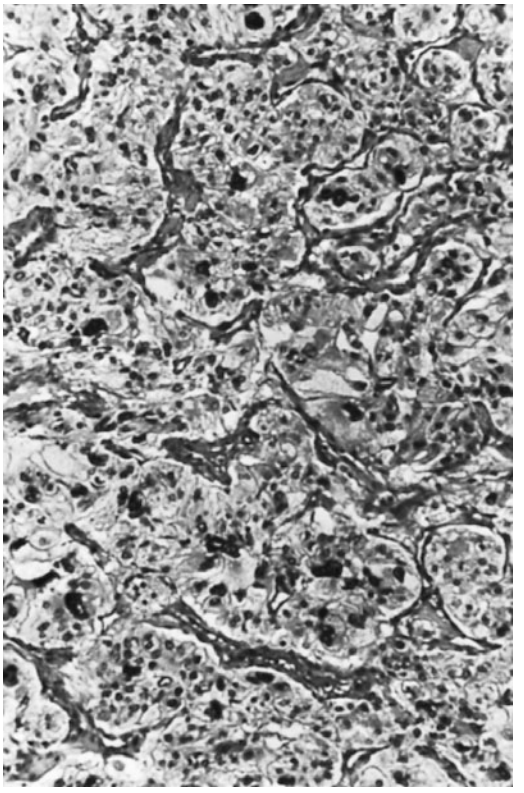
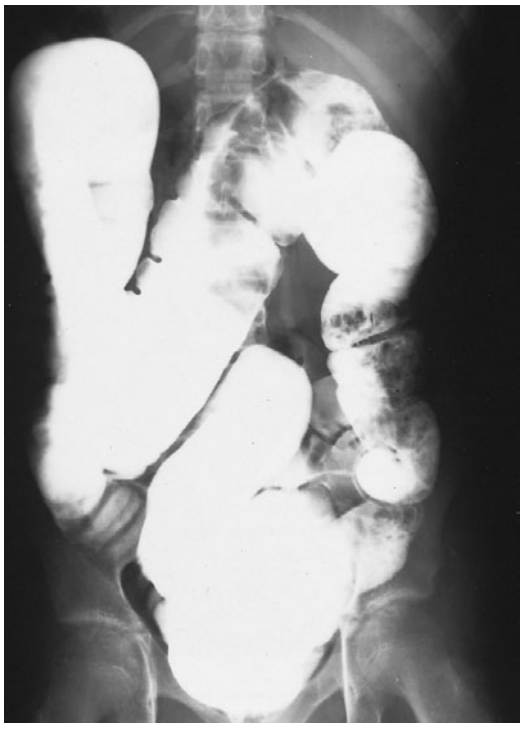


B

Fig. 12–26. *Multiple endocrine neoplasia, type 2B*. (A) Bilateral pheochromocytomas. One on left is much larger than that on right. (B) Photomicrograph showing polyhedral cells separated by thin connective tissue septa, rich in blood vessels.

Fig. 12–27. *Multiple endocrine neoplasia, type 2B*. (A) Barium demonstrates megacolon. (B) Hyperplastic neuromatous infiltrate with ganglion cells in intestinal walls between muscle layers.



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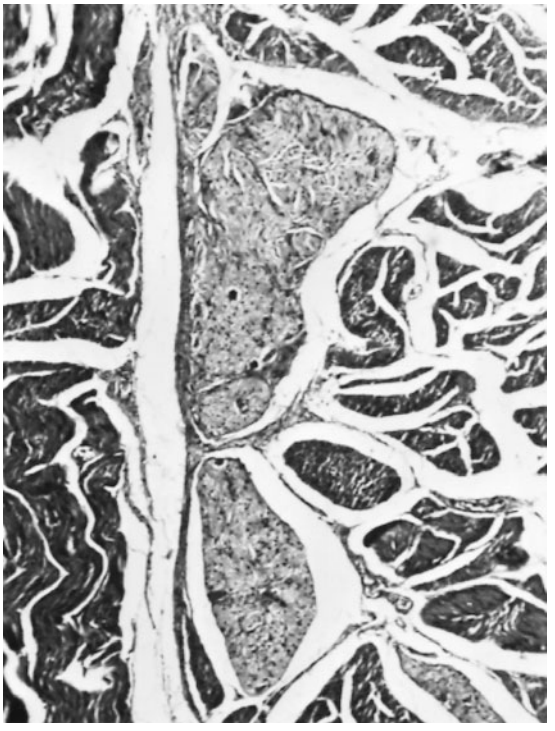

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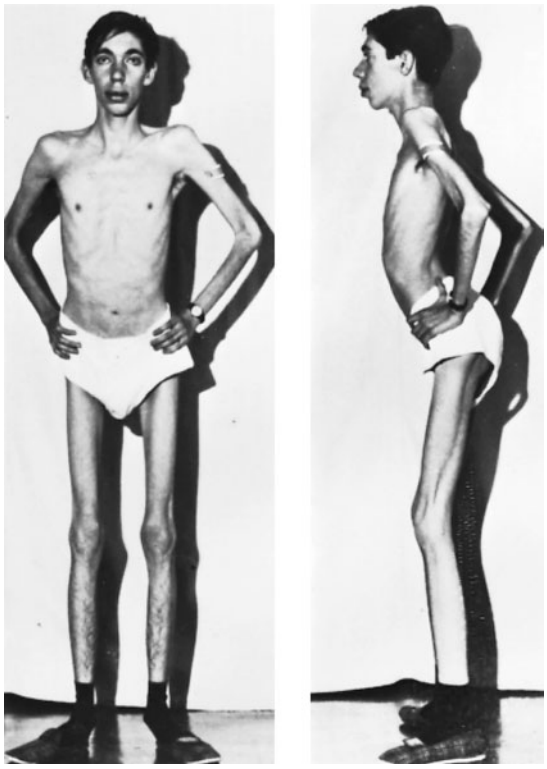

A B

Fig. 12–28. *Multiple endocrine neoplasia, type 2B*. (A,B) Asthenic habitus with muscle wasting and lumbar lordosis. (A,B from M Levy et al, Arch Fr Pediatr 27:561, 1970.)

intervals until age 35 (38). Several measurements were used in detection of recurrence, metastases, or growth of residual tumor using both serum and urinary assays (7). The pentagastrin stimulation test with or without calcium infusion was employed for producing maximum calcitonin secretion (21,79,88). Intradermal injection of 1:1000 histamine produces a wheal but no flare in patients with medullary carcinoma of the thyroid, a finding that is probably related to calcitonin gene-related peptide (5,41,71). It appears to be a type of dysautonomia and is probably related to the deficient tears seen in 40% of patients. Irregular calcification of the tumor metastases to lungs, liver, and bone (50) may be demonstrated in about 10% (30) by radionuclide scanning with technetium 99m (50,69). Fine needle aspiration biopsy has been used effectively in patients with palpable tumor (79). Fluorescamine can be employed for cytology on smears pretreated with formaldehyde gas (79).

Increased vanilmandelic acid and altered epinephrine/norepinephrine ratios demonstrate pheochromocytoma (47,89). Radiographically, the kidney may be displaced downward or eggshell calcification of the upper pole may be found (44). Preferred methods of imaging are CT and ultrasound. Scintigraphy may aid in diagnosis of pheochromocytoma or its metastases (8,35,57). Intestinal ganglioneuromatosis has a characteristic appearance on barium enema, such as alternating areas of spasm and dilatation (30).

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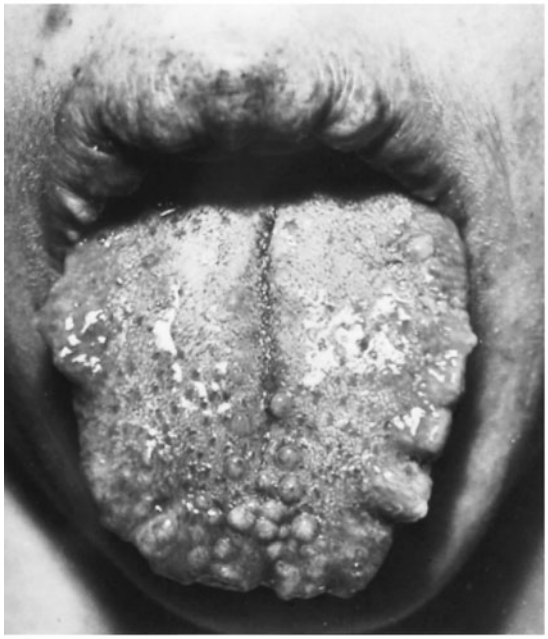

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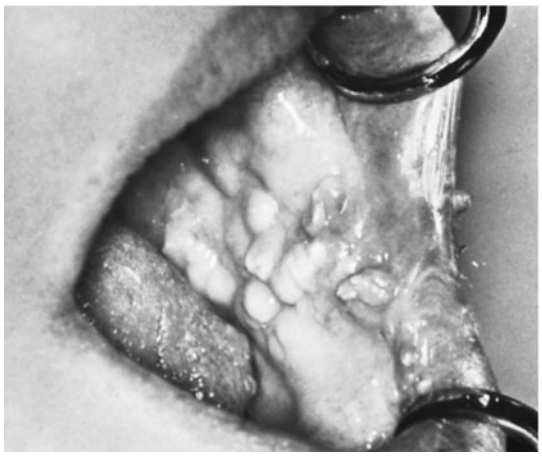

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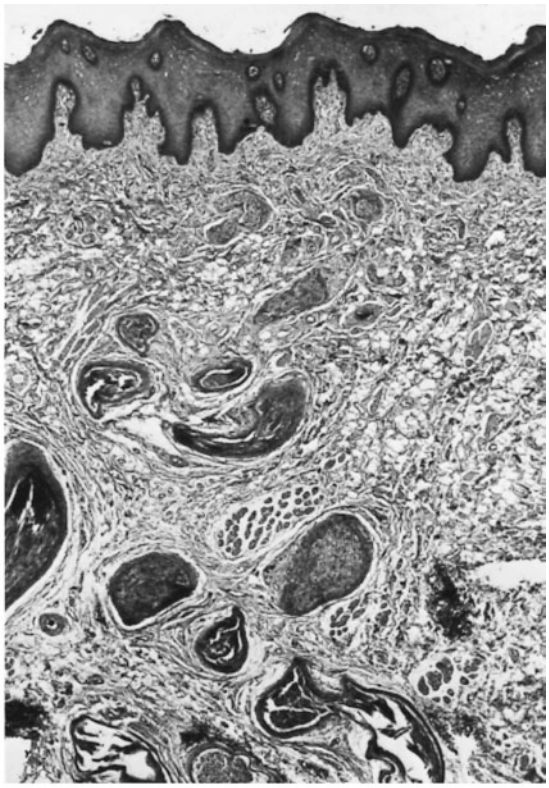

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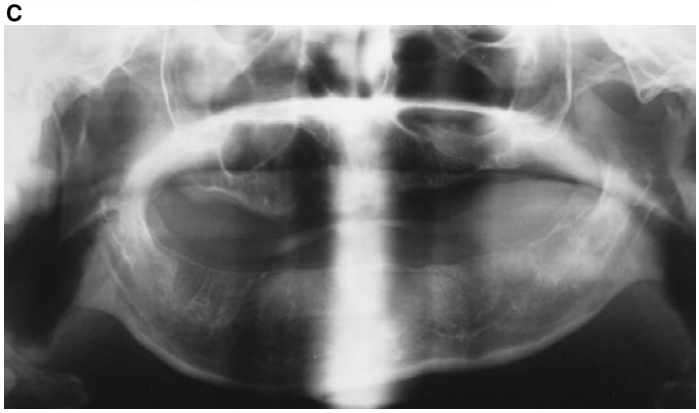

D

Fig. 12–29. *Multiple endocrine neoplasia, type 2B*. (A) Mucosal neuromas of lips and anterior and lateral dorsum of tongue. (B) Neuromas of buccal mucosa. (C) Congeries of axons of nerves. Histochemically, these are cholinesterase negative. (D) Widened mandibular canal. (A from KW Bruce, Oral Surg 7:1150, 1954. B from HE Simpson, Oral Surg 19:228, 1965.)

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Multiple odontoma-esophageal stenosis syndrome

Herrmann (3) reported a young male with huge tumors of the maxilla and mandible containing 1200 and 900 teeth, respectively, in various stages of development, including geminated and invaginated teeth. In 1973, Schmidseder and Hausamen (5) studied the same patient, noting that his two sons (one dying from pneumonia soon after birth) also manifested multiple odontomas of both jaws in infancy. The surviving infant was found to have a liver disorder and pulmonary stenosis. Subsequently, a daughter was born who again manifested odontomas. The boy experienced recurrences of odontomas that exhibited a higher degree of differentiation. He also suffered esophageal stenosis, as did his father (7).

Bader (1) reported multiple odontomas of both jaws in a female infant with calcified aortic stenosis, congenital cylindric bronchiectasis, leiomyomatosis of the esophagus with stenosis, hyperplasia of the myenteric plexus, and chronic interstitial cirrhosis of the liver. GL Barnes (personal communication, 1974) observed sibs with odontomas in four quadrants, malrotation and stenosis of the bowel, and iris colobomas.

Multiple odontomas were documented in male sibs by Schmitz and Witzel (6), but associated anomalies were not mentioned. Beisser (2) and Malik and Khalid (4) also reported multiple bilateral odontomas in both jaws.

In view of the occurrence of what appears to be a syndrome of multiple odontomas, chronic interstitial cirrhosis of the liver, and esophageal stenosis in two generations, it must be assumed that the disorder is inherited as an autosomal dominant trait. In case of Schmitz and Witzel (6), the parents of the male sibs were normal.

References (Multiple odontoma-esophageal stenosis syndrome)

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The neurofibromatoses (NF1 Recklinghausen type, NF2 acoustic type, other types)

In 1849, Robert Smith (160), the First Professor of Surgery at Dublin Medical School, reported the clinical and necropsy findings in two cases of neurofibromatosis and cited 75 references from the earlier medical literature. He did not recognize that the tumors contain neural elements, however, and it was von Recklinghausen's (175) publication in 1882 that convinced the medical world that neurofibromatosis (NF) was a distinct entity. A recent survey is that edited by Viskochil (174).

The reader is referred to the following sources for more detailed coverage: general aspects (30,33,39,81,111a,123,130,131,133,178), NF1 Recklinghausen type (8,15,31,39,79,81,106,131), NF2 acoustic type (17,48–50,79,110,112,131,142,154), tumors and neoplasms (27,44,64, 75,96,104,121,177,181), cutaneous manifestations (15,38,39,83,88,111, 183,187,191), skeletal findings (73,74,78,87,95,156), central nervous system manifestations (41,110,139), ophthalmologic features (54,56,60, 104,128,192), endocrine findings (148), pediatric aspects (23,36,37,46, 73,148,187), and animal models (68,149, see 131).

Types of neurofibromatosis. These have been classified by Cohen (32).

Neurofibromatosis, type 1 (NF1). This classic form of neurofibromatosis accounts for about 90% of all cases. The mutation rate has been calculated to be 1×10^{-4} mutations per gamete per generation (39), the highest in humans. Clementi et al (29) found a mutation rate of 6.5×10^{-5}. Major features include six or more café-au-lait spots, cutaneous neurofibromas, and Lisch nodules. Axillary freckling develops in approximately 66% of all patients. Inheritance is autosomal dominant with about 50% of cases representing new mutations.

Neurofibromatosis, type 2 (NF2). The hallmark consists of bilateral acoustic neuromas. Symptoms are usually caused by pressure on the vestibulocochlear and facial nerve complex, the first symptom usually being hearing loss that often begins during the teenage years or early twenties, but occasionally may occur as early as the first or as late as the seventh decade of life. Café-au-lait spots and cutaneous neurofibromas are also present, but occur less commonly than in NF1. Neurofibromas are easy to overlook; they are generally less than 2 cm in diameter, minimally raised, and often have a roughened surface that may have more prominent hairs than the surrounding skin. Axillary freckling is uncommon. On occasion, deep plexiform neurofibromas may result in palpable masses. Tumors of the central nervous system are especially common, Schwann cell tumors occurring most frequently. However, multiple tumors of meningeal or glial origin may also occur. Other Schwann cell tumors may develop along the cranial nerves or spinal roots (110). Some patients with NF2 have multiple schwannomas in the absence of acoutic tumors, meningiomas, or ocular pathology (86). Purcell and Dixon (127) reported schwannomatosis with meningiomas, gliomas, and astrocytomas. Presenile lens opacities or subcapsular cataracts occur in about 50%. Lisch nodules are uncommon. NF2 has autosomal dominant inheritance with penetrance of over 95%. Because NF1 and NF2 may both have central and peripheral manifestations, the previously used terms "peripheral neurofibromatosis" for NF1 and "central neurofibromatosis" for NF2 have been discarded as misleading and confusing (110).

Neurofibromatosis, type 3, Riccardi type. This type of neurofibromatosis has features of NF1 and NF2. Café-au-lait spots are usually pale, few in number, and may be large. Cutaneous neurofibromas are especially common on the palms. A multiplicity of brain tumors occurs, including acoustic neuromas, meningiomas, and spinal/paraspinal neurofibromas. Optic gliomas do not occur. Lisch nodules are absent. Brain tumors are usually of early onset with a rapid course that precludes procreation. To date, all cases have been sporadic (131).

Neurofibromatosis, type 3, intestinal type. In this form, neurofibromatous involvement is limited to the gastrointestinal tract. Onset of symptoms is delayed until adulthood and some carriers are asymptomatic until their middle or late adult years. Increased risk of intestinal problems include those of bleeding, intussusception, and obstruction (65,105). Inheritance is dominant and most likely autosomal, although no male-to-male transmission has been recorded as of this writing (65). Reciprocal translocation between chromosomes 12 and 14 has been described in one family and may be due to chance, or to linkage of the gene for intestinal neurofibromatosis to one of the breakpoints in chromosome bands 12q13 and 14q13 (172).

Neurofibromatosis, type 4. This is a residual category of variant phenotypes for patients who do not fit neatly into any other known type (131) (NF1, NF2, or NF3, Riccardi type).

Neurofibromatosis, type 5, segmental neurofibromatosis. Neurofibromas and café-au-lait spots restricted to one area of the body have been recorded frequently (39,59,84,89,91,115,117,120,131, 137,141,143,147,167a). Evidence is consistent with somatic mosaicism for NF1 mutations. Combemale et al (35) reviewed 88 cases. Wolkenstein et al (189) found that segmented NF is about 30 times less common than classic NF1.

Familial spinal neurofibromatosis. Although spinal neurofibromatosis is a serious complication in 1%–2% of NF1 patients and occurs more commonly in NF2, several families have only spinal neurofibromatosis (9,32).

Duodenal carcinoid syndrome. In this triad, duodenal carcinoid tumor and pheochromocytoma occur together with neurofibromatosis (32).

Etiology. Genetic aspects, chromosome map location, and the molecular biology of NF1 and NF2 have been discussed by many authors (8,14,15,22,23,32,43,47,53,58,70,79,81,82,86,94,107,109,116,129,131, 132,134,142,144,150,154,157,158,169,172). Inheritance is autosomal dominant. It has been reported in monozygotic twins (171).

NF1 is caused by mutations in a tumor suppressor gene that maps to chromosome region 17q11.2. The first hit is a germline mutation, with second hits occurring in developing tumors. The mRMA encoded is 11–13 kb with at least 59 exons. Four alternatively spliced transcripts have been identified (157). There are at least eleven NF1-related sequences, nine of which are located near centromere sequences of seven different chromosomes (129,151). Approximately 82% of the germline mutations that have been characterized to date severely truncate neurofibromin, the encoded protein (157,170). Hoffmeyer et al (70) reported the skipping of exons containing premature-termination codons. Klose et al (94) noted two independent mutations in the same family.

NF2 is caused by mutations in a tumor suppressor gene that maps to chromosome region 22q12.2. This has been ascertained after a high rate of acoustic neuromas has been found in those with chromosome abnormalities (168). Mutations have been identified in approximately two-thirds of affected individuals. The gene produces a protein called merlin or schwannomin. Merlin is absent in nearly all schwannomas (153). Increased expression of merlin impairs cell motility, adhesion, and spreading (58). A first-hit germline mutation is followed by second hits in developing tumors (107,155). Evans et al (47) found that somatic mosaicism is likely to be a common cause of NF2 in sporadic cases.

Biljsma et al (17) noted a G→A transition at the donor splice site of exon 5 in both affected and those at risk in the NF2 family.

Phenotypic/molecular correlations. In NF1, large deletions occur with greater frequency in patients with mental retardation, severe learning disorder, minor anomalies, and many cutaneous or plexiform neurofibromas of early onset (103,190). However, large NF1 deletions cannot be predicted solely on the basis of the clinical phenotypes (169).

In NF2, with missense and splice site variants, a milder phenotype has been demonstrated. In protein-truncating mutations, the phenotype is more severe (48,144).

Unusual aspects of neurofibromatosis. Whether the neurofibromatosis-Noonan syndrome (2,4,5,28,92,113,124,146,167) represents a true syndrome or variable expression of NF1 has been debated. A discrete entity may occur in a minority of reported patients who lack Lisch nodules, have few neurofibromas of the skin, and lack internal neurofibromas: The condition breeds true in affected families. Café-au-lait spots are also known to be a feature of classic Noonan syndrome. In most cases of neurofibromatosis-Noonan syndrome, Noonanoid features represent variable expression of NF1. One family has been reported in which Noonan syndrome and NF1 segregated separately (14,21). Watson syndrome, a combination of pulmonic stenosis, café-au-lait spots, and mental deficiency (3,98,167,179) has mild signs of both NF1 and Noonan syndrome. Allanson et al (6) showed linkage to the NF1 gene.

Asperen et al (10) reported a mother and son with NF1 and overgrowth with a Weaver syndrome–like phenotype. The proband had more than six café-au-lait spots, Lisch nodules, axillary freckling, and numerous neurofibromas. NF1 was confirmed at the molecular level.

Legius et al (102) reported a 2-year-old boy with NF1 and encephalocraniocutaneous lipomatosis. Findings included more than five café-au-lait spots and increased T2-weighted signals in the basal ganglia on MRI scan. An NF1 mutation was confirmed. The patient also had hemimegalencephaly, regional alopecia, lipomas of the occipital region, and seizures.

Neurofibromatosis, type 1. The classic form of neurofibromatosis, as described by von Recklinghausen (175), appears with a frequency of one case per 2500 to 3000 births and occurs approximately once in 200 individuals with mental deficiency (39). About 80,000 people in the United States are affected (131). Inheritance is autosomal dominant with almost 100% penetrance (131). Although it has been suggested that 25% of all cases represent new mutations (116), an earlier study (39) and a recent, large study (131) show that 50% represent new mutations, and an increase in paternal age at the time of conception has been found as an associated feature (134). Some authors (116) have suggested that maternal neurofibromatosis increases the overall severity of the disorder in affected offspring of the mothers, but in a large, well-controlled study (132), no significant differences in overall severity were found between maternal affected, paternal affected, and sporadically occurring cases.

Many of the features such as café-au-lait spots, neurofibromas, sphenoid bone dysplasia, and pheochromocytoma are of neural crest origin (131,133,178). Other findings, such as cerebral cortical heterotopias and optic gliomas, appear to be derived from the neural tube itself. Still other findings, such as pseudoarthrosis, coarctation of aorta, renal artery stenosis, rhabdomyosarcoma, and leukemia, appear to be of mesodermal origin (131,133).

Natural history. Natural history has been discussed by a number of authors (13,131,161). Over 40% of patients have some manifestations at birth, and over 60% by the second year of life (52). Café-au-lait spots usually develop first, with multiple lesions present within the first year of life. In about 50%, axillary freckling appears later. Cutaneous neurofibromas appear around the onset of puberty and increase in number throughout life. An increased number appear during pregnancy (45). Lisch nodules, best observed in slit lamp examination, begin to appear in early childhood and have been observed in almost all affected adults (79). Average height is reduced and 16% are below the third centile (131).

About 33% of all patients develop one or more complications. Plexiform neurofibromas occur in 30%. About 6% of those over 18 develop some form of malignancy. Other important complications include neurological problems in 10% (including epilepsy, aqueductal stenosis, and spinal neurofibromas), scoliosis in 5%, pseudoarthrosis in 3%, gastrointestinal neurofibromas in 2%, endocrine neoplasms in 2%, and renal artery stenosis in 2% (79). Approximately 8%–9% have mental retardation, but learning disabilities of various kinds affect 25% (131).

Growth. Clementi et al (30) studied growth in 528 NF1 patients. Impaired height affected only a subset of subjects and did not seem to be related to disease severity. Although endocrinopathies can also affect growth, only 3.8% of patients were so affected. Slight overweight was found in NF1 adults, particularly males.

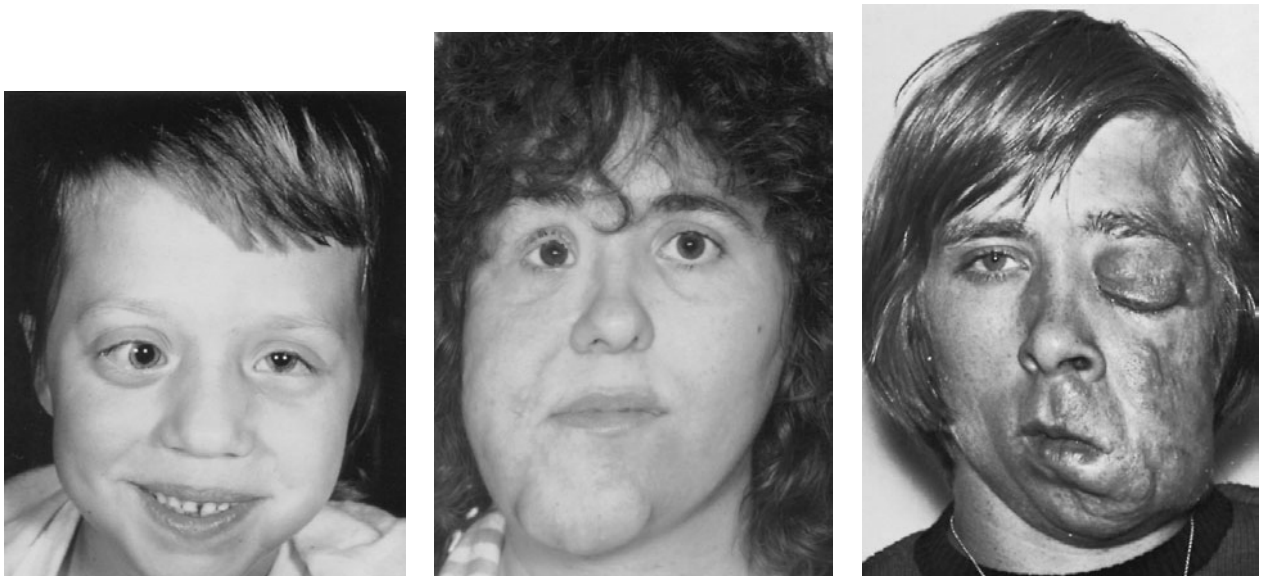
Macrocephaly was a feature in most subjects and was not related to hydrocephalus found in 2.3% of patients. OFC velocity in NF1 girls was the same as that of normal girls, but in NF1 boys, the OFC pubertal growth spurt was much more pronounced and delayed than in normal boys. A disproportion between OFC and height in boys was evident and appeared to be related to disease severity. In children less than 6 years of age, macrocephaly was found in 50%, short stature in 25%, hypertelorism in 64%, and thoracic abnormalities in 37% (31).

Neoplasia. The most distinctive and common skin neoplasm is the neurofibroma, especially the plexiform variety (63). Fialkow et al (51) analyzed neurofibromas from glucose-6-phosphate dehydrogenase A–B heterozygotes and concluded that each tumor had multiple cell origin, with tumorogenesis minimally involving 150 cells.

Neoplasms may be present at birth or appear during childhood or even later. They vary greatly in size with localized enlargement of many nerve trunks in larger neurofibromas. They are most striking on the skin, with some patients manifesting few, hundreds, or even thousands of individual neurofibromas and others having large unilateral pendulous masses (Fig. 12–30). Many organs may be involved, including stomach, intestines, kidney, bladder, larynx, and heart (19,23,24,42,69,138). In the head and neck region, the most commonly affected sites are the scalp, cheek, neck, and oral cavity (57,97,108). Neurofibrosarcomatous transformation has been reported in 3%–12% (52,67,74, 79,96). Schwannomas, meningiomas, astrocytomas (especially optic gliomas), ependymomas, and rarely medulloblastomas have been observed (41,75,83,131,139).

A variety of other tumors and neoplasms have been recorded, including cutaneous angiomas in 53% (181), subungual glomus tumors (93a,123a), subcutaneous leiomyomas (52), carcinoid tumor (52,77), xanthogranulomas with excessive frequency in young patients (121,131), subcutaneous neurofibromas in and about the cervical spinal cord in about 2%–5% (131), pheochromocytoma in about 1% or less (75,131), neuroblastoma (75), rhabdomyosarcoma (75), Wilms tumor (75,177), leukemia with a striking excess of nonlymphocytic forms, especially juvenile chronic myelogenous leukemia (27,75,131), adenocarcinoma of pancreas (131), lipoma (52), liposarcoma (44), and virilizing adrenal carcinoma (52).

Skin. In addition to nodular tumors of the skin, café-au-lait spots are found in over 99%. The smooth-edged pigmented macules are usually present at birth, but may take months, or even a year, to appear (Fig. 12–31). They increase in size during the first decade and vary in size from 1 to 2 mm to over 15 cm. Their distribution is random over the body except for a disproportionately small number on the face (130). The color varies from yellowish to chocolate-brown. The presence of six or more café-au-lait spots greater than 1.5 cm in diameter has come to represent the criterion for diagnosing neurofibromatosis, although fewer are present in some instances (38,39,130,140,187). Axillary freckling is present in approximately 50% (145) and, if present, is a significant diagnostic clue. Inguinal freckling may also be found (30). Giant pigment granules are found in café-au-lait spots (119). Pigmented hairy nevi may also be noted (63,163). Cutaneous blue-red and pseudoatrophic macules and palmar melanotic macules have been reported as additional



A B C

Fig. 12–30. *Neurofibromatosis*. Various craniofacial features of neurofibromatosis. (A) Unilateral exophthalmos due to bony defect of the posterosuperior orbital wall. Facial asymmetry. (C) Severe involvement with unilateral neurofibromatosis. (C from J Coblin and B Reil, J Maxillofac Surg 3:23, 1975.)

cutaneous signs (183,191). Dermatoglyphic findings include an excess of digital central pocket patterns (176). Stein et al (163) reported a case of NF1 that presented as epidermal nevus syndrome.

Central nervous system. Mental deficiency with an IQ under 70 occurs in about 8%–9%. Learning disabilities, present in 25%, include easy distractibility, impulsiveness, deficient visual-motor coordination, excessive scatter of scores from one set of test items to another, and language and vocabulary deficits (131). Seizures are seen in about 5% (131), and frank hydrocephaly with aqueductal stenosis (76) as well as asymptomatic ventricular dilation (76,131) have been recorded. Distortion of cortical architecture from glial proliferation and neuronal heterotopias deep in the cerebral white matter have been described (41,63,139). Rosman and Pearce (139) suggested that neuronal heterotopias, best explained by cortical neuron migration arrest during brain development, might be linked to mental retardation. Ventriculomegaly with Chiari type 1 malformations has been observed in NF5 (3). Riviello et al (136) reported two cases of aqueductal stenosis and reviewed 25 cases in the literature, estimating a frequency of about 1%.

Eyes. Any part of the eye may be involved. Neurofibromas of the eyelids have been occasionally observed. Intraorbital lesions may produce proptosis and muscle palsies. Sphenoid bone dysplasia may produce pulsating exophthalmos. Phakoma, congenital glaucoma, corneal opacity, detached retina, optic atrophy, and congenital ptosis of eyelids have also been reported (54,56,60,108,128). Lisch nodules of various sizes may be found anywhere in the iris (80) and are an almost constant feature (Fig. 12–32). These lesions are melanocytic hamartomas and are seen only in NF patients. Lisch nodules have a direct relationship to increasing patient's age and severity of skin lesions (192).

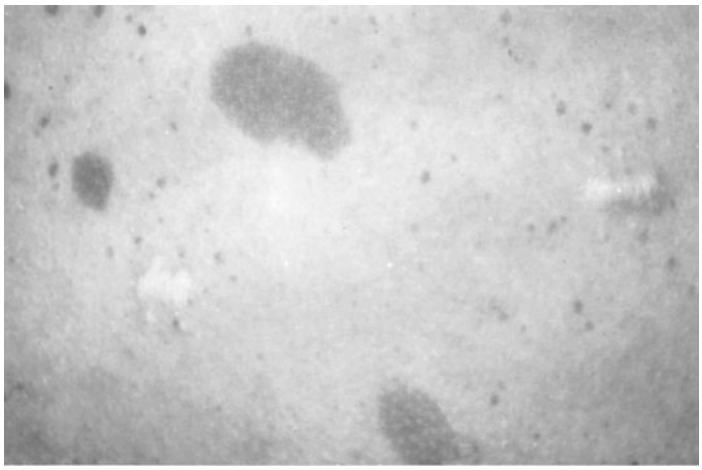
Skeletal system. Bony abnormalities have been particularly well discussed by Crawford (36) and Crawford and Bagamery (37). Scoliosis, the most common skeletal defect observed in NF (37), ranges from mild to severe curvature; the etiology is thought to be secondary to a localized neurofibroma eroding and infiltrating bone. Other spinal defects include kyphosis, cervical spine abnormalities, and spondylolisthesis. Commonly observed are subperiosteal erosive changes caused by pressure from proliferating neurofibromatous tissue in the periosteum and overlying soft parts. Central "cystic" lesions of bone result from expansive growth of neurofibromas within the medullary cavity in some patients. Still others (152) have shown fibrous connective tissue. In other cases, no cause for central lesions can be found (87).

Pseudoarthroses (commonly with bowing of the tibia and fibula, occasionally the radius) are also common (72,90). Bony defects of the skull, especially of the posterosuperior orbital wall, overgrowth of cranial bones, and craniofacial asymmetry have been reported. Macrocephaly is a well-known association (131,136). Hypertelorism has been found in 24% in the series reported by Westerhof et al (184). A variety of other anomalies may be observed, including hemihyperplasia of a limb or digit, spina bifida, absent patella, elevated scapulas, congenital dislocations (especially of the hip, radius, and ulna), clubfoot, syndactyly, and complete or partial absence of limb bones (37,39,63,74,78,87,122,135). Postaxial polydactyly was noted in one affected family by Merlob et al (114).

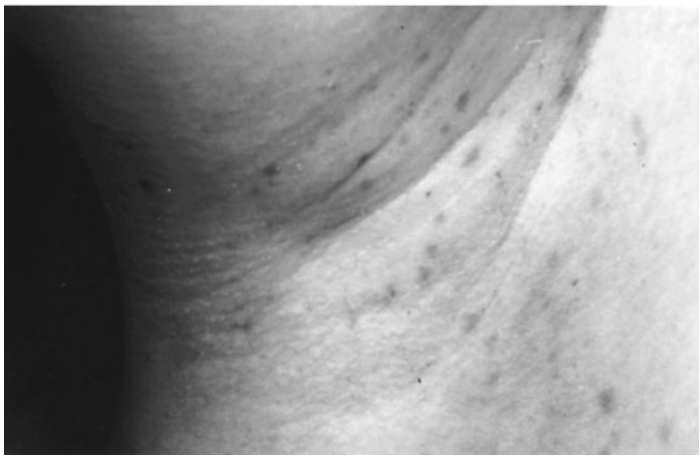
Endocrine system. Findings have been well reviewed by Saxena (148). In childhood, the most common endocrine abnormality is sexual precocity (99). Other findings have included hypopituitarism, hypogonadism, gigantism, acromegaly, delayed sexual development, obesity, hypoglycemia, diabetes insipidus, goiter, myxedema, and hyperparathyroidism.

Cardiovascular system. Cardiovascular anomalies are low-frequency findings: pulmonic valvular stenosis, supravalvular aortic stenosis, coarctation of aorta, ASD, congenital heart block, stenotic renal arteries, and other defects (7,42,61,63,93,138,159). Vascular malformations of the parotid gland have been reported (49).

Oral manifestations. The frequency of oral lesions in the past was stated to be 4%–7%, but recent studies of a large series of patients by Shapiro et al (156) ascertained by clinical and complete radiographic studies suggest a higher frequency. D'Ambrosio et al (40) reported an excellent study of jaw and skull changes, noting intraoral manifestations in 66% and skeletal involvement of the maxilla and mandible in 58%. Their overall sample had involvement of some kind in 92%. Although the age range was 6–66 years, we assume that children made up a small percentage of the sample. Most common are oral neurofibromas, enlarged fungiform papillae, intrabony lesions, wide inferior alveolar canals, and enlarged mandibular foramina (12,156). Tumors may involve any oral soft tissue, although there is some predilection for the



A



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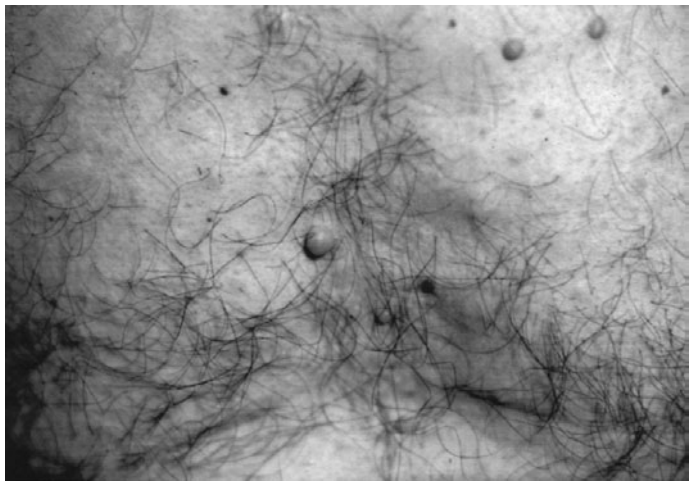


C

Fig. 12–31. *Neurofibromatosis*. (A) Café-au-lait spots. (B) Axillary freckling. (C) Typical small neurofibromas of chest. (A from JV Wander and TK Das Gupta, Curr Probl Surg 14:3, 1977. C from MM Cohen Jr, G Neri, R Weksberg, Overgrowth Syndromes. Oxford University Press, New York, 2000.)

tongue (11,62,85,100,162,166,180,186,188). Tongue lesions, consisting mostly of macroglossia and/or single or multiple tumors, have a sex ratio of almost 2M:1F (12) (Fig. 12–33). Lesions of the bony maxilla and mandible are uncommon (135,173,188), but with marked involvement of the face there may be combined maxillo-zygomatico-temporomandibular

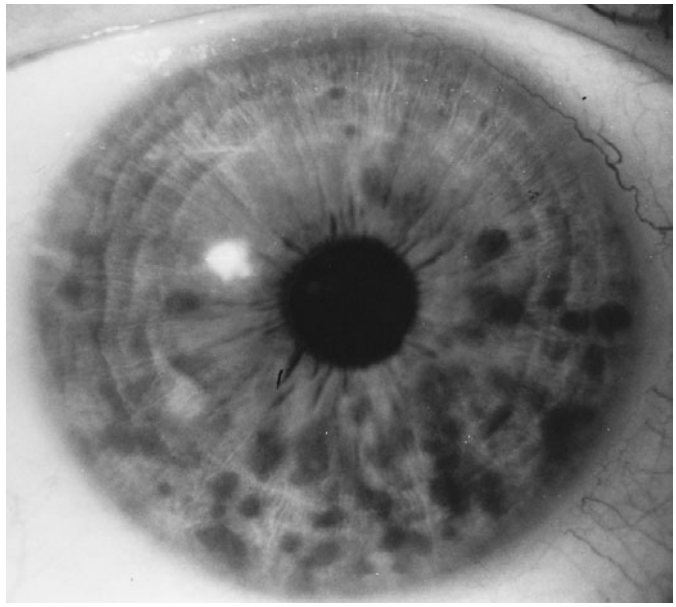


Fig. 12–32. *Neurofibromatosis*. Lisch nodules. (Courtesy of CG Summers, Minneapolis, Minnesota.)

hypoplasia not from pressure atrophy but from maldevelopment of these bones (95). Hyperplasia of the soft oral tissues has been described associated with underlying bony hypoplasia (185). Teeth are consequently in malposition, with total or partial retention. No enamel or dentin defects have been reported (185). Lee et al (101) found increased bone density, enlarged mandibular foramen, lateral bowing of ramus, increased dimensions of coronoid notch, and decrease in mandibular angle. Ruggieri et al (143a) and Ardekian et al (8a) reported a unique case of giant cell granulomas of the mandible and femora in a patient with typical NF1. (A similar case was described by S. Hersh, Cleveland, 2000).

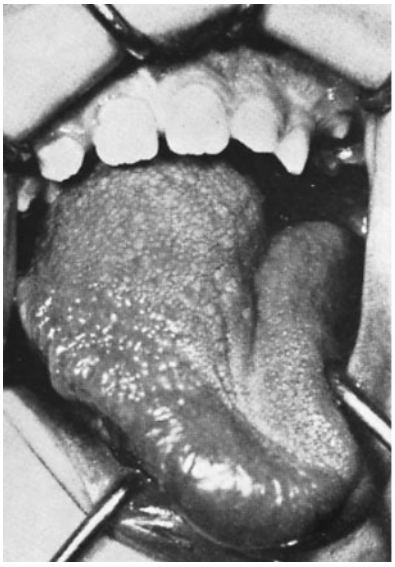
Other findings. Fibrosing alveolitis has been an associated finding (126,178). Velopharyngeal insufficiency with no cause identified after extensive workup was recorded in seven patients (125). The reader is referred to several sources for other low-frequency abnormalities (23,39,46,131).

Differential diagnosis. Neurofibromatosis should be distinguished from *multiple mucosal neuroma syndrome* (*multiple endocrine neoplasia, type 2B*), *Klippel-Trenaunay syndrome*, *multiple lipomatosis*, hemihyperplasia/multiple lipoma syndrome, *LEOPARD syndrome*, and *hemihyperplasia* (*hemihypertrophy*). The café-au-lait spots of *McCune-Albright syndrome* tend to be more markedly scalloped (coast of Maine appearance) in contrast to the smooth-edged lesions (coast of California appearance) of neurofibromatosis (140,187). Stephan et al (165) described isolated cases of cutaneous angiomatosis and macrocephaly in association with the Klippel-Trenaunay syndrome. The *Bannayan-Riley-Ruvalcaba syndrome* (192), characterized by macrocephaly, multiple lipomas, and hemangiomas with dominant inheritance should be excluded, as should *Proteus syndrome* (32,33).

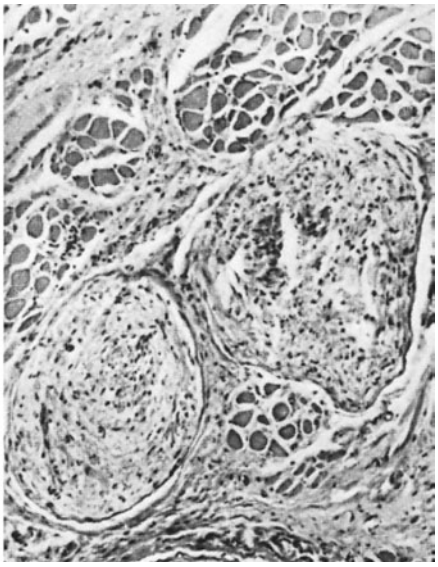
Café-au-lait macules have been associated with disseminated nonossifying fibromas of the long bones and jaw under the name of Jaffe-Campanacci syndrome (20,118,163). The jaw lesions resemble giant cell granulomas. Café-au-lait spots may, by themselves, be an autosomal dominant trait. The gene does not map to the NF1 site (18,25). However, Abeliovich et al (1) found linkage with NF1.

In *Noonan-like/multiple giant cell lesion syndrome*, a severe Noonanoid phenotype occurs together with giant cell lesions of bones, joints, and/or soft tissue; pulmonic stenosis is found in some cases (34).

Gorlin and Koutlas (55) reported an autosomal dominant syndrome of multiple cutaneous schwannomas, multiple melanotic nevi and multiple leiomyomas of the vagina.



A



B

Fig. 12–33. *Neurofibromatosis*. Oral involvement. (A) Neurofibromatosis tumor of tongue. (B) Photomicrograph of plexiform neurofibroma of tongue seen in A.

Johnson-McMillan syndrome is characterized by alopecia, hyposmia, conductive hearing loss, microtia, and hypogonadism. A mother and son with the syndrome also have multiple café-au-lait spots and mild retardation (66,88a,88b).

It should be carefully noted that single or even multiple neurofibromas or schwannomas without neurofibromatosis are frequently observed by surgeons and pathologists. Familial glioblastoma multiforme was reported without neurofibromatosis by Chemke et al (26).

Laboratory aids. Biopsy of individual lesions is useful for establishing the diagnosis in questionable cases. The café-au-lait macules of NF1 tend to have more large pigmented granules than those in McCune-Albright syndrome (16). Johnson and Chorneco (88) reported more dopa-positive melanocytes/mm^2 in the café-au-lait macules of neurofibromatosis than in those of normal individuals. The density of melanin macroglobules is significantly higher in biopsies of café-au-lait macules of patients with NF1 than in patients with NF2 or normal controls (111). Soft-tissue neurofibromas have been found to take up 99mTc DTPA. The localization of this radioisotope in soft-tissue benign neoplasms of NF facilitates their identification by scintigraphy (86). In questionable cases, NF1 mutations may be identified. MRI has been used to diagnose NF2 presymptomatically (50).

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Peutz-Jeghers syndrome

The syndrome of mucocutaneous melanotic pigmentation associated with hamartomatous intestinal polyposis was probably first described in 1896 by Sir Jonathan Hutchinson (39), although he was not aware of the presence of polyposis at the time. Follow-up by Parkes Weber (58) of one of his patients revealed the cause of death to be intussusception. Credit for pointing out the relationship between these ostensibly unrelated conditions goes to Peutz (60), a Dutch physician who, in 1921, described the syndrome in three generations. This family was reexamined in 1999 (83). Knowledge of the disorder, however, did not become widespread until Jeghers et al (41), in 1949, published a comprehensive account of 10 cases. Dozois et al (22) were the first to point out the increased rate of ovarian tumors in female patients. Dormandy (20) Klostermann (43,44) and Tomlinson and Houlston (73) provided excellent summaries of the clinical features of the syndrome. Giardiello et al (31) showed that the overall risk of cancer is considerably higher than previously supposed. An excellent review is that of Westerman et al (83a).

The syndrome has autosomal dominant inheritance with high penetrance (20,41,44,78). Almost 35% of cases represent new mutations (7). The gene has been mapped to 19p13.3 (1,35,55) and represents germline mutations in a novel serine threonine kinase, *STK11/LKB1*, a tumor suppressor gene (36,42,54,82,83). The mutations cause truncation of the encoded protein inactivating it. Loss of heterozygosity has been demonstrated (36). Not all patients with Peutz-Jeghers syndrome can be linked to this gene (53,56). A second locus at 19q13.4 has been found (9a,53,54), but this needs confirmation.

Gastrointestinal system. Polyposis of the gastrointestinal tract is the clinically most important component of the syndrome. The polyps are hamartomatous in origin (6,7,21). Bartholomew et al (7) suggested the following frequencies: jejunum, 65%; ileum, 55%; large intestine and rectum, 36% each; stomach, 23%; duodenum, 15%. A higher frequency of gastric and colonic polyps was found by Utsunomiya et al (78). Bartholomew et al (7) indicated, in their survey of 117 cases, that 43% had a family history of both polyps and pigmentation and 13% of pigmentation alone.

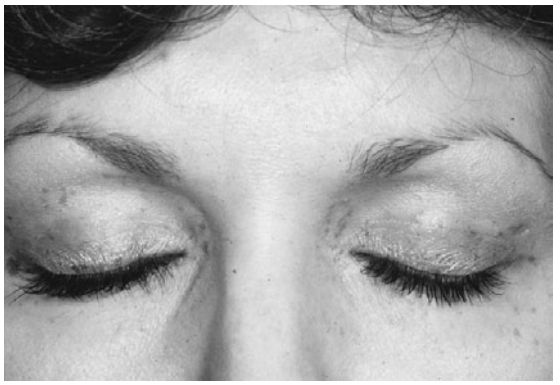
Thus, polyps may be found anywhere in the mucus-secreting portion of the gastrointestinal tract and may make themselves apparent by producing obstruction or intussusception. The number per patient is variable, but far less than in familial adenomatous polyposis. Usually the intussusception is self-resolving, but it may lead to serious small bowel obstruction and death. The age of onset of symptoms varies from a few weeks to 82 years (average, 29 years), and may present somewhat earlier in males (26). However, about 70% experience some type of gastrointestinal symptoms prior to diagnosis: intermittent colicky pain (85%) and melena or rectal bleeding (35%) (7). Rectal prolapse occurs in 7%–30% (27,74,83). In the majority of patients, the period before diagnosis is about 5 years. Hypochromic anemia due to bleeding from polyps has been found in 15%–35% (83).

The polyps are usually described as benign hamartomas, varying in size from 0.5 to 7.0 cm in diameter (26,82). Dormandy (20) suggested that these growths arise from primitive adenomatous vesicles embedded in the intestinal wall (Fig. 12–34). This view has been supported by other investigators (6,7,65,82) and adenomatous epithelium may be found in the hamartomas. Protein-losing enteropathy has been noted (39a).

Malignancy has been discussed by a number of authors (14,28,38, 39a,48,62,65,78,83). It is generally believed that malignant tumors develop in 10%–20%, a 20-fold increase over the general population. In a review of cases with malignant transformation, Dozois et al (21) found no parallelism between location of the malignant tumor and the site of polyps—that is, the most common locations for the adenocarcinomas (stomach and colon) are the least likely to be sites of polyps. In the extensive long-term study of Giardiello et al (31), cancer developed in 48%. A similar figure was determined by Spigelman et al (71). There was an increased risk for neoplasms to develop at both gastrointestinal and nongastrointestinal sites (31). The mean interval between diagnosis of the syndrome and diagnosis of cancer was 25 ± 20 years (range: 1–64 years). Neoplasms occurred in 8 of 13 families and, in a few pedigrees, were not clustered. Nongastrointestinal cancers included a 100-fold excess of pancreatic carcinoma and others such as ductal carcinoma of breast, adenocarcinoma of lung, and multiple myeloma in addition to colonic malignancy and ovarian tumors. Within the gastrointestinal tract, only adenomatous polyps became malignant, never hamartomatous polyps. Reasons for the lower malignancy rates found by other investigators (21,48,78) were well analyzed by Giardiello et al (31).

Microscopically, gastrointestinal hamartomas represent focal overgrowths in improper proportions of tissues indigenous to that part of the gastrointestinal tract (64). A branching-tree or frondlike arrangement with a core of smooth muscle and stromal tissue may be seen scattered

A



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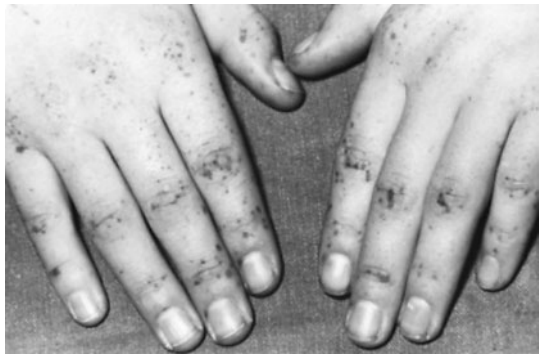

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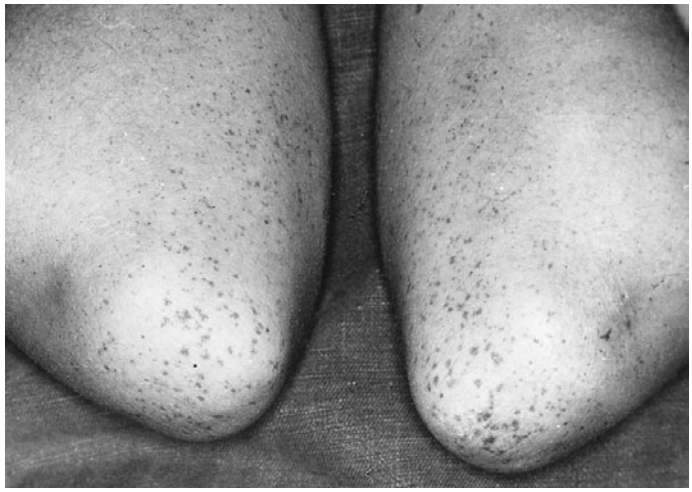


E

Fig. 12–34. *Peutz-Jeghers syndrome*. (A) Note extensive melanotic pigmentation of lips, numerous very small freckle-like spots about mouth, nose, and eyes. (B) Compare mild faded involvement of eyelids with patient shown in A. (C) Melanotic pigmentation on fingers. (D) Pigmented macules on hands. (E) Spotting in the region of the elbows. (A courtesy of J Calnan, London, England. C,E courtesy of G Klostermann, G Thieme Verlag, Stuttgart, Germany. D from K Yamada et al, J Dermatol (Tokyo) 8:367, 1981).

throughout the growths (Fig. 12–35). Frequent mitotic figures are characteristic. The growths may extend to the serosal surface.

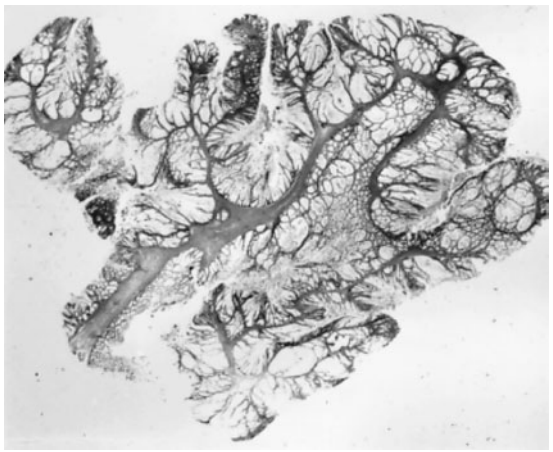
Enteritis cystica profunda characterized by mucosal glands and mucinous cysts that penetrate the tunica muscularis of the small and large bowel has been documented (2,46). The condition, in our opinion, represents extreme hamartomatosis or pseudoinvasion.

Polyps of other organs include the nose (19,20,33,40,44,60,83,89), mouth (49), choanae and antrum (40,49), uterus (44,62,89), ureter and bladder (20,33,56,60,69), gallbladder (29), bile duct (67), and esophagus (3,57). Bronchial adenosis has also been noted (20,33,60).

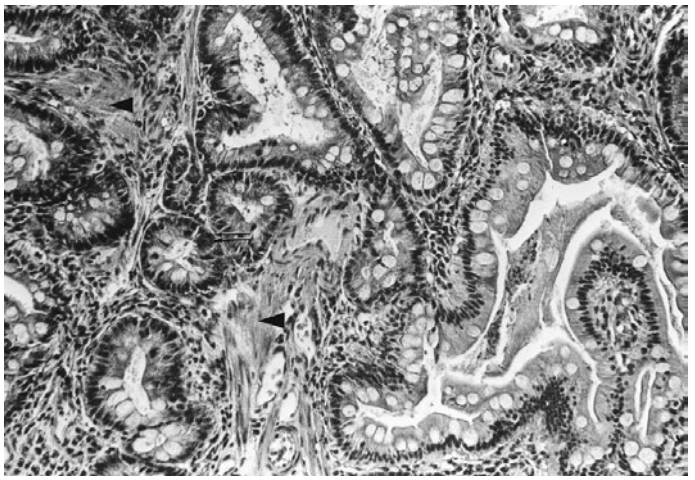
Skin. In about 50%, numerous, usually discrete, brown to bluish-black macules are present on the skin, especially about the body orifices—perioral, periorbital, perianal, and perigenital (75) (Figs. 12–34A and 36). Though some patients exhibit only a few pigmented macules, others are markedly pigmented. Pigmented spots occur on the extremities in about 65% (7,52,72,78), fingers, toes, (85,89), sometimes on the palms or soles, or, occasionally, in other areas, such as the umbilicus, axilla, or shoulder (30,89). Pigmentation of the nails has also been described (45,79) and of psoriatic plaques (5,52). The mucocutaneous pigmentation appears in about 75% during the first or second year of life, before the onset of abdominal symptoms, and seems to fade somewhat at puberty. It may, however, appear as late as the eighth decade.

Ovarian cysts and tumors and uterine adenocarcinoma. Ovarian tumors occur in about 10%–14% of female patients (16,21). They may be found even in very young children (21). Granulosa cell tumors (8,15,17,21,22,33,41,62) have been associated with precocious puberty (17,68). Brenner tumor, dysgerminoma, (22,77) and cystadenoma (22) have also been noted. Cervical adenocarcinoma has been found in at least 20 cases (2,50,51,61,86).

Scully (66) suggests that a distinctive ovarian neoplasm, which he called "sex cord tumor with annular tubules" (SCTAT), may be part of the syndrome. The tumors tend to be bilateral, often of microscopic size, frequently calcified, and nonmalignant. The neoplasm, probably derived from granulosa cells, produces endometrial hyperplasia. Christian (17) reviewed the literature and reported 15 patients with ovarian tumors among 125 female patients with the syndrome and questioned whether SCTAT is a tumor or a hamartoma. Hart et al (34) classified SCTAT as a distinctive annular and membranous variant of the granulosa cell tumor in view of the morphologic similarities and clinical behavior. In a review of 74 cases of SCTAT, Young et al (86) found that 27 patients



A



B

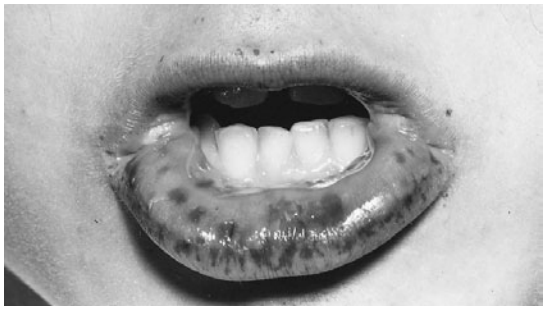
Fig. 12–35. *Peutz-Jeghers syndrome*. (A) Low-power view of polyp from large intestine. Note arborization of nonstriated muscle. (B) Photomicrograph of adenomatous polyp. (A from JD Reid, Cancer 18:970, 1965. B from KJ Walecki et al, Pediatr Radiol 14:62, 1984.)

had the syndrome and four of these also had cervical adenomas. Young et al (87) found three different gynecologic neoplasms: SCTAT, well-differentiated mucinous adenocarcinoma of the cervix, and a distinctive sex cord–stromal tumor.

Testicular tumors. Cantú et al (16) reported a 6-year-old boy with feminizing sex-cord tumor, and Dubois et al (24) and Coen et al (18) reported SCTAT in young boys (3–5 years). A number of authors (23,37,84,88) have found bilateral large cell Sertoli cell tumors, gynecomastia, rapid growth, and advanced bone age.

Other neoplasms. Breast carcinoma (9,32,47,63,76), pancreatic adenocarcinoma (12,31), and bile duct carcinoma (11) have also been reported.

Oral manifestations. On the lips, especially the lower, and on the oral mucosa, round, oval, or irregular, rarely confluent macules of bluish-gray pigment of variable intensity may be seen (90). They vary in size from 1 to 12 mm and are usually somewhat larger than those on the skin. About 98% of 117 patients had pigmentation of the lips, and 88% had involvement of the buccal mucosa (7). Less frequently pigmented are the palate and gingiva. Only rarely are the tongue and the oral floor involved (44,60,72). There does not appear to be any relationship between the



A

B

Fig. 12–36. *Peutz-Jeghers syndrome*. (A,B) Melanotic pigmentation of the lips. (A from LG Bartholomew et al, Gastroenterology 32:434, 1957. B from M Zingsheim, Hautarzt 17:85, 1966.)

amount of oral pigmentation and the degree or distribution of the visceral polyposis (Fig. 12–36).

Several investigators have pointed out that labial pigment also tends to fade at puberty, and that the pigment on the buccal mucosa fades to a lesser degree (41,44,78,83), thus being helpful in diagnosis (6,7). Rarely, pigmentation may be present without polyposis (20,41,89).

Pigmentation of other mucosal surfaces, viz. conjunctival (4,76), nasal (20,49), and anal (59), may also be seen. Pigmented oral papillomatosis (49) has been reported.

Differential diagnosis. Oral mucosal pigmentation may be seen normally in over 90% of blacks or members of other dark-skinned races and in 5% of whites (25,90). Solitary melanotic macule of the oral mucosa or lip (usually of vermilion border of lower lip of females) must be excluded (13,70). Laugier-Huntziker syndrome is characterized by acquired melanotic pigmentation of the lips, oral mucosa, longitudinal nail beds, and, occasionally, genitalia (10,80). In Addison's disease, the cutaneous pigmentation is generalized and often increased along body folds and scars. The distribution of freckles does not ordinarily occur perioorally or labially, and intraorally is more generalized. Lentiginosis profusa (*LEOPARD syndrome*) is generalized over the skin but does not involve mucosal surfaces. Lentiginosis also occurs in *Carney syndrome*. Oral pigmentation may rarely occur in *McCune-Albright syndrome*. Polyposis and pigmentation have been described in association with alopecia and nail dystrophy, that is, Cronkhite-Canada syndrome (see *Gardner syndrome*). Still other causes of oral pigmentation have been discussed (52).

Other forms of polyposis of the intestinal tract are usually limited to the colon. These include familial polyposis coli, *Gardner syndrome*, juvenile polyposis, and disseminated polyposis of the colon and rectum. These and other types are discussed in the section on Gardner syndrome.

Sex cord tumor of the ovary may occur in women without Peutz-Jeghers syndrome. In contrast to those with the syndrome, the tumors tend to be unilateral, large, rarely calcified, and mixed with Sertoli and/or granulosa cells; they are malignant in about 15%.

Laboratory aids. The presence of labial and/or oral pigmentation should suggest a thorough history and examination of the gastrointestinal

tract by proctoscopic and radiographic means. Diagnosis of early intussusception may be possible by ultrasonography (81).

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Proteus syndrome (and encephalocraniocutaneous lipomatosis)

Proteus syndrome is a complex and variable disorder consisting of overgrowth of hands and/or feet, asymmetry of limbs, connective tissue nevi, epidermal nevi, vascular and lymphatic malformations, and cranial hyperostoses. The syndrome was first delineated by Cohen and Hayden (18), who reported a newly recognized disorder in two similar patients. They further distinguished the condition from neurofibromatosis and Klippel-Trenaunay syndrome. Four years later, Wiedemann et al (56) reported four patients and named the condition after the Greek god Proteus, who could change his shape to avoid capture. Well over 120 cases have been reported, and many other unreported patients are being followed in medical clinics (3,11,18).

Table 12–11. Clinical features of Proteus syndrome

Features	Previously reported cases	Joseph Merrick
Growth		
Asymmetry of limbs	38/38	+
Partial gigantism of hands and/or feet	31/38	+
Skeletal		
Bone hypertrophy	31/38	+
Scoliosis/kyphosis/ abnormal vertebrae	20/38	+
Joint limitation/angulation	17/38	+
Skull hyperostoses	20/38	+
Skin		
Verrucous epidermal nevi	26/38	+[a]
Thickening of skin and subcutaneous tissue	23/38	+
Lipomas[b]	26/38	+
Vascular anomalies[c]	20/38	–
Dilated veins	15/38	–
Unspecified subcutaneous masses	31/38	+
Craniofacial		
Macrocephaly and/or frontal bossing	7/38	+
Epibulbar tumor	5/38	–
Enlarged eye	6/38	–
Strabismus	9/38	–
Prognathism	3/11	–
Performance		
Mental deficiency[d]	11/37	–
Motor delay	6/38	–
Seizures	2/13	–

[a] Treves writes of "papillomatous" skin, which in one area merges into "a mere roughening of the skin." The latter may represent a verrucous epidermal nevus.
[b] Pelvic lipomatosis has been found in three instances, thus increasing the total number of patients affected with lipomas.
[c] Vascular anomalies include hemangiomas, lymphangiomas, "venous dilation," "purplish discoloration," and varicosities.
[d] Mental deficiency is a variable feature, so Merrick's normal mentation is fully compatible with Proteus syndrome.
From MM Cohen Jr, Proc Greenwood Genet Ctr 6:187, 1986.

There has been long-standing confusion in attempts to distinguish between Proteus syndrome and neurofibromatosis (NF1). Connective tissue nevi found in Proteus syndrome are distinct from lesions found in neurofibromatosis (12). Cohen (8–10) provided evidence that Joseph Carey Merrick, pejoratively known as the "Elephant Man," had Proteus syndrome and not, as previously thought, neurofibromatosis (Table 12–11).

Somatic mosaicism lethal in the nonmosaic state, an etiologic hypothesis for Proteus syndrome, was postulated by Happle (23,26). Mosaicism may arise either from a genetic half chromatid mutation or from early somatic mutation. Characteristics of such a disorder include sporadic occurrence, 1:1 sex ratio, mosaic distribution of lesions, and variable extent of involvement, but never diffuse involvement of the entire body or an entire organ system (23). Two known instances of monozygotic twins discordant for Proteus syndrome (17,33,51) lend support to the hypothesis of somatic mosaicism. DNA fingerprinting has shown single band differences in one of these pairs of monozygotic twins discordant for Proteus syndrome. Differences have also been found in the normal and affected areas of another Proteus patient (51).

Purported instances of transmission from parent to child (52) are not convincing. Happle (25,26) discussed the possibility of "paradominant inheritance," should a rare example of familial Proteus syndrome be recorded in the future. According to this hypothesis (25), heterozygosity for a paradominant mutation would confer phenotypic normality and the

allele could be transmitted unperceived for generations. The gene carrier would exhibit Proteus syndrome when a somatic mutation occurred during embryogenesis, giving rise to a cell line that would be either hemizygous, from allelic loss, or homozygous, from a point mutation. On rare occasions, more than one relative might be affected. Because the trait is neither simply mendelian nor entirely non-mendelian but sometimes tends to imitate dominant transmission, Happle (25) proposed the term "paradominance."

Mosaic distribution of lesions and variable extent of involvement implies that criteria for the diagnosis of Proteus syndrome should be loose rather than overly rigid (11,53). Encephalocraniocutaneous lipomatosis (ECCL) possibly represents a significantly more localized form of Proteus syndrome. Comparison of individual cases of ECCL (1,22,42,49) demonstrates a continuum, not two distinct entities that share some common manifestations. For example, in ECCL, cutaneous, craniofacial, and meningeal lipomas, usually unilateral, occur, but cutaneous lipomas below the head and neck and visceral involvement have been found in some cases. Other patients have had mental deficiency, seizures, malformations of the central nervous system, epibulbar dermoids, connective tissue nevi, and focal alopecia. In some instances, hyperostoses of the calvaria have been noted. All of these defects, except possibly focal alopecia, have been seen in Proteus syndrome. Happle (28,30) believes that Proteus syndrome and ECCL are separate entities. The association of ECCL with an NF1 mutation, reported by Legius et al (38), is likely coincidental.

Natural history. Although birth weight may be increased in Proteus syndrome, with some newborns weighing 4000 g or more, normal birth weight and even small-for-gestational-age infants have been observed. At birth, patients with Proteus syndrome are usually normal or show mild to moderate alterations, hyperplasias, or hamartoses. Vascular malformations may be present. Patients with highly significant hyperplastic overgrowth of limbs at birth are very unlikely to have Proteus syndrome. Most often they have Klippel-Trenaunay syndrome or hemihyperplasia/multiple lipomas syndrome. The most remarkable postnatal growth in Proteus syndrome occurs during the first few years of life. However, a few patients may even be short during childhood. The syndrome is characterized by disproportionate overgrowth of bone and soft tissue. Somatic growth during adolescence and final height attainment are apparently normal. Bone and soft-tissue overgrowth tend to plateau after adolescence (3,4,7,11,21), although there are some exceptions and an occasional neoplasm has been noted from age 20 to 30 or older. Some patients have died of unusual causes, including suffocation, cerebellar abscess secondary to otitis media, laryngospasm, pulmonary embolism following a surgical procedure under general anesthesia, invasive metastatic mesothelioma, and invasive papillary adenocarcinoma of the testis (9,11,21,41).

Facial phenotype with mental deficiency. Cohen (11) described a facial phenotype in Proteus syndrome patients with mental deficiency and, in some cases, seizures and/or brain malformations. Manifestations include dolichocephaly, long face, minor downslanting of palpebral fissures and/or minor ptosis, low nasal bridge, wide or anteverted nares, and open mouth at rest. These facial manifestations may even override the severe craniofacial distortion produced by bony overgrowth in some cases (Figs. 12–37 and 12–38).

Connective tissue nevi. Connective tissue nevi are common, and are facultative, not obligatory, i.e., they may or may not be present. They have been recorded most frequently on the plantar surface of the feet, but can also be found on the hands, abdomen, and nose (11). When present, a connective tissue nevus is almost pathognomonic for Proteus syndrome (Fig. 12–39). Histologically, connective tissue nevi are characterized by highly collagenized connective tissue (33). MRI characteristics have been documented (53a).

Epidermal nevi and other skin lesions. Epidermal nevi are etiologically and pathogenetically heterogeneous (24). In Proteus syndrome, nevi are evident in early life and may be found on the neck, trunk, or extremities. Lesions may be linear, whorled, or verrucous, and, in some cases, may exhibit abrupt midline margins (3,4,7,17–19,54,55). Infrequently, a single café-au-lait spot may be observed. Areas of patchy dermal hypoplasia and of hypopigmentation have also been noted (9,18, 29,31,50,54,55,57). Coexistence of lesions can be found in some cases.

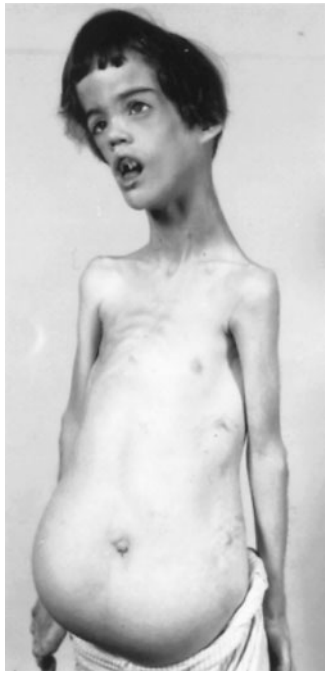

Fig. 12–37. *Proteus syndrome*. Unusual craniofacial appearance, kyphoscoliosis, and protuberant abdomen. (From JT Fay and SR Schow, J Oral Surg 26:739, 1968.)

Vascular malformations. Vascular malformations may be of the capillary, venous, or lymphatic type, or may occur as combined channel anomalies—for example, capillary and venous channel or capillary, venous, and lymphatic channels. They are developmental anomalies lined by flat endothelium exhibiting a normal, slow rate of turnover. They grow proportionately with the patient; they never regress, but they can expand. So-called combined tumors such as "angiolipomas" probably do not occur; they probably represent lipomas with a vascular stroma. So-called "lymphohemangioma" is a misnomer for combined lymphatic-capillary malformation. Varicose veins have been reported in the hypogastric and inguinal region and on the legs (3,4,9,13,18,20,37,43,44,56).

Lipomas and dysregulation of adipose tissue. Lipomas in Proteus syndrome are composed principally of mature adipocytes. Decreased and increased fat can be found in the same patient at different sites in the body, indicating dysregulation of adipose tissue (7,11,27,29,36,52). Lipomas may be confined or infiltrative. Although histopathologic examination always shows benign adipose-tissue cells, the location of lesions is of great importance. Superficial lesions tend to be confined and may be self-limited in growth, although this is not always the case. On the other hand, intraabdominal and intrathoracic lipomas have increased potential for invasive behavior, despite benign histologic appearance (19). Infiltration of the spinal canal has been reported (35,52).

Unusual tumors. Cohen (11,16) and Gordon et al (21) showed that several unusual types of tumors are occasionally associated with Proteus syndrome: ovarian cystadenoma (most commonly unilateral; two cases bilateral), various types of testicular tumors, central nervous system tumors (particularly meningiomas), and monomorphic adenoma of the parotid gland (39). Bilateral cystadenomas of the ovary are rare in children and adolescents and therefore of diagnostic value in Proteus syndrome. In adults, bilateral ovarian involvement is found in a significant percentage of cystadenocarcinomas (21). Monomorphic adenoma of the parotid gland is very uncommon, occurring most frequently in elderly

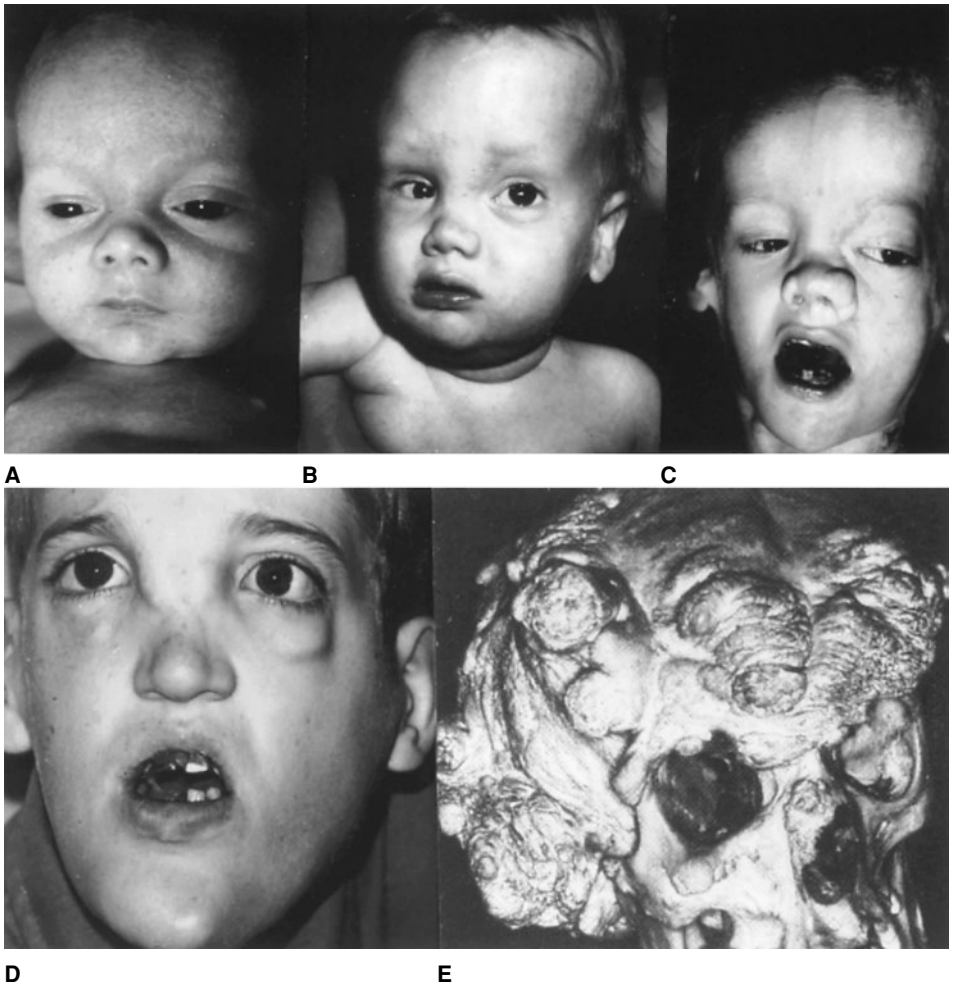

Fig. 12–38. *Proteus syndrome*. Craniofacial features. (A–C) Evolution of features. (A) Patient at 1 month. (B) Same patient at 5 months. (C) Same patient at 5.5 years. (D) Boy developing hyperostoses of nasal bridge, left infraorbital region and mandible. (E) Hyperostoses in Joseph Merrick's skull. [A–C from JAR Tibbles and MM Cohen Jr, Br Med J 293:683, 1986. D from MM Cohen Jr and PW Hayden, Birth Defects 15(5B):291, 1979. E from M Howell and P Ford, The True History of the Elephant Man, Allison and Busby, London, 1980.]

men. The presence of this tumor in two adolescent girls with Proteus syndrome (11,18,21) is highly significant. Multiple tumors are found in some cases (11,17,21).

Skeletal abnormalities. Disproportionate overgrowth, commonly asymmetric in nature, can involve the arms, legs, hands, feet, and digits (3,4,9). Scoliosis and kyphoscoliosis are common (7,9,20,34,41,46, 54,56). Genua valga has also been observed (7,19,34,46), and heel valgus has been noted in a number of instances (7,9,18,34). Megaspondylodysplasia is also common; cervical, thoracic, or lumbar vertebrae may be affected (2,4,45,57). When the cervical vertebrae are involved, the neck can appear elongated (20,37,52); the appearance of the neck can be exaggerated by dysregulation of adipose tissue with decreased neck fat. Overgrowth may affect other bones, such as the metatarsals (3) and the ribs (7,45). Bony protuberances of the hands and feet (3,9) have been observed (7,18,54,55,56), and, on occasion, the long bones of the legs and arms may be involved.

Hyperostoses are bony overgrowths that are not true tumors. Cohen (9,11) used the term hyperostoses in preference to exostoses and osteomas; the latter two terms should be avoided, because both have somewhat different patterns of osseous organization. Hyperostoses may occur in calvarial, facial, nasal, alveolar, and mandibular bone (5,20a). They may be small or they may grow to be large in size, producing striking asymmetry (47). They are most common in the calvaria and least common in nasal and alveolar bone. Hyperostosis of the external auditory canal is uncommon in Proteus syndrome (9,18).

Spleen and thymus. Although limb overgrowth is most common in Proteus syndrome, perhaps any organ may be involved. An uncommon manifestation, found in four patients, is pronounced splenomegaly; one instance was associated with a history of reduced platelet counts. Another uncommon manifestation is enlargement of the thymus (3,4,6).

Central nervous system. Intelligence may be normal, although some degree of mental deficiency has been evident in about 20% of cases and seizures have been documented in approximately 13%. However, a number of patients have had various brain malformations (9,11,18,39,48). Meningiomas have been discussed above (20a).

Pulmonary abnormalities. Hotmisligil (35) estimated that about 16% of patients had pulmonary abnormalities (n = 55). Cystic anomalies were reported in two patients by Wiedemann et al (56). One patient had progressive dyspnea at rest and frequent superinfection. About 12%–13% of patients have had such cystic lung changes. Serious and potentially lethal lung involvement has been emphasized by Newman et al (45).

Renal abnormalities. A variety of renal abnormalities have been recorded, including nephrogenic diabetes insipidus, kidney cysts, vascular malformations of the bladder and kidney, ureterectasis, heminephromegaly, duplicated renal collecting system, and hydronephrosis (11,35,36).

Other abnormalities. Epibulbar dermoids, retinal dysplasia, and a host of other anomalies have been reported in some cases (17,19a,20a,53). Rare findings include rectal polyposis, muscular atrophy, mixed mesenchymal bronchial hamartoma (19), and vocal cord nodule (50).

Differential diagnosis. The two disorders most commonly confused with Proteus syndrome are *Klippel-Trenaunay syndrome* and

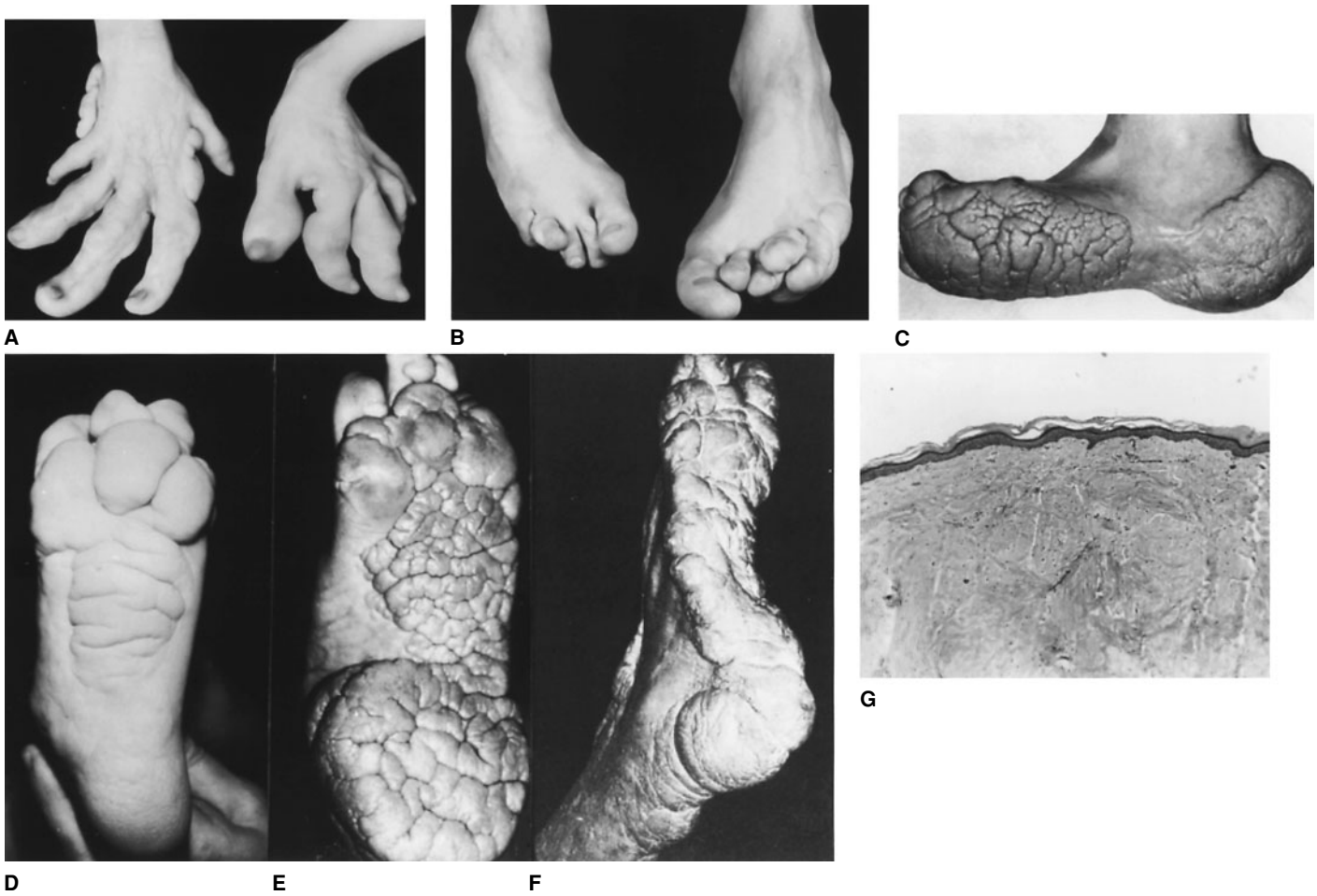

Fig. 12–39. *Proteus syndrome*. (A–F) Enlargement of hands and/or feet associated with gigantic fingers and/or toes, sometimes with fibrous overgrowth. Note "moccasin" lesion in C. (D–F) Evolution of "moccasin" lesion typical of Proteus syndrome. (D) Patient at 5.5 years. (E) Second patient at 13 years. (F) Third patient at 29 years (plaster cast of the Elephant Man's foot). (G) Photomicrograph of fibrous lesion from foot. Note highly collagenized fibrous connective tissue and no evidence of neurofibroma. (A,B courtesy of N O'Doherty, Dublin, Ireland.) C,E from MM Cohen Jr and PW Hayden, Birth Defects 15 (5B):291, 1979. D from JAR Tibbles and MM Cohen Jr, Br Med J 193:683, 1986. F from M Howell and P Ford, The True History of the Elephant Man, Allison and Busby, London, 1980.]

hemihyperplasia/lipomatosis syndrome (3,4,17). Hemihyperplasia with multiple lipomas is a distinct subset of *hemihyperplasia*. Cutaneous capillary malformation may occur in some instances. Mild-to-moderate signs are present at birth. Progressive overgrowth does not occur. Rather, it tends to be commensurate with growth of the child (3,13). Hemifacial hyperplasia with meningeal involvement is still a different disorder (32). Lipomas may occur in *Gardner syndrome* in association with osteomas of the frontal bone, maxilla, or mandible. In *Maffucci syndrome*, the vascular anomalies are commonly venous and occur together with enchondromas. These tumors have not been found in Proteus syndrome (14,43,44). Some patients with striking hyperostoses of the skull and facial bones have been diagnosed as having "Thanos syndrome," a condition that does not exist (15). Isolated plantar cerebriform collagenomas is still debatable (4,40).

A Proteus-like condition has been noted (3,32a), some examples having PTEN mutations (57).

References [Proteus syndrome (and encephalocraniocutaneous lipomatosis)]

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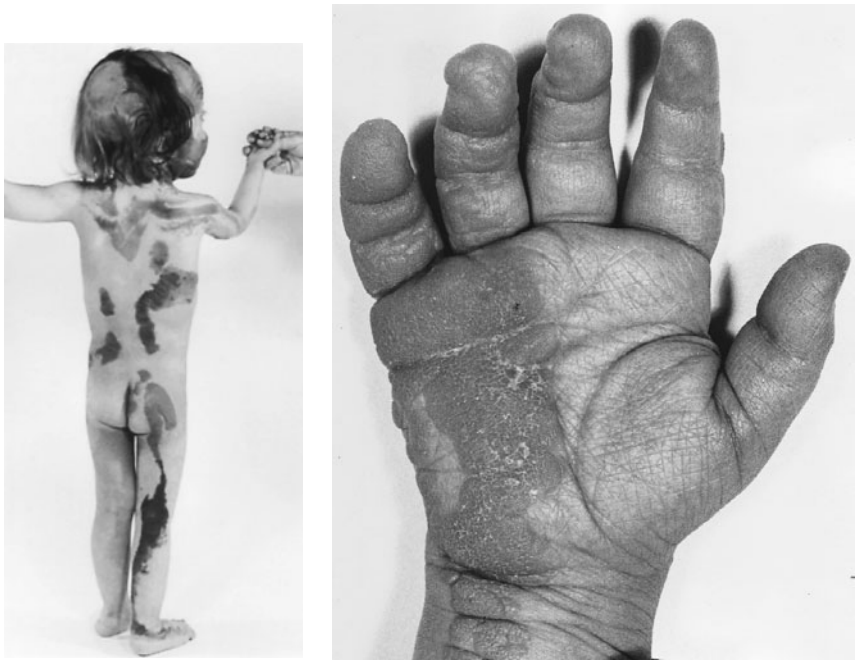
Schimmelpenning syndrome (formerly "epidermal nevus syndrome")

Schimmelpenning syndrome is characterized by sebaceous nevi, together with cerebral, ocular, and skeletal abnormalities (Table 12–12). The epidermal nevus is nonspecific, and Happle (26,27) has shown that there are

Table 12–12. Features of the Schimmelpenning syndrome

Findings	Percent (n = 60)
Cutaneous	100
Epidermal nevi	
Nevus unius lateris	(60)
Ichthyosis hystrix	(20)
Linear nevus sebaceus	(10)
Localized acanthosis nigricans	(20)
Other verrucous or mixed lesions	(33)
Hemangiomas	37
Dermatomegaly	15
Hypopigmentation	10
Café-au-lait spots	10
Many melanocytic nevi	10
Skeletal	70
Kyphosis/scoliosis	28
Ankle and foot deformities	15
Genua valga	5
Hemihypertrophy (hemihyperplasia)[a]	15
Short limbs	10
Finger and toe deformities	10
Cranial and facial bone deformities	15
Bone cysts	3
Vitamin D–resistant rickets	2
Neurologic	50
Mental deficiency	40
Seizures	33
Hemiparesis	14
Cranial nerve involvement[b]	8
Ocular	33
Extension of nevus to lid	19
Lipodermoid	15
Nystagmus	2
Coloboma and cortical blindness	2

[a] Or localized gigantism in some instances. Involves both bone and soft tissue.
[b] VI, VII, and VIII.
Adapted from LM Solomon and NB Esterly, Curr Prob Pediatr 6(1):1, 1975.



A B

Fig. 12–40. *Schimmelpenning syndrome*. (A) Involvement of hair, face, neck, back, buttocks, and legs of a 4.5-year-old child. (B) Hand lesion of patient shown in A. (A,B from B Lieber, Monatsschr Kinderheilkd 137:585, 1979.)

several well-defined conditions with epidermal nevus: Schimmelpenning syndrome, nevus comedonicus, pigmented hairy epidermal nevus, Proteus syndrome, and CHILD syndrome. Nomenclature in the past has been very confusing (1,38,43,63,66) and has been reviewed elsewhere (24). A good early history has been compiled by Hornstein and Knickenberg (29).

The syndrome has been described by Schimmelpenning (57) in 1957, Feuerstein and Mims (19) in 1962, and many others (4,45,50). Over 100 cases have been recorded (14,18,62,72), and both general and specific reviews have been published (10,14,16,22,30,38,40,44,46,48,62,63,66,68). Less certain are patients with incomplete documentation (24,35,37).

All cases are sporadic. The sex ratio is 1:1. The syndrome is likely to be caused by the action of an autosomal dominant lethal mutation that survives by mosaicism (26,27). Supporting the concept of somatic mosaicism are two reports of discordant monozygotic twins (15,58). There is also one affected dizygotic twin (39). Most observed instances of affected or partially affected family members are suspect and are unlikely to represent Schimmelpenning syndrome (4,7,47,62). Deletion of the PTCH gene has been demonstrated in 8 of 20 sebaceous nevi (71).

Cutaneous manifestations. The sebaceous nevus is the hallmark of the syndrome. When the scalp is involved, broad patches may be present. Some cases may be associated with partial alopecia (21,28). Elsewhere, sebaceous nevi always follow the lines of Blaschko (28). Lesions may be of any size (26,27). Histopathologic examination shows hyperplastic sebaceous glands. However, before puberty, organoid differentiation may be minimal or absent in scalp lesions and at any age when the trunk or extremities are involved (26,27) (Figs. 12–40 and 12–41).

Central nervous system. Defects of the central nervous system have been well documented (6,14,17,20,25,31,32,36,43,46,49,56) and the subject has recently been reviewed by Gurecki et al (25). Seizures and moderate to severe developmental delay are common. Other reported findings have included hemimegalencephaly, hemiatrophy, migrational defects, and vascular anomalies. Also noted have been agenesis of the corpus callosum (6,17), central precocious puberty (31,70), and Dandy-Walker malformation (17).

Ocular defects. The most common ocular manifestation is extension of the epidermal nevus to involve the eyelid, eyelid margin, and conjunctiva (Fig. 12–41C). Other abnormalities have included coloboma of the lid and/or iris and retina, epibulbar lipodermoid, corneal opacity and pannus formation, oculomotor dysfunction, nystagmus, optic nerve hypoplasia, and cortical blindness (19,30,32,34,45,49,52,59,64,65,68).

Skeletal abnormalities. Asymmetry of the skull, hypoplastic nasal and orbital bones, and frontal bossing have been observed (50,52,64). Other defects have included incomplete development of various bones, vertebral defects, incomplete formation of the talus, camptodactyly, clinodactyly, brachydactyly, ischial and pubic hypoplasia, incomplete rib formation, abnormal clavicles, shortening of limb bones, kyphoscoliosis, posterior luxation of the ankle, pes equinovarus, and genua valga (39,40,42,52,55,62,63). Vitamin D–resistant rickets has been recorded in a number of patients (2,5,12,23,31,51,60,64,72). Cystic bone changes (giant cell granulomas) have been recorded rarely (8,70) and are problematic (see *Differential diagnosis*).

Oral manifestations. The most extensive review is that of Murakami et al (53). Features may include hemihyperplastic tongue, papillomatous lesions, ameloblastoma, oligodontia, hypoplastic teeth, malformed teeth and odontodysplasia (3a,7,9,11,41,44,45,50,54,61,67,72) (Fig.12–42). Cleft palate (4) and bifid uvula (32) are probably coincidental.

Other findings. A number of other findings have been noted, including coarctation of the aorta, unusual origin of the subclavian artery, PDA, myocardiopathy, horseshoe kidney, chondroblastoma, and intrahepatic cystic biliary adenomas (6,13,45,49,50,62).

Differential diagnosis. Happle (26,27) has shown that epidermal nevi are of various types, which may be found in CHILD syndrome, nevus comedonicus, pigmented hairy epidermal nevus, and *Proteus syndrome* as well as Schimmelpenning syndrome. Happle (26) has also discussed less-well-delineated conditions with epidermal nevi. *Encephalocraniocutaneous lipomatosis* is subsumed under the rubric of Proteus syndrome. In our opinion, much of the early literature has retrospectively merged several entities (62,63). Neoplasms recorded in the syndromes (3,16,38,44,47,48) are also suspect and may have been recorded within a spectrum of overlapping conditions. These neoplasms have been reviewed elsewhere (24).

Cystic lesions of bone reported in Schimmelpenning syndrome are rare and may be coincidental (33). Unilateral polyostotic fibrous dysplasia in

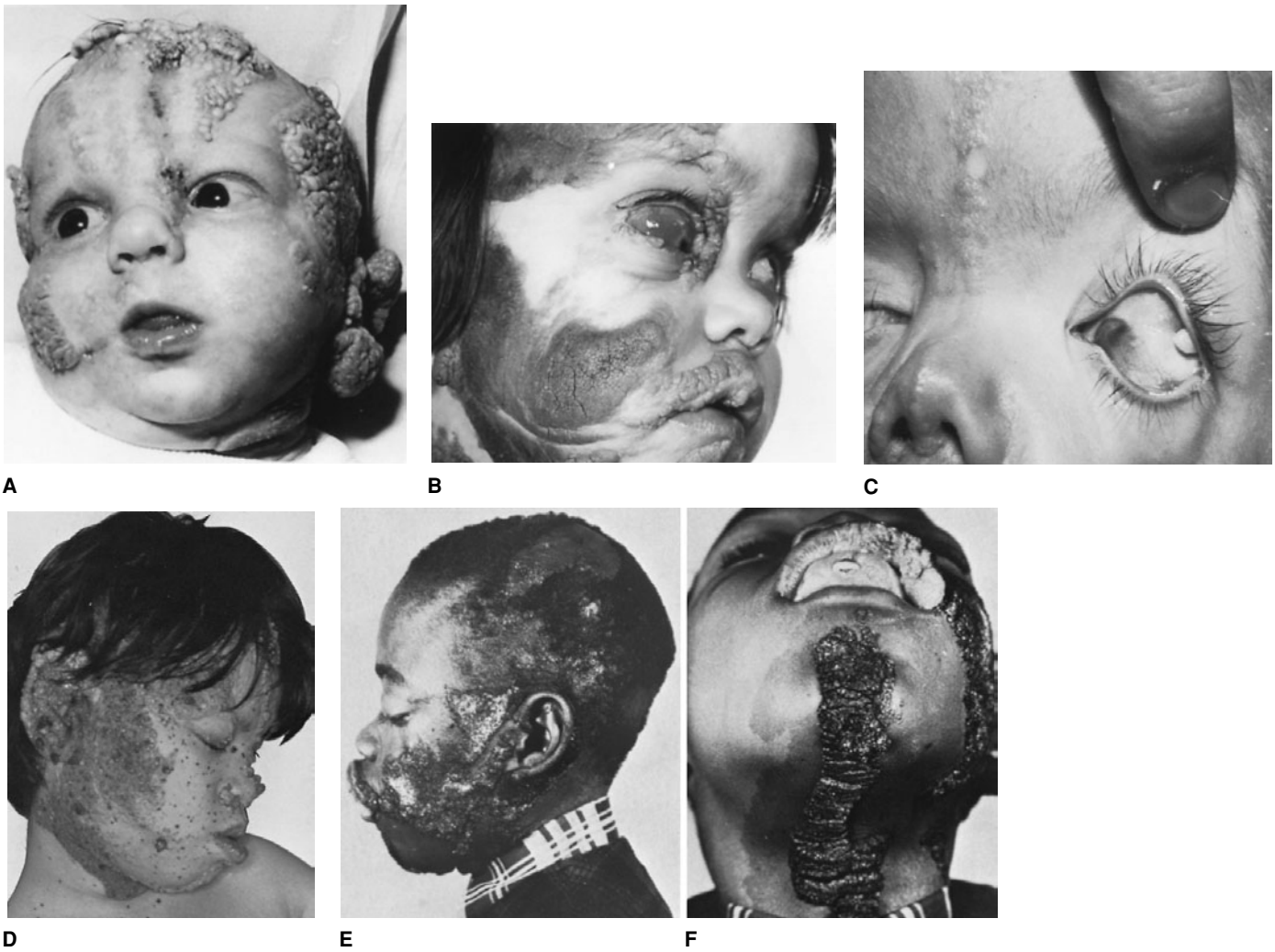


Fig. 12–41. *Schimmelpenning syndrome*. (A) Involvement of face and scalp. (B) Similar involvement in another patient. Corneal vascularization with clouding and blindness. (C) Linear nevus extending from forehead to tip of nose in mentally retarded female with hydrocephaly and seizures, epibulbar dermoid. (D) Similar alterations in other children. (E,F) Ten-year-old male with linear distribution, focal alopecia, hyperpigmented areas. Patient was blind and had epileptiform seizures. (A courtesy of B Pattberg, Berlin, Germany. B from B Leiber, Monatsschr Kinderheilkd 127:585, 1979. C from PM Marden and HD Venters, Am J Dis Child 112:79, 1966. D courtesy of G Sugarman and W Reed, Los Angeles, California. E,F from JE Kelley et al, Oral Surg 34:774, 1972.)

one case (70) is not well documented. Bitter (8) reported a true giant cell tumor of jaw bones, but the histology shows giant cell granuloma. Kaplan et al (33) also noted giant cell granuloma.

Fryburg and Greer (21) noted epidermal nevus with cutis aplasia congenita.

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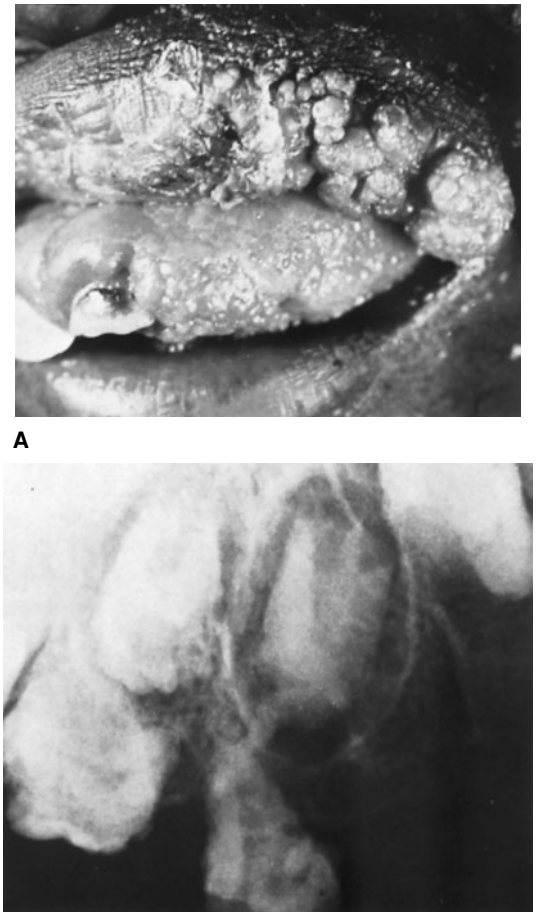

Fig. 12–42. *Schimmelpenning syndrome*. (A) Labial and gingival involvement. (B) Radiograph of teeth showing hypoplasia of enamel and dentin reminiscent of odontodysplasia. (A,B from JE Kelley et al, Oral Surg 34:774, 1972.)

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Tuberous sclerosis

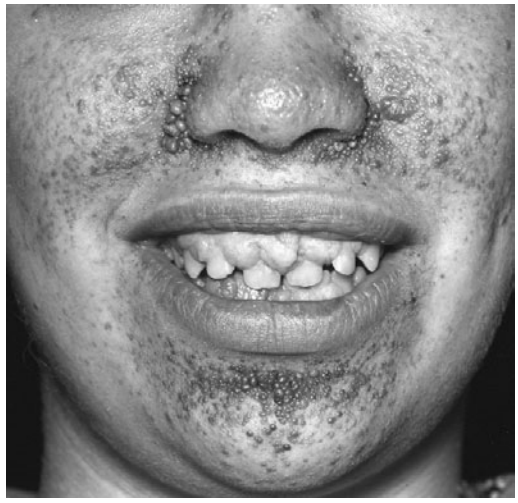
In tuberous sclerosis, the classic triad consists of seizures, mental deficiency, and angiofibromas. Bourneville (9,9a), in 1880, gave the first detailed description of the neurologic symptoms and cerebral pathology in three patients and coined the term "tuberous sclerosis." Another paper, coauthored with Brissaud, was published in 1900 (10). However, as early as 1862, Von Recklinghausen (114) described an infant with cardiac myomas and sclerotic lesions of the brain. In 1890, Pringle (84) reported a 25-year-old mildly retarded woman with facial lesions that he called "adenoma sebaceum," a term coined earlier by Balzer and Ménétrier (4). Historical aspects of the disorder have been especially well reviewed by Gomez (33) and Morgan and Wolfort (72). Tuberous sclerosis is also known as Bourneville-Pringle syndrome, epiloia, and adenoma sebaceum syndrome. The last term, so long used, should be abandoned because facial lesions are angiofibromas, not sebaceous adenomas. Several important reviews are available (14,33,46,57,82,87). We especially recommend the comprehensive 1991 review (33) and a discussion of diagnostic criteria (49a,83).

Tuberous sclerosis is characterized by a potential for hamartomatous growth in multiple organs and has a broad range of expression (Table 12–13). The classic triad of seizures, mental retardation, and angiofibromas (Fig. 12–43) represents one end of the spectrum of severity; mild cases can be difficult to detect. Autosomal dominant inheritance with very variable expressivity has been demonstrated (14,31,33,53). About two-thirds of the cases are sporadic (50,77,96). Gonadal mosaicism has been found in 6% (92,93,113,121). Lack of penetrance exists but appears to be relatively uncommon (5,114). There is reduced biologic fitness. Mutations in one of two genes, TSC1 at 9q34 and TSC2 at 16p13.3, cause tuberous sclerosis (3,13,18,24,28,52,83,111,122). Although linkage study suggests that the two forms are of equal frequency (43,52,98), mutational analysis indicates that TSC1 mutations are in the minority and may represent only 15% (1,19a). TSC2 mutations are more severe (4a).

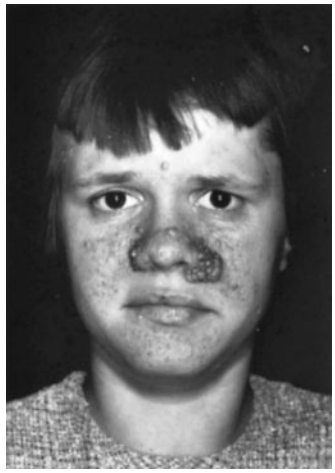
Table 12–13. Diagnostic criteria for tuberous sclerosis

Primary criteria (only one required for diagnosis)	Secondary criteria (two required for diagnosis)
Facial angiofibromas	Infantile spasms
Ungual fibromas	Hypopigmented macules
Cortical tuber (at necropsy)	Shagreen patch
Subependymal hamartomas (at necropsy or on CT)	Single retinal hamartoma
	Bilateral renal angiomyolipomas or cysts
Multiple retinal hamartomas	Cardiac rhabdomyoma
Fibrous plaque on forehead	First-degree relative with a primary diagnosis of tuberous sclerosis

Adapted from MR Gomez, Tuberous Sclerosis, Raven Press, New York, 1979.



A



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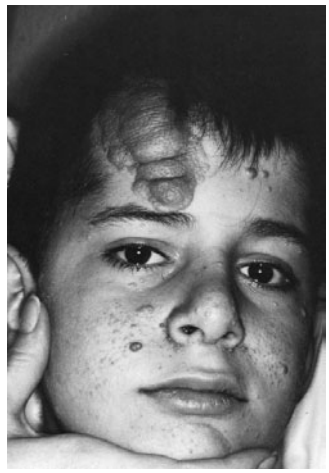


C

Fig. 12–43. *Tuberous sclerosis*. (A–C) Characteristic distribution of facial angiofibromas. Compare severity of lesions. Note gingival hyperplasia secondary to diphenylhydantoin therapy in A. Note large fibromatous mass on forehead in C. [A from BE Medley et al, Semin Roentgenol 11:35, 1976. B from R Goodman and RJ Gorlin, The Face in Genetic Disease, Mosby, St. Louis, 1970. C from MM Cohen Jr in Orofacial Genetics, Stewart RE, Prescott GH (eds), Mosby, St. Louis, 1976.]

Mosaicism is a potential cause of failure of molecular diagnosis (56,113). Loss of heterozygosity has been demonstrated in hamartomas from both TSC1- and TSC2-related patients, indicating that they are both tumor suppressor genes (35,36,42,104). There is no solid evidence that the phenotype is significantly different in TSC1 and TSC2 patients (83) (vide infra). Hamartin is the product of the TSC1 gene (50), while tuberin is the product of the TSC2 gene (43,111). The TSC2 gene has a small region of homology to the GTPase activating protein GAP3.

Jones et al (50) and Young et al (122), however, suggested that mutations are less common among sporadic cases and mental retardation less frequent in TSC1 cases. Kwiatkowska et al (55) noted that mutations are found in only 15%–20% of spontaneous TSC1 examples. In both TSC1 and TSC2 cases, the mutations lead to premature truncation of the respective proteins. There is no genotype–phenotype correlation in TSC1 cases (112).

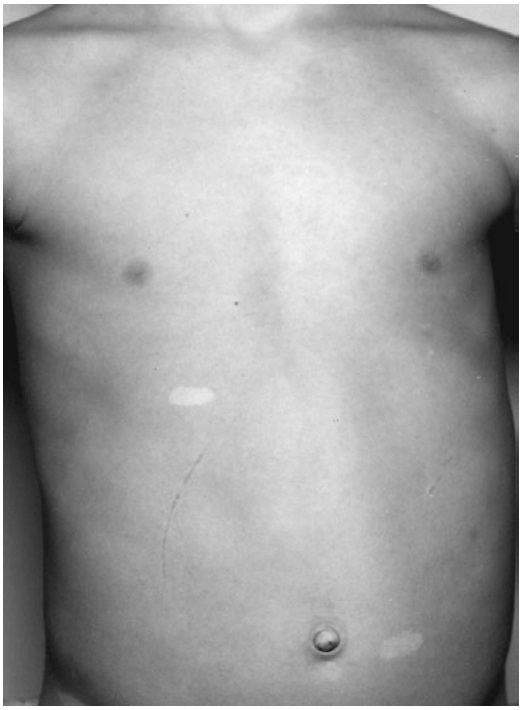


Fig. 12–44. *Tuberous sclerosis*. Note hypomelanotic macules. (Courtesy of MR Gomez, Rochester, Minnesota.)

Incidence is 1 in 6000 births (47,77,96). Published estimates of the prevalence of clinically ascertained tuberous sclerosis in institutions for the mentally retarded range from 0.32% to 1.1% (33). Surveys of autopsy data indicate a frequency of approximately 2.5%–2.8% (33).

The studies of Cassidy et al (14) and Gomez (33) clearly show that minimal diagnostic criteria for tuberous sclerosis can be used only if family members at risk are thoroughly evaluated. Detailed skin examination was the most sensitive diagnostic test (96%). However, as skin findings may not be present in infancy and early childhood, other tests can be useful, including cranial CT (67%), funduscopic examination through dilated pupils (33%), and renal ultrasound (50%–70%) (14). Using such criteria, Gomez (33) has listed the findings for primary and secondary diagnosis of tuberous sclerosis (Table 12–7). All manifestations are, however, age dependent. The reader is also referred to official diagnostic criteria (83).

Skin. Hypomelanotic macules are the earliest and one of the more commonly (65%) observed skin lesions (Fig. 12–44). They are often present at birth, but sometimes they can be observed only with a Wood's lamp. Most hypomelanotic muscles are leaf-shaped or round on one end and tapered on the other. Forty percent have 5 or more lesions (118). In about 20%, depigmented hair patches are found. They may be the first sign of the disorder (65). Confetti-like hypopigmentation of the lower legs (10%–20%) and multiple acrochordons of the neck were noted in a family that did not map to TSC1 (120).

Symmetric facial angiofibromas occur in 70%–85%. They are pink or reddish with a smooth glistening surface. They tend to be limited to the nasolabial folds, cheeks (butterfly distribution), perioral area, and, less often, the forehead and scalp. The upper lip, except for the area beneath the nose, is usually spared. They are rarely present at birth but typically appear during ages 5–10 years and progress during adolescence, and may occur as late as 25 years (73). Rarely, the facial angiofibromas are segmental, presumably representing postzygotic mutation (2,64).

Other findings include raised leathery plaques in the lumbosacral area or rarely on the chest wall (shagreen patches) (6) (35%–55%), periungual or subungual fibromas (Fig. 12–45), usually appearing at

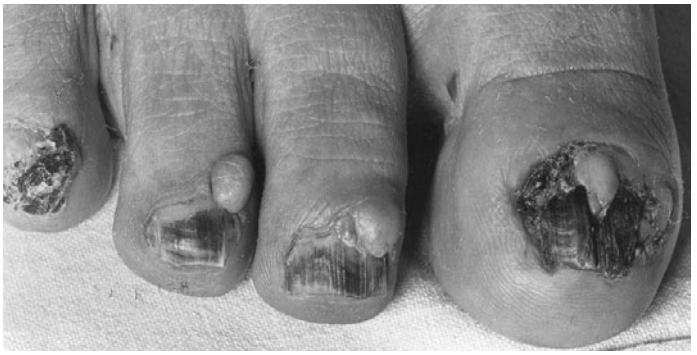


Fig. 12–45. *Tuberous sclerosis*. Subungual fibromas. (Courtesy of A Lodin, Stockholm, Sweden.)

puberty; and pedunculated cutaneous nodules or skin tags (molluscum fibrosum pendulum) (14%) (26,33,49,91,118). The subungual fibromata increase in frequency with age. They are seen in almost 90% of those older than 30 years. Fryer et al (29) has discussed forehead plaque as a presenting sign in tuberous sclerosis. When present, they are smooth patches of slightly raised skin with a reddish or yellowish discoloration.

Performance and central nervous system. Brain MRI is most sensitive for tubers, but brain CT is better for ascertaining calcium-containing subependymal giant cell astrocytomas. Hamartomatous calcification, if not present at birth, may develop as early as 5 months of age and progress throughout infancy and childhood. Hamartomatous foci consist of subependymal nodules and cerebral or, far less often, cerebellar cortical tubers (Fig. 12–46A). Olfactory nodules can also be seen (23).

Seizures occur in about 80%–90%. Approximately 30% have focal seizures, and 15% have both generalized and partial seizures. The frequency of various types of seizures are as follows: tonic–clonic seizures (41%), infantile spasms (30%), myoclonic seizures (16%), atypical absence (7%), tonic seizures (6%), and akinetic seizures (4%). Partial seizures break down as follows: motor seizures (16%), complex symptoms (10%), and unknown types (2%) (32,46,69,78,117).

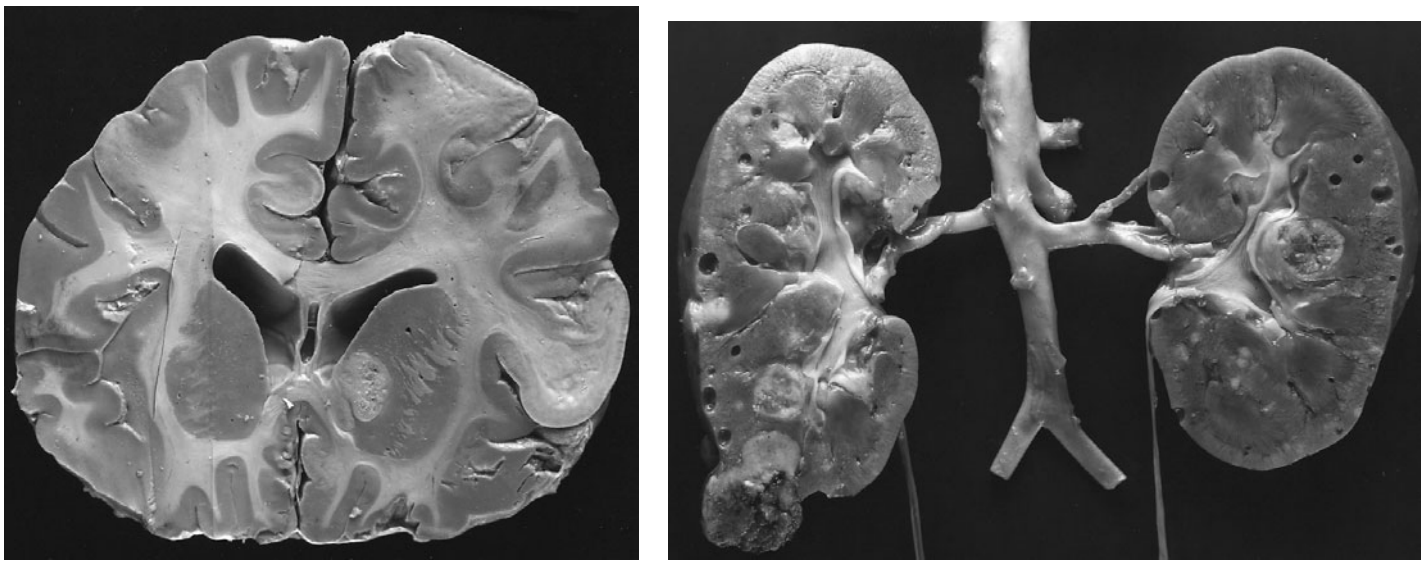
Approximately 40% have mental deficiency (117). A close correlation has been established between seizures and mental retardation, 89% of all individuals having seizures being mentally subnormal. In addition, the age of seizure onset and the severity of mental subnormality are directly related (32). Fryer et al (30) reported an affected family through five generations with no history of seizures or mental retardation.

Approximately 56% have intracranial calcifications (Fig. 12–47A,B) (69). Most occur in the cerebrum, 63% of lesions being bilateral, the remaining 37% being unilateral. Cerebellar calcifications occur in approximately 12%. The calcification is progressive: in children below 1 year 15%, below 5 years 35%, but by 14 years 50%–60% (69).

Increased intracranial pressure caused by tumor obstruction of cerebral spinal fluid circulation occurs infrequently, and less than 4% of patients have separated cranial sutures. Midventricular dilatation occurs in about 50% (69,80). Space occupying lesions, usually subependymal giant cell astrocytomas, cause obstruction of the foramen of Monro in 10%–20% (69). Convincing examples of other types of central nervous system tumors are extremely rare (12,85).

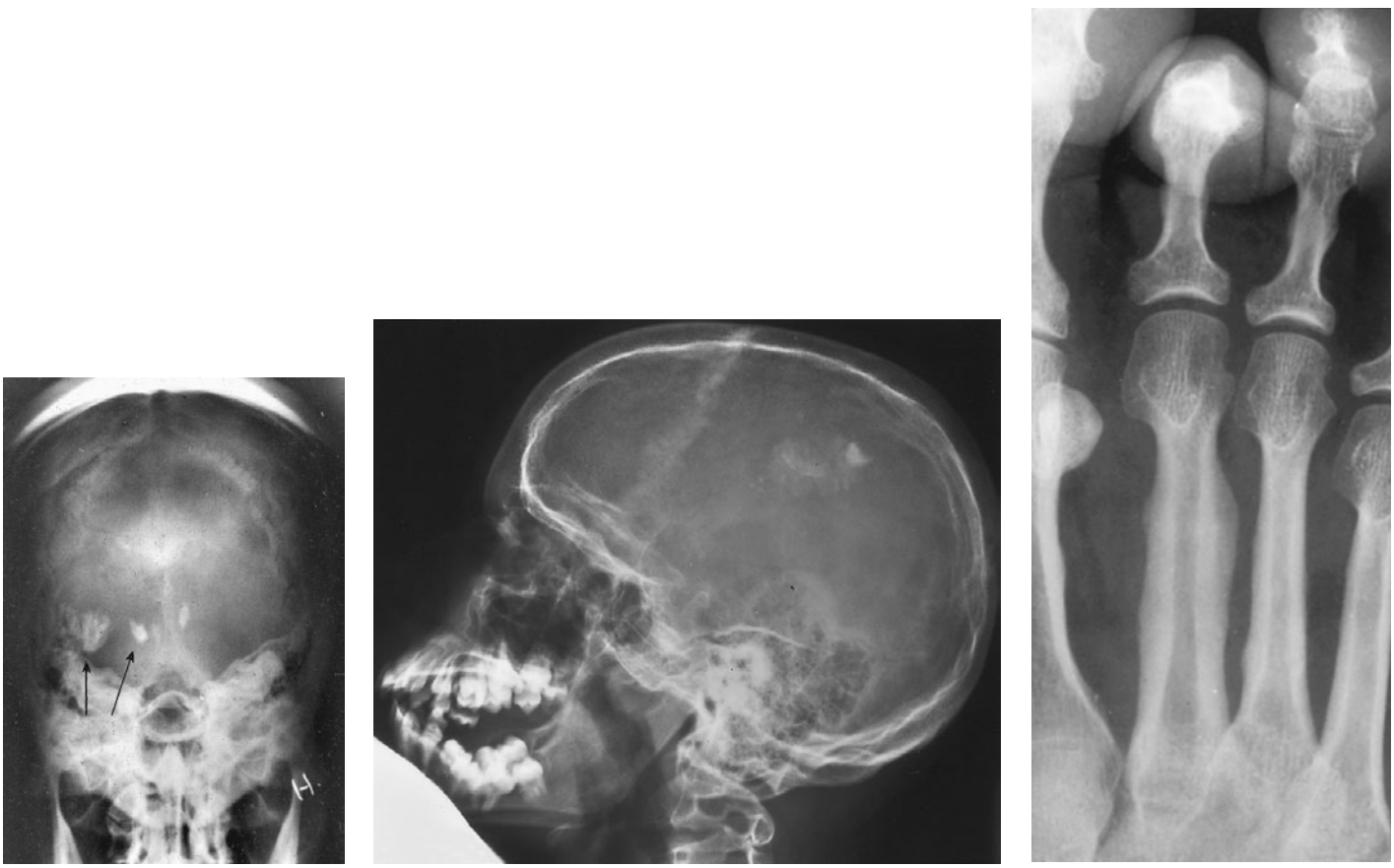
Childhood autism (25%–40%) may be related to temporal lobe tubers. Dementia in adults is almost always associated with the presence of seizures or growth of a tumor, which frequently causes obstruction with increased intracranial pressure (32,48).

Skeletal system. Approximately 65% have cystlike areas in the phalanges and irregular periosteal new bone formation along the shafts of the metacarpals and metatarsals (Fig. 12–47C). Less frequently, the long bones are involved (86,101). Gigantism of a single digit of the hand has been reported on several occasions (16,54,59,76,90a,105,108a).



A B

Fig. 12–46. *Tuberous sclerosis*. Gross pathological specimens. (A) Coronal section through brain showing bilateral cortical tubers, larger on the right. Subependymal nodule, right basal ganglia. (B) Multiple angiomyolipomas of kidneys. (A,B from BE Medley et al, Semin Roentgenol 11:35, 1976.)



A B C

Fig. 12–47. *Tuberous sclerosis*. Radiographs. (A) Intracranial calcifications. (B) Calcification in large posterior frontoparietal cortical tuber. (C) Lytic lesions of hand bones. (A courtesy of A Lodin, Stockholm, Sweden. B from BE Medley et al, Semin Roentgenol 11:35, 1976. C from TD Hawkins, Br J Radiol 32:157, 1959).

Ocular findings. Retinal hamartomas are found in approximately 50%. Two basic types of retinal lesions occur. The most common type is smooth, semitransparent, relatively flat, circular, or oval-shaped with distinct boundaries, being grayish or yellowish in color and being found in 55% of patients with retinal lesions. The opaque and nodular type occurs in approximately 45% of patients with retinal hamartomas. The lesions are elevated and multinodular, resembling the grains of tapioca, salmon eggs, or mulberries. They frequently occur along the disc margin or halfway toward the periphery of the retina. Some patients have retinal hamartomas with the morphologic characteristics of both types. This accounts for 15% of patients with hamartomas (90).

Renal abnormalities. Renal abnormalities, seen in 60%, are angiomyolipomas (Fig. 12–46B) (19,89) and, less commonly, polycystic kidneys (89,119). The multiple renal cysts, seen in 2%–3%, apparently represent a contiguous gene syndrome on 16p13.3 that involves the PKD1 gene. These lead to renal failure (100). Approximately 50%–65% of autopsied cases have angiomyolipomas (19,110). These are multiple (90%), bilateral (85%), and appear earlier in life than the isolated tumor (19). Their prevalence increases with age (75). They are seldom troublesome, although exceptions have been noted (25,33,39,63,70a,71,89). Renal angiomyolipoma by itself is a major diagnostic criterion for tuberous sclerosis (110). Renal cell carcinoma has been documented in 2% of patients (7,19). They can be multiple and bilateral, but more commonly are unilateral, and have been reported in TSC1 cases (99).

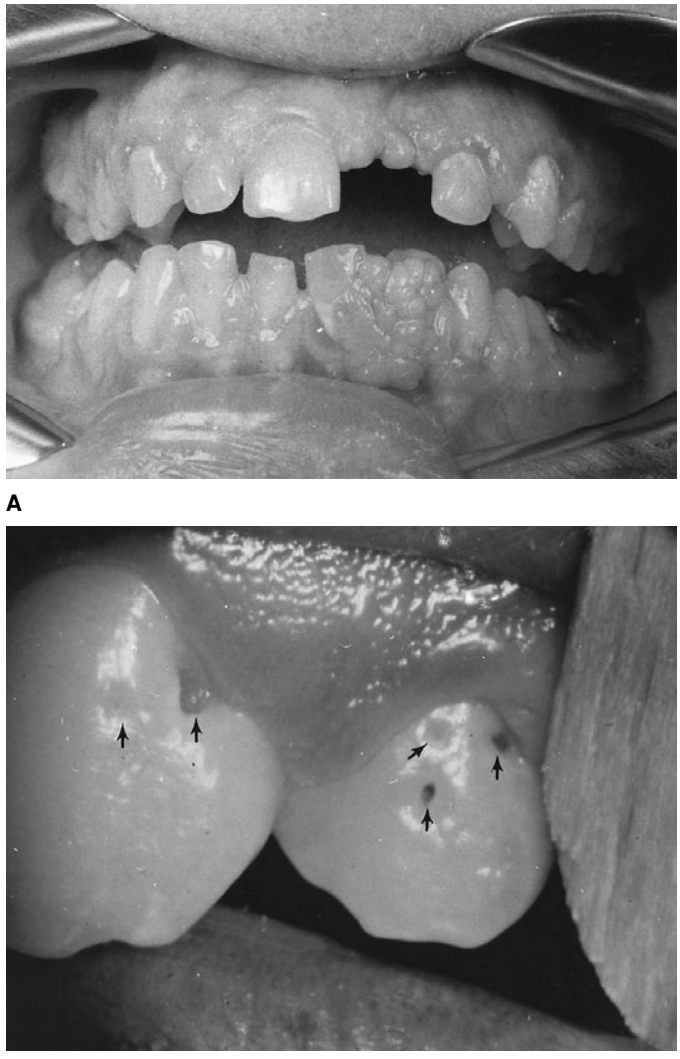
Histologically disturbing changes occur in the spindled smooth muscle cells that form disorganized sheets, sinuous bands, or small clusters between the fat cells and frequently spread centrifugally from vessel walls. The frequent findings of hyperchromatic nuclei, pleomorphism, and occasional mitotic activity are atypical histologic features, but should not be taken as evidence of malignancy (43,89). An instance of Wilms tumor has been recorded (36).

Cardiac manifestations. Approximately 30% have cardiac rhabdomyomas, and about 50% of patients with cardiac rhabdomyomas have tuberous sclerosis (40,116). Most rhabdomyomas occur intramurally, and only a small percentage represent intracavitary tumors. Cardiac signs and symptoms occur on the basis of obstruction of blood flow, myocardial involvement with secondary deterioration of ventricular function, or disturbance of cardiac rhythm. Wolff-Parkinson-White syndrome was found in 20% (8,70,74). Most lesions are multiple rather than single, and their most frequent occurrence in infants suggests that the entity is a hamartoma rather than a neoplasm (20,33,62). They tend to regress with age (106).

Other findings. Cystic disease of the lungs, pulmonary lymphangiomyomatosis (honeycomb lung), occurs almost exclusively in females (11F:1M), presenting in the third decade (58,69). There is good evidence that this is caused by novel TSC2 mutations (107,123). Conversely, about 5% of women with tuberous sclerosis exhibit pulmonary lymphangioleiomyomatosis (2a). Hemangiomas of the spleen and angiomyolipomas of the liver occur in 50%, usually as small (1–2 cm) lesions. Hamartomas have also been noted in the thyroid, pancreas, and testes (17,22,33). Rectal polyposis has been found in 1 of 15 patients (34). Various endocrinopathies have been recorded (101), including precocious puberty.

Oral manifestations. The oral mucosa may be the site of nodular fibrous growths (Fig. 12–48A). Approximately 35%–45% of patients have such lesions (118). Most frequently they occur on the anterior gingiva but may be found on the oral cheek or lingual mucosa (61,79,104). Enamel pits (Fig. 12–48B) have been observed (44,110). In some series, the frequency has been very high—from 50% (27,60,97) to 100% (68). The deciduous teeth are similarly involved (95). Calcifying epithelial odontogenic fibroma (94) and, especially, intraosseous fibrous lesions of the jaws have been documented (21,67,108,119).

Differential diagnosis. Most frequently mistaken for facial angiofibromas are multiple trichoepitheliomas, syringocystadenomas, colloid milia, atypical xanthomas, or, occasionally, intradermal nevi.



A

B

Fig. 12–48. *Tuberous sclerosis*. Oral lesions. (A) Gingival fibromas. (B) Pit-shaped enamel defects. (B from Vikilzadeh and R Happle, Hautarzt 31:336, 1980.)

Radiographic differential diagnosis of the skull should include *Sturge-Weber angiomatosis*, calcifying subdural hematoma and calcifying neoplasms, cytomegalic inclusion disease, toxoplasmosis, rubella, HTLV III intrauterine infections, and *hyalinosis cutis et mucosae*. Long-bone changes in tuberous sclerosis should be differentiated from those of *neurofibromatosis*, fibrous dysplasia, enchondromatosis, gout, sarcoid, and hypertrophic arthritis. Shagreen patches may also be seen in association with osteopoikilosis and *Proteus syndrome*. Rarely, *Klippel-Trenaunay* syndrome has been observed with tuberous sclerosis (33,109).

Laboratory aids. Laboratory aids include Wood's lamp examination of the skin, cranial CT and MRI, renal ultrasound, and radiographs of the hands, feet, and skull (69,102). Cardiac ultrasound is sensitive in children less than 2 years but is not helpful in adults. Imaging studies are positive in over 90%, CT being more useful for detection of subependymal nodules and MRI being more accurate for the number and location of cortical subcortical lesions (11,66). Funduscopic examination through dilated pupils, preferably with fluorescein angiography, is essential. Disclosing solution can be used to demonstrate enamel pits. All parents of patients with tuberous sclerosis should be thoroughly examined before recurrence risk counseling is given.

Prenatal diagnosis has been accomplished through detection of cardiac rhabdomyoma by ultrasound and echocardiography (3a,15,51,81).

Mutational testing is difficult, expensive, and not commercially available. There are over 400 mutations in TSC1 and TSC2 genes found to date, with a wide spectrum of types throughout both genes.

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Chapter 13
Syndromes Affecting the Skin and Mucosa

Aplasia cutis congenita

Aplasia cutis congenita is the localized or widespread absence of skin at birth. First described by Cordon in 1767 (17), the defect became more widely known with Campbell's report (14), in 1826, of two sibs with involvement of the scalp vertex. Over 550 cases have been reported to date. Clinical associations, classification, and etiology have been discussed in several noteworthy reviews (21,22,27,31,33,65,104,105,108).

Lesions are commonly present as ulcerated or membranous defects of variable size near the midline of the scalp vertex (Figs. 13–1 and 13–2). Small lesions are usually located at or in proximity to the parietal hair whorl (109). Absent hair is a constant feature. The defect is single in most cases (75%), but double, triple, or multiple vertex defects may occur (23). Although most single defects (66%) are oval-shaped and small (0.5–3 cm), more extensive defects over 10 cm in diameter have been reported (21). Defects may involve the epidermis only or may extend to full skin thickness. Osseous involvement of the calvaria, found in 20%–30%, is detected radiographically by demonstrating an area of bone deficiency underlying the cutaneous defect (21).

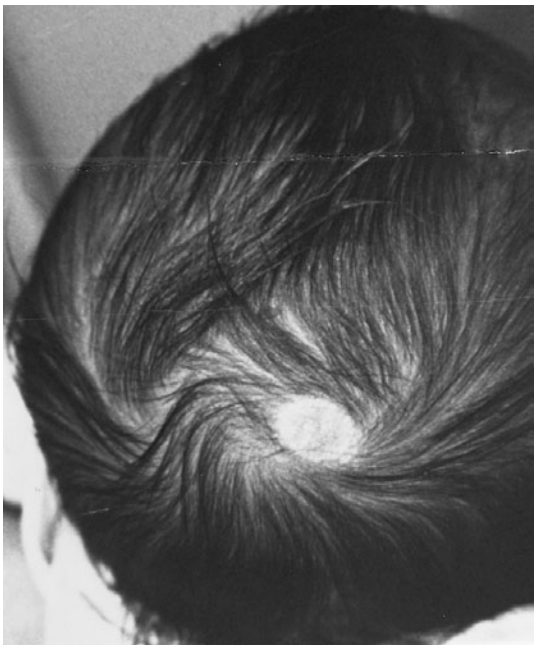
Small, superficial midline defects tend to heal gradually without complications during the initial week after birth, leaving a residual atrophic or hypertrophic scar with alopecia. Healing of a calvarial defect is generally complete during the first year of life (21). Extensive scalp defects, which may extend to involve the dura (21,65), pose a significant risk for infection, potential meningitis, venous thrombosis (67), and sagittal sinus hemorrhage (9,14,21,39,97).

A male newborn has been reported with congenital symmetrical abdominal skin defects and alopecia of the scalp in a spiral pattern. The distribution of both skin anomalies was reminiscent of the lines of Blaschko, suggesting somatic mosaicism as a possible cause for the defects (46).

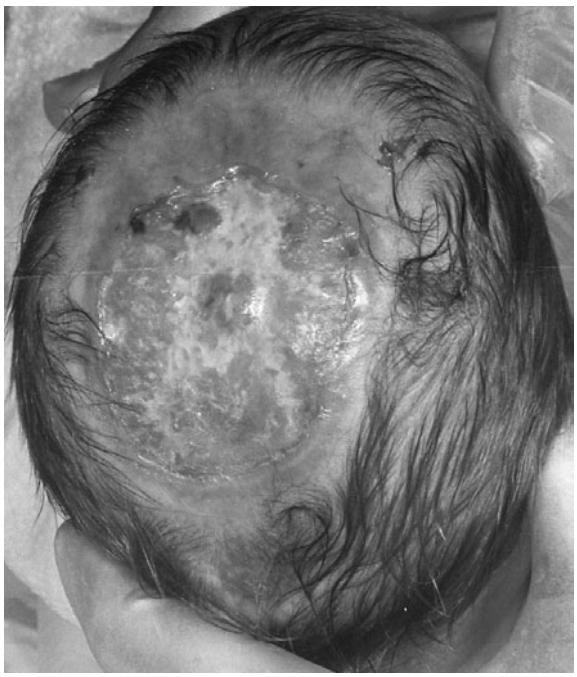
Although most cases are sporadic, many familial instances have been recorded. Autosomal dominant inheritance with incomplete penetrance and variable expressivity occurs most frequently (35,79,93,108,122), but autosomal recessive inheritance is implicated occasionally, usually in offspring of consanguineous parents (41,79). Concordant monozygotic (50) and discordant monozygotic (124) twins have been documented. Aplasia cutis congenita involving the trunk and/or limbs is etiologically heterogeneous, and familial examples have been noted in some instances (32,94) (Fig. 13–2).

Aplasia cutis congenita is a feature of many syndromes and also occurs on a disruptive (71,73,104), infectious (3,103,107,109), and teratogenic basis. Association with many isolated malformations has been documented as well (27). Der Kaloustian et al (23) have reported on 2 families having members affected with the Poland sequence and the aplasia cutis congenita of Adams-Oliver syndrome. Conditions associated with aplasia cutis congenita are summarized in Table 13–1. Those not involving the head, neck, or scalp are excluded from this table (27).

Fig. 13–1. *Aplasia cutis congenita*. (A) Healed oval lesion of aplasia cutis congenita at site of parietal hair whorl. (B) Extensive ulcerative lesion in trisomy 13 syndrome. (A from MJ Stephan et al, J Pediatr 101: 850, 1982.)



A



B

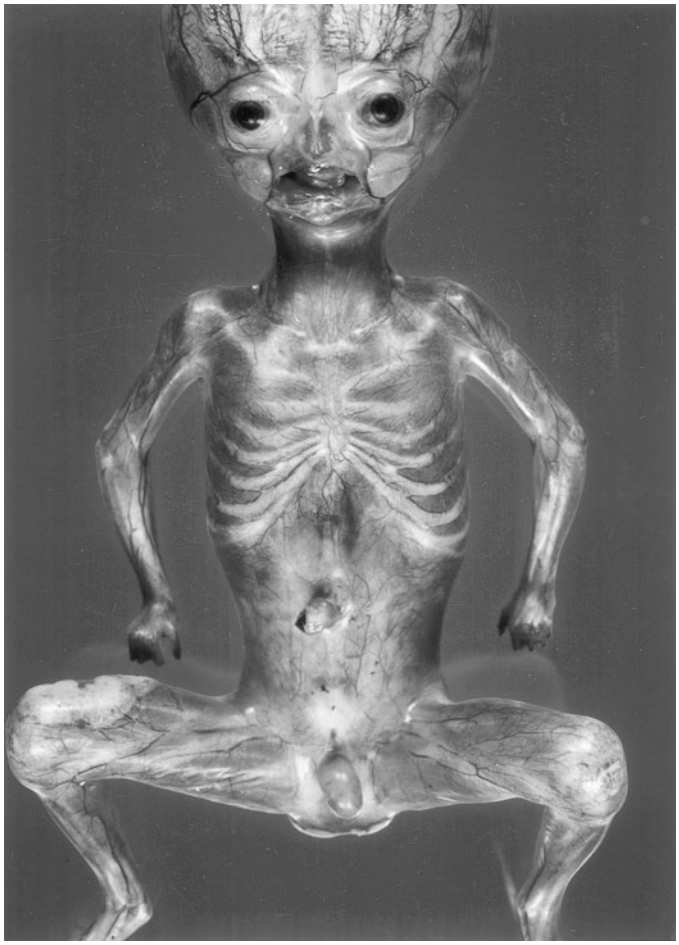


Fig. 13–2. *Aplasia cutis congenita*. Extensive form. (From MS Park et al, J Med Genet 35:609, 1998.)

Differential diagnosis. Congenital scalp defects should be considered separately from aplasia cutis congenita involving the trunk and extremities. Differential diagnosis includes localized scalp infection, congenital dermoid cyst, small meningocele, heterotopic brain or glial tissue (54,83), and traumatic lesions secondary to fetal scalp monitoring (11). As the child grows and scarring of the cutis aplasia lesions occurs, sebaceous nevus, and alopecia of pseudopelade type may be confused with it. Particular care must be taken to distinguish linear or stellate lesions of aplasia cutis congenita from linear alopecia seen in "en coup de sabre" morphea.

Isolation of herpes simplex type 2 virus has been reported from a newborn with three occipitoparietal ulcerated scalp defects, with serologic confirmation of elevated antiherpes complex IgM (109). These lesions healed spontaneously with local scarring.

For extensive aplasia cutis congenita involving the trunk and extremities, it is important to exclude various types of *epidermolysis bullosa* (5,6,33,123). Clinically helpful clues of epidermolysis bullosa include frequent oral mucosal involvement and development of further lesions after birth. If doubt remains, ultrastructural examination of a skin biopsy from the margin of a lesion will distinguish epidermolysis bullosa and define the genetic type. We have kept in our classification the condition described by Jones et al (58) since epidermolysis bullosa is only one manifestation of a syndrome comprising aplasia cutis congenita, cleft palate, and ectrodactyly. Nonfamilial truncal and extremity aplasia cutis congenita have sometimes been attributed to thromboplastic emboli derived from a fetus papyraceous resulting from death of a co-twin early in the second trimester of pregnancy (76,78). In other cases, when no fetus papyraceous is discovered, the emboli may originate from the placenta itself (73). *Restrictive dermopathy* should also be excluded.

There is insufficient evidence either to establish or eliminate a direct causal relationship between fetal aplasia cutis congenita and the use of methimazole in cases of pregnancies complicated by maternal hyperthyroidism (118). However, since propylthiouracil is an equally effective antithyroid agent and has not been associated with aplasia cutis congenita, it should be the preferred thioamide for the treatment of hyperthyroidism during pregnancy (75).

Laboratory aids. Histologic sections from a skin biopsy will confirm the diagnosis in uncertain cases. The defective area is devoid of elastic fibers, dermal papillae, and normal blood vessels. No well-demarcated border between normal skin and aplasia cutis congenita is observed; rather, there exists an intermediate zone of skin within which dermal appendages such as hair papillae, sebaceous glands, and sweat glands are found to be small to rudimentary and to decrease in size and number centripetally with gradual transition from normal skin to the ulcer of aplasia cutis (120). Aplasia cutis congenita may also be a rare cause of elevated amniotic fluid alpha-fetoprotein levels, and a distinct acetylcholinesterase electrophoretic band (24,37).

References (Aplasia cutis congenita)

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Table 13–1. Disorders associated with aplasia cutis congenita[a]

	References
I. Etiology	
A. Chromosomal	
Del(4p) (Wolf-Hirschhorn syndrome)	43,49
Del(13q)	Personal communication, J Fenyk
Monosomy distal 12q, trisomy distal 1q	62
Tetrasomy (12p) (Pallister-Killian syndrome)	126
Trisomy 13 (Patau syndrome)	1,14
B. Monogenic	
1. *Autosomal dominant*	
Adams-Oliver (ACC with terminal phalangeal anomalies and congenital heart anomalies)	2,7,29,55,64, 90,108,110,127
Alopecia areata, ear anomalies, and perianal skin tags	56
Autosomal dominant ACC	79,93,108,122
Ectodermal dysplasia-abnormal facies	70
Postaxial polydactyly	13,25
*S*calp-*E*ar-*N*ipple syndrome	29,89
Syndactyly and supernumerary nipples	44
Tricho-odonto-onychodysplasia and dyshydrosis with nipple-breast hypoplasia	96,113
Unilateral facial paresis, dermal sinuses, and ear malformations	4
2. *Autosomal recessive*	
Atrophic alopecia, ocular defects, and scarring tendency of skin	72
Autosomal recessive ACC	79,104
Ectodermal dysplasia/clefting syndrome	8
Familial 46,XY gonadal dysgenesis with anomalies of ectodermal and mesodermal structures	10
Intestinal lymphangiectasia	9
Johanson-Blizzard syndrome	57
Knobloch-Layer syndrome	63,98,99
Limb, eye, and brain anomalies (variant of Adams-Olivers syndrome?)	84
Setleis syndrome (bitemporal "forceps" marks with ACC)	61,77
3. *X-linked*	
Goltz-Gorlin syndrome	40,121
Hereditary motor and sensory neuropathy type I (Charcot-Marie-Tooth disease, type I) with aplasia cutis congenita	15
MIDAS syndrome (*MI*crophthalmia, *D*ermal *A*plasia and *S*clerocornea)	45
C. Teratological	
Methimazole	60,80,82,115
Valproic acid	52
D. Infectious	
Congenital herpes simplex	107,109
Congenital varicella	3,103,114
E. Disruptive	
Amniotic rupture sequence	47
Fetus papyraceous	71
F. Unknown	
Arteriovenous fistula, prominent scalp veins, high-arched palate	101
Choanal atresia, laryngomalacia, imperforate anus, congenital hip dislocation	65
Cleft palate, epidermolysis bullosa, ectrodactyly	58
Delleman syndrome (oculo-cerebro-cutaneous syndrome)	20
Ectodermal dysplasias (various types of tricho-odonto-onychial subgroup)	88,112,113
Ectrodactyly, ectodermal dysplasia, cleft lip/palate, scalp defects	59
Schimmelpenning syndrome	34,68
Extensive aplasia cutis congenita	86
Facial dysplasia, myopia, delayed dentition, short stature	106
High myopia and cone–rod dysfunction	38
Hypoplastic midface, broad nasal bridge, prefrontal lipoma, epicanthus, ectodermal dysplasia	36,67,70
Limb anomalies and tetralogy of Fallot	74
Megalocornea, scoliosis, short stature	92
Multiple hamartomas, giant pigmented nevocellular nevus, and central nervous system malformation	81
Oculo-ectodermal syndrome	26,36,111
Ridged metopic sutures, depressed nasal bridge, upward-slanting eyes, cleft lip and palate, low-set ears, short neck, dextrocardia, hydrocele, talipes equinovarus	100
Sakati syndrome	16
Spear-Mickle syndrome	16,102
Vertebral and eye anomalies, short stature (VECS)	90
II. Systemic distribution of associated findings	
A. Central nervous system	
Congenital midline porencephaly	125
Craniospinal rachischisis	42
Early telencephalic defects	30
Holoprosencephaly	65–67
Hydranencephaly	30
Hydrocephaly	14,53
Leptomeningeal angiomatosis and aneurysm of distal posterior cerebral artery	91
Meningocele	53
Occult spinal dysraphism	48
Spastic paralysis and mental retardation	95
Tethered cord	87
B. Cardiovascular system	
Arteriovenous malformation	101,116
Coarctation of the aorta	18
Congenital heart defects	19
Patent ductus arteriosus	19
Valvular heart disease	82
Ventricular septal defect/ pulmonary stenosis	85
C. Gastrointestinal system	
Cleft lip–palate	53,65
Intestinal lymphangiectasia	9
Omphalocele	117
Tracheoesophageal fistula	19
D. Ophthalmological system	
Atrophic alopecia, ocular defects and scarring tendency of skin	72
High myopia and cone–rod dysfunction	38
Knobloch-Layer syndrome	63,98,99
Oculo-ectodermal syndrome	26,36,111
E. Miscellaneous	
Closure defects of ventral body wall and/or neural tube	51
Cutis marmorata	119
Extensive aplasia cutis congenita	86
Piebaldism	12

[a] Conditions with aplasia cutis congenita not involving the head, neck, or scalp are excluded from this table.

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Aplasia cutis congenita, ear malformations, facial paresis, and dermal sinuses (Scalp-Ear-Nipple syndrome, Finlay-Marks syndrome)

In 1979, Anderson et al (2) reported a Mexican-American family in which four generations were affected with aplasia cutis congenita of the scalp, ear defects (uni- or bilateral lop ear, conductive and possibly mixed hearing loss), dermal sinuses (both pretragal and parasternal), and unilateral facial palsy. Hypoplastic facial canals were verified by tomography in those with facial palsy. Finlay and Marks (4) and other authors (1,3–9) reported somewhat similarly involved families with the SEN syndrome, an autosomal dominant disorder of *S*calp defects (aplasia cutis congenita), *E*ar abnormalities (small or rudimentary tragus, antitragus, and lobule), and rudimentary or absent *N*ipples (Fig. 13–3). Turnpenny (personal communication, 2000) suggested anticipation.

Differential diagnosis would include *branchio-oto-renal syndrome*. Approximately 30 cases have been described. Aplasia cutis congenita of the scalp has been an almost constant feature as has dysplastic pinnae. Hypoplasia of the nipples was noted in about 60%. Scanty hair has been reported in 35% and hypohidrosis in about 50% of those tested. Nail dysplasia is seen in 40% and variable tooth anomalies in 75%. Cutaneous syndactyly and/or campotdactyly have been observed in 75%.

References [Aplasia cutis congenita, ear malformations, facial paresis, and dermal sinuses (Scalp-Ear-Nipple syndrome, Finlay-Marks syndrome)]

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Aplasia cutis congenita with epibulbar dermoids (oculo-ectodermal syndrome)

In 1993, Toriello et al (9) reported two unrelated boys with aplasia cutis congenita, epibulbar dermoids, and cutaneous hyperpigmentation (Figs. 13–4 and 13–5). Later, Gardner and Viljoen (5) and Evers et al (3) described similar cases in girls. Strabismus and epicanthal folds may also be part of this condition, but hyperpigmentation of the skin has not been described in the last two reports. The genetic basis of the condition is uncertain.

Differential diagnosis includes *oculocerebrocutaneous (Delleman) syndrome*, which presents with orbital cysts, cerebral malformations, dermal defects, skin appendages, skeletal defects and mental retardation (1). Another condition to consider is mild *Proteus syndrome*, which includes areas of scalp alopecia, ocular choristomas, seizures, lipomas, connective tissue nevi, mental retardation, and cerebral malformations (8). Finally Chaurasia and Goswami (2) in 1971, Frieden (4) in 1986, Lering et al (7) in 1988, and Lees et al (6) in 2000, described patients with scalp, skin, and eye anomalies that are distinct from the presentation of aplasia cutis congenita with epibulbar dermoids (9).

References [Aplasia cutis congenita with epibulbar dermoids (oculo-ectodermal syndrome)]

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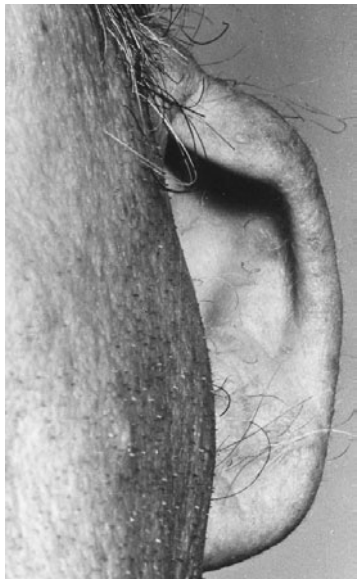
A



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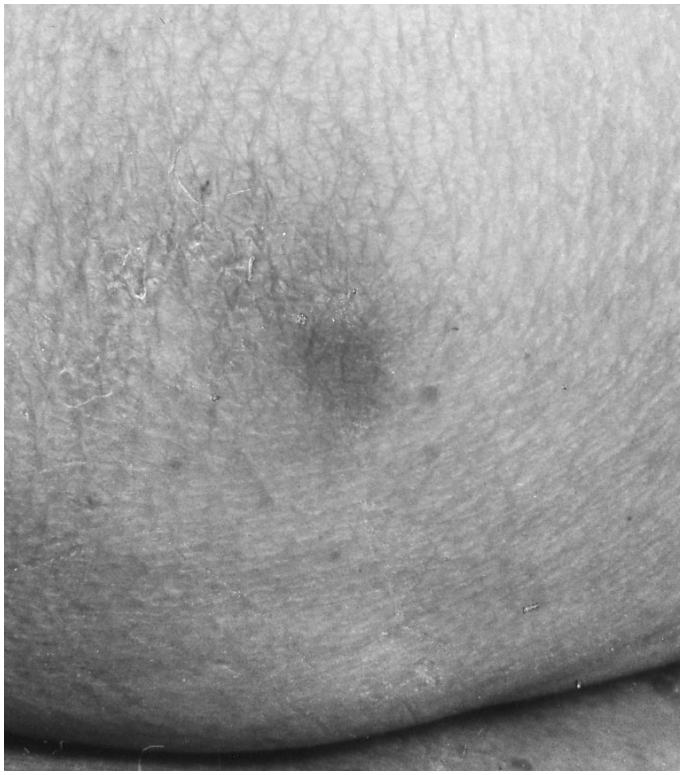

C

Fig. 13–3. *Aplasia cutis congenita, ear malformations, facial paresis, and dermal sinuses*. (A) In and adjacent to midline, over posterior scalp, are firm raised nodules not covered by hair. (B) Superior helix is largely absent but rudiment is downturned. (C) Rudimentary nipple manifest by brown flat area only. (From AY Finlay and R Marks, Br J Dermatol 99:423, 1978.)

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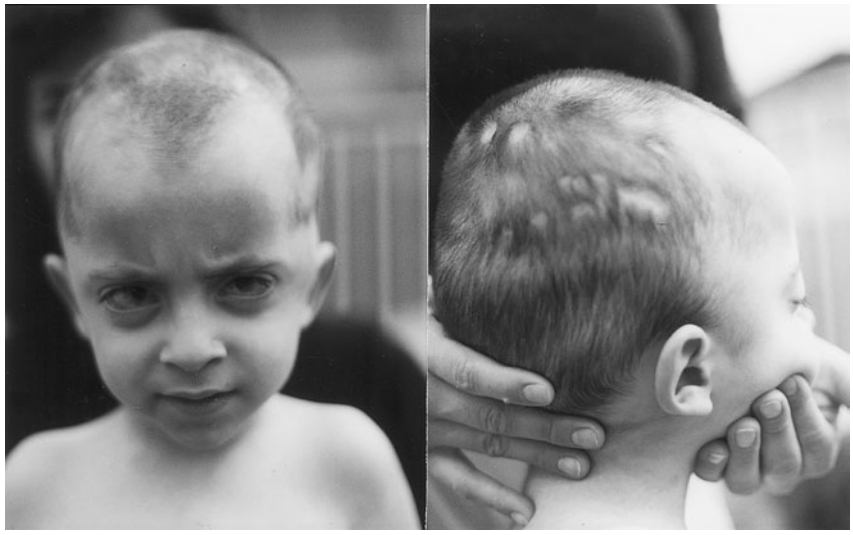
Aplasia cutis congenita, high myopia, and cone-rod dysfunction

In 1996, Gershoni-Baruch and Leibo (1) reported a brother and sister, born to consanguineous parents with congenital nystagmus, cone–rod dysfunction, high myopia, and aplasia cutis congenita on the midline of the scalp vertex.

This condition is distinct from other forms of cone and rod dysfunction (2). Leung et al (3), in 1988, described two sibs with aplasia cutis congenita of the scalp associated with ocular defects such as myopia, keratoconus, nystagmus, atrophic irides, and atrophic pigment epithelium. The critical difference from the condition described by Gershoni-Baruch and Leibo (1) is their particular tendency to develop permanent atrophic linear or macular scars following minor trauma to the forearms, hands, and lower legs.



A B

Fig. 13–4. *Oculo-ectodermal dysplasia*. Numerous areas of scalp aplasia. Epibulbar dermoids had been removed.

References (Aplasia cutis congenita, high myopia, and cone-rod dysfunction)

1. Gershoni-Baruch R, Leibo R: Aplasia cutis congenita, high myopia, and cone–rod dysfunction in two sibs: A new autosomal recessive disorder. Am J Med Genet: 61:234–242, 1989.
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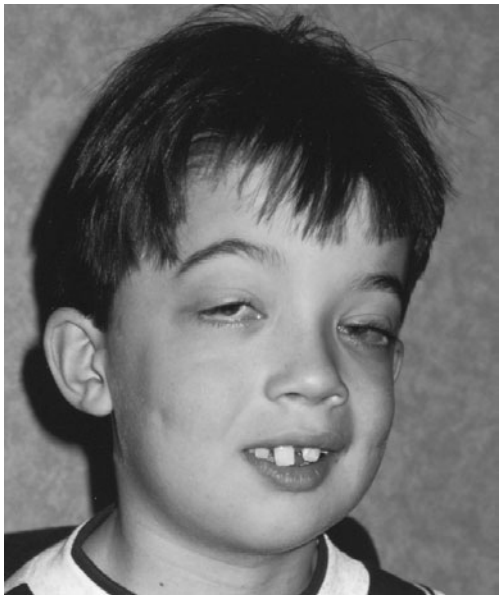
Vertebral and eye anomalies, cutis aplasia congenita, and short stature (VECS)

Prasad et al (1), in 1998, described a six-year-old female with short stature, prominent eyes due to megalocorneae, pointed chin, cutis aplasia of the scalp, nasal lacrimal duct obstruction, sagittal craniosynostosis, and kyphoscoliosis with multiple segmentation defects of the thoracic vertebrae, and eleven pair of ribs.

Fig. 13–5. *Oculo-ectodermal dysplasia*. Note strabismus in same child at age 10 years.



Reference [Vertebral and eye anomalies, cutis aplasia congenita, and short stature (VECS)]

1. Prasad C et al: Vertebral and eye anomalies, cutis aplasia, and short stature (VECS): A new syndrome? Am J Med Genet 77:225–227, 1998.

Ascher syndrome

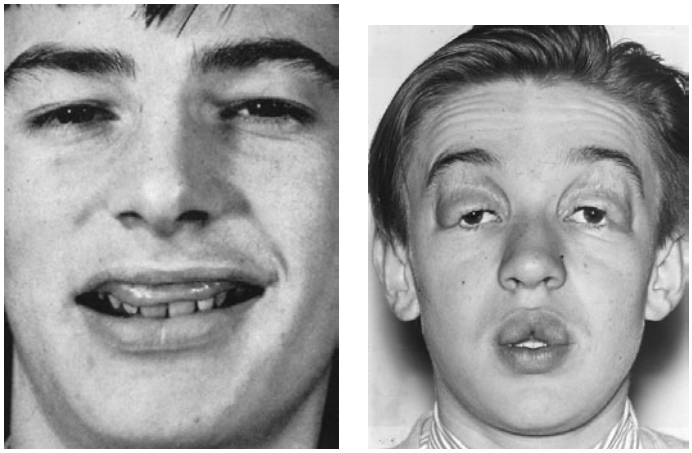
In 1920 and 1922, Ascher (1,2) brought to the attention of ophthalmologists the syndrome of blepharochalasis, double lip, and nontoxic thyroid enlargement, although the combination of blepharochalasis and double lip was described in 1909 by Laffer (17). Subsequently, additional examples of the complete syndrome were reported (8,9,13–15,20,22). Examination of other reports (3–7,10–12,18–21,23–31) indicates that blepharochalasis may occur as an isolated abnormality, as may double lip. Blepharochalasis was described as an isolated finding as early as the nineteenth century (12). In Ascher syndrome, autosomal dominant transmission has been suggested (3,11,21,27), many sporadic cases apparently representing fresh mutations. We are aware of blepharochalasis and double lip that was shown to be Ehlers-Danlos syndrome type VII.

Eyes. Sagging eyelids are striking. The upper lids and less commonly the lower lids are characterized by relaxation of the tarsal fold, which allows the tissue between the eyebrow and the edge of the lid to hang slack over the palpebral fissure. The lid skin is markedly thin and atrophic. Atrophy and drooping of the lid often follow repeated angioneurotic edema-like episodes. In several cases, swelling of the lids has appeared during the first 8 years of life. In others, its occurrence was noted at about the time of puberty (16,25). The swelling of the lids and the enlargement of the lips may occur simultaneously (8,22) (Figs. 13–6 to 13–8). Double lip has been reported in association with cheilitis glandularis (6).

Gross surgical examination of tissue removed from the relaxed skin of the lid has shown prolapsed orbital fat or, more frequently, hyperplastic lacrimal gland tissue. The lids, on microscopic examination, have exhibited an increased number of blood vessels, but no unanimity of opinion exists about changes in the elastic fibers (20).

Lips. The lip, almost always the upper, is the site of a horizontally running duplication located between the inner (pars villosa) and outer (pars glabrosa) parts of the lip (20). The fold cannot be seen when the lips are closed, but only when the patient is smiling or talking. The enlargement of the lip may exist from childhood (3,5,11). Rarely, the lower lip is also enlarged (7,11) (Figs. 13–6 to 13–8).

Microscopic examination of the excessive labial tissue usually reveals loose areolar tissue and hyperplastic mucous glands, numerous blood-filled capillaries, and infiltration with plasma cells and lymphocytes (3,5,7,10,15).



A B

Fig. 13–6. *Ascher syndrome*. (A) Note transverse crease with "doubling" of upper lip and sagging of lateral portion of upper eyelids. (B) Patient with appearance similar to that of patient in A. (A from MC Oldfield, Br J Surg 47:58, 1959. B from K Stehr, Dtsch Med Wochenschr 87:1148, 1962.)

Thyroid. Thyroid gland enlargement is variable and not usually associated with toxic symptoms. Barnett et al (3), however, reported a patient with hypothyroidism and myxedema. Enlargement may appear several years after eyelid involvement (2), but usually appears during the second decade. It may be evident only on scanning with radioactive iodine (22).

Differential diagnosis. Blepharochalasis and double lip may each occur as isolated anomalies. Most instances of so-called double lower lip are actually lip sinuses of the transverse furrow type (23). Floppy eyelid syndrome, the combination of blepharochalasis and chronic papillary conjunctivitis, has been discussed by Goldberg et al (12). The *Melkersson-Rosenthal syndrome* (cheilitis glandularis, facial paralysis, and fissured tongue) and vascular neoplasms (hemangioma, lymphangioma) should be considered. The syndrome of *acromegaloid features and thickened oral mucosa* should be excluded as well as *dermatosparaxis* (EDS VIIC).

References (Ascher syndrome)

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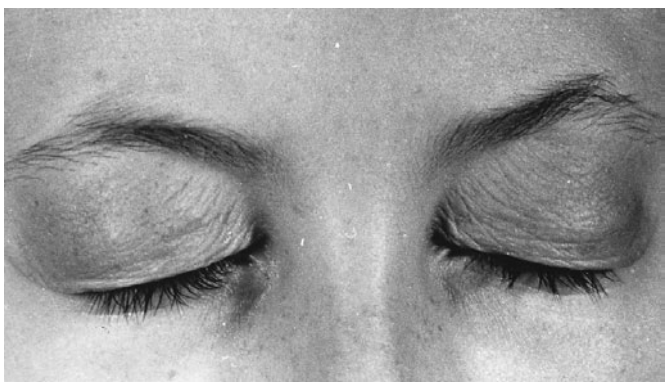
Fig. 13–7. *Ascher syndrome*. Blepharochalasis. (From R Michalowski, Dermatol Wochenschr 149:232, 1964.)



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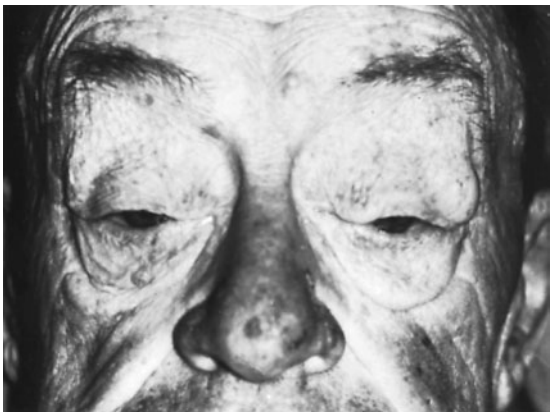
Acromegaloid features and thickened oral mucosa (Hughes syndrome)

Hughes et al (4) described a four-generation kindred in which 13 individuals were affected with a progressively coarse acromegaloid facial appearance and thickening of the lips and oral mucosa. Inheritance is autosomal dominant.

The most striking features are thickened lips without true doubling, overgrowth of the oral mucosa resulting in exaggerated rugae and frenula, and thickened upper eyelids leading to narrow palpebral fissures. Both facial appearance and large doughy hands remind the observer of acromegaly (3) (Figs. 13–9 and 13–10).

In 1992, Dallapiccola et al (1) reported a family with the same disorder affecting a mother and 4 children. Another example was described by DaSilva et al (2).

In differential diagnosis *pachydermoperiostosis, Ascher syndrome*, and *multiple mucosal neuroma syndrome* should be excluded. In Hughes syndrome, the skin was not furrowed. The nose becomes rather significantly bulbous, far more than that seen in pachydermoperiostosis. Although the oral mucosa becomes thickened in Ascher syndrome, it is not to the degree found in Hughes syndrome and, although the hand joints are hyperextensible (Fig. 13–10), there is no clubbing as there is in pachydermoperiostosis.



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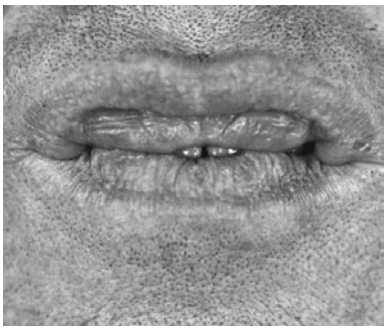

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Fig. 13–8. *Ascher syndrome*. (A,B) Compare similar alterations in older patients (A courtesy of AF Morgan, Seattle, Washington.)

It is important not to confuse this condition with another Hughes syndrome [thrombosis, thrombocytopenia, and recurrent spontaneous abortions associated with antiphospholipid antibodies (3)].

References [Acromegaloid features and thickened oral mucosa (Hughes syndrome)]

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Cutis laxa syndromes

Cutis laxa (CL) is characterized by skin that hangs in loose folds. There are many forms, some genetic and others acquired. Confusion existed in the early literature, since the various Ehlers-Danlos syndromes (EDS) also had that designation. Although the term *cutis laxa* was used as early as 1833 by Alibert (2), the generalized form was probably first described by Graf (36) in 1836.

The term *cutis laxa* indicates loose, lax, droopy skin. It may be present at birth or may appear at different stages of growth and development. This physical finding is associated with a heterogeneous group of conditions. Thus, we have divided the conditions in which the skin is the most striking and important finding into groups according to the three patterns of inheritance: autosomal recessive, autosomal dominant, and X-linked. In doing this, we have discussed separately several well-defined syndromes (e.g., *De Barsy, Costello, SCARF, gerodermia osteodysplasticum, Bamatter, Ehlers-Danlos*), where other findings are as or more striking than the associated cutis laxa. The acquired forms of *cutis laxa* are mentioned under "Differential diagnosis."

Autosomal recessive form. In the most common of these forms, birth weight is normal but often there is mild postnatal growth deficiency. Most of these children die by the third year of life. Affected sibs (35,71,72,97,107) and parental consanguinity (1,25,50,61,72,96,112)

Fig. 13–9. *Acromegaloid features and thickened oral mucosa*. (A) Thickened lips, fullness of upper eyelids leading to narrowed palpebral fissures. (B) Similar coarse features and bulbous nose. (A courtesy of HE Hughes, Cardiff, Wales. B from HE Hughes et al, J Med Genet 22:119, 1985.)

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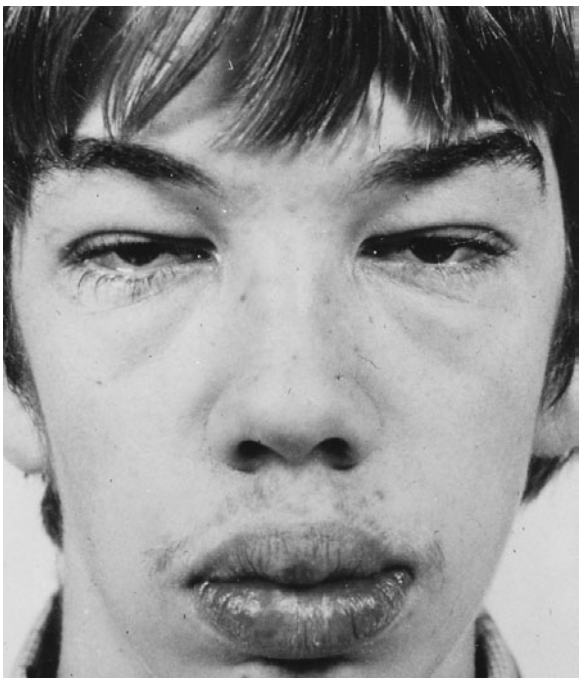

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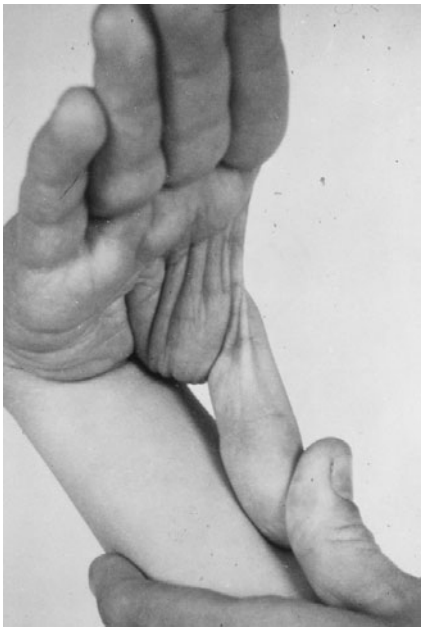


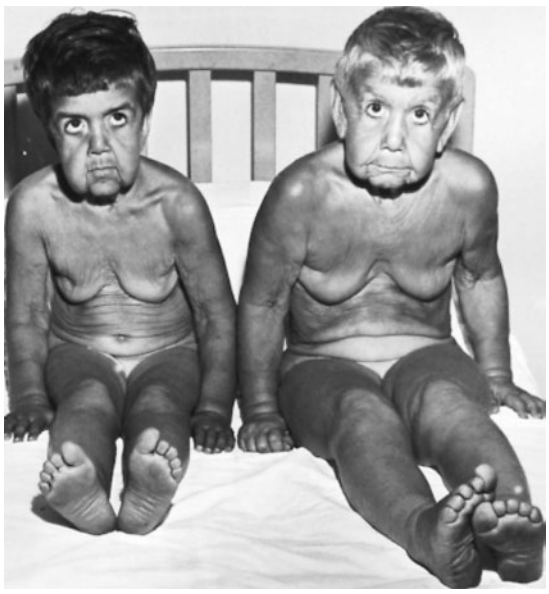
Fig. 13–10. *Acromegaloid features and thickened oral mucosa*. Hyperextensible joints. (From HE Hughes et al, J Med Genet 22:119, 1985.)

indicate autosomal recessive inheritance. The defect appears to be in lysyl oxidase which maps to 5q23.3–q31.2 (40,55). We believe that the syndrome reported by Dallaire et al (18) does not represent a separate disorder as they suggest.

Facies and skin. Due to accentuation of skin folds, the infant appears aged. The upper lip is long and the columella is short. Blepharochalasis and, at times, ectropion add to the aged appearance (35,38,94). The skin of the entire body appears too large. There is no hyperelasticity, fragility, or difficulty in healing (Fig. 13–11).

Cardiorespiratory. Tachypnea, pneumonitis, and airway obstruction associated with emphysema are common features. This results in severe hypoxemia, respiratory failure, cor pulmonale, and right ventricular

Fig. 13–11. *Cutis laxa, recessive type*. Affected sibs look much older than their chronologic ages of 5 and 6 years. (Courtesy of FA Balboni, Garden City, New York.)



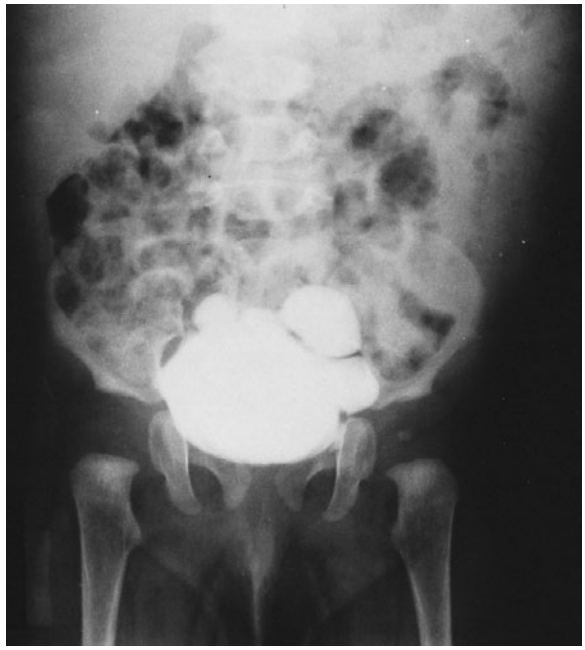


Fig. 13–12. *Cutis laxa, recessive type*. Multiple herniae of bladder.

enlargement. These findings, together with diaphragmatic hernia, lead to early demise (35,38,94,97). The emphysema results from generalized elastolysis. Bundle branch block (35), pulmonary artery stenosis (72,112), and dilated and tortuous carotid, vertebral, and pulmonary arteries, and dilated aortic root (35,109,112) have been noted.

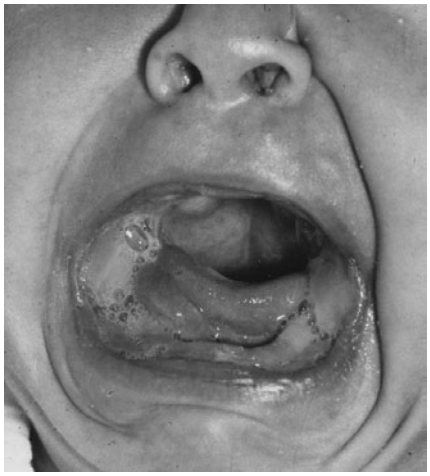
Musculoskeletal. Hernia is common, including inguinal (1,14,35,71, 94,97), diaphragmatic (1,16,35,96), and ventral and/or umbilical (35,97) types. Loose joints are rarely noted (1).

Gastrointestinal. Diverticula of the gastrointestinal tract involving the pharynx (50), esophagus (35,94), and rectum (35,71,72,97) have been documented.

Genitourinary. Bladder diverticula have been described by several authors (1,34,35,50,94,97) (Fig. 13–12). Vaginal prolapse has also been noted.

Oral. The voice is deep and resonant in quality due to laxity of the vocal cords (6,35,114). There is also looseness of the oral and pharyngeal mucosa (35) (Fig. 13–13).

Fig. 13–13. *Cutis laxa, recessive type*. Oral mucosa hangs loosely. (Courtesy of AH Mehregan, Monroe, Michigan.)



Cutis laxa, with late closure of fontanels, intrauterine growth retardation, and hyperlaxity of joints was possibly described first by Debré et al in 1937 (23). Several other authors have reported examples of this condition (1,3,8,27,28,33,47,48,52–54,56,75,78,81,84,86,90,101,108). It should be noted that the patient reported by Theopold and Wildhack (101) is a cousin of the patients reported by Fittke (27). Possibly the patient described by Schirren et al (93) had this condition. Inheritance is probably autosomal recessive, but most patients are female (53,78,86,90). The rate of parental consanguinity is high. Genevieve et al (32a) described 3 of 7 affected with cutis laxa, cleft palate, and mental retardation.

Birth weight and length are under the 10th centile. Delayed postnatal growth, mild gross motor retardation, poor feeding, mild mental retardation, frontal bossing, sagging jowls, reversed V-shaped eyebrows, epicanthic folds, sunken nasal bridge, and apparent mild hypertelorism are common. In addition to congenital cutis laxa, which is especially severe over the abdomen, hands, and feet, there is late closure of the fontanels, especially the anterior one. The skull sutures are markedly separated. The hips, either one or more often both, are congenitally dislocated in 85%. All joints, especially those of the hands, exhibit generalized laxity, which leads to unusual positioning. All appear to have fifth finger clinodactyly. Talipes equinovarus has been noted in a few cases. The subcutaneous veins of the abdomen are markedly dilated and the abdominal musculature is lax. Large inguinal hernias have been noted. Less constant findings include downslanting palpebral fissures, macular coloboma, myopia, iris hypoplasia, single transverse palmar crease, and hydronephrosis (3,93). Cleft lip has been reported (78).

Fig. 13–14. *Cutis laxa*. Autosomal dominant type of cutis laxa in 15-year-old girl who looks older than her middle-aged mother. (From P Beighton, Br J Plast Surg 23:285, 1970.)

Autosomal dominant form. This form is less common than the autosomal recessive type and runs a quite benign course (5,6,11, 17,19,45,83,94,96,99,102,109,113). Perhaps the earliest published example is that of Rossbach (88) in 1884. Onset is usually somewhat later than that in the recessive forms. Drooping of eyelids and sagging facial skin, together with accentuation of the nasolabial and other facial folds, produce an aged appearance. The nose is often hooked, the nostrils everted, and the philtrum long. An affected pubertal child will often look older than the unaffected parent (Fig. 13–14). Complications are few and lifespan is normal.

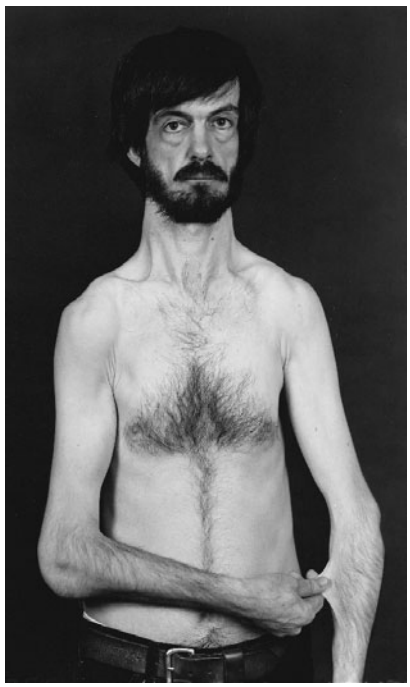
Rarely associated abnormalities have included hoarseness (5,11,45), pulmonary artery stenosis (45,109), mitral valve prolapse (11), hernia (96), bronchiectasis (6), joint dislocations (11), tortuosity and dilatation of carotid arteries and aorta (24,45), dilation of sinuses of Valsalva (11), and coarctation of the aorta (5,102).

In 1998, an elastin gene mutation was reported producing abnormal tropoelastin and abnormal elastic fibers in autosomal dominant cutis laxa (26,100). The elastin gene maps to 7q11.2 (26). Mutations occur in exons 30 and 32.

X-linked form or occipital horn syndrome (formerly Ehlers-Danlos syndrome type IX). First reported by Lazoff et al (62) in 1975, the occipital horn syndrome is characterized by occipital exostoses, soft and easily bruisable skin, hyperextensible joints, and widening and bowing of multiple long bones (9,12,13,59,67,81a,91,105,110). At least 20 cases have been reported (105).

The syndrome is clearly X-linked. Female heterozygotes may exhibit mild signs (46). No affected male has reproduced. The disorder maps to Xq13.3 in the Menkes disease gene (51,64,73a), known as *ATP7A* (37).

The face, neck, and trunk are long and thin (9,13) (Fig. 13–15A). The hyperelastic, soft, and bruisable skin with resultant atrophic scars and the hyperelastic joints are not as marked as in EDS type I or as mild as EDS type II. Varicose veins have been frequently noted (91) (Fig. 13–15B).



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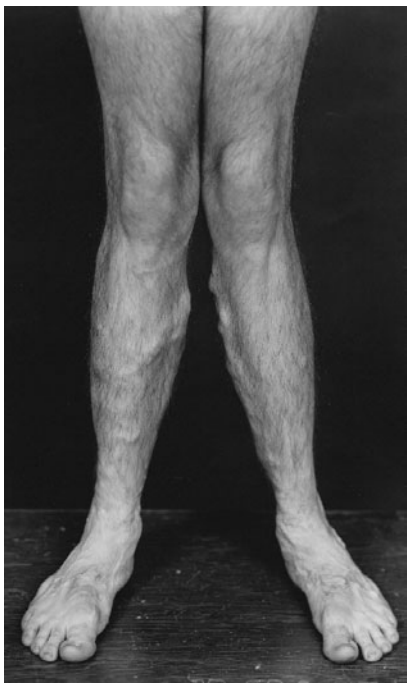

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Fig. 13–15. *Occipital horn syndrome*. (A) Patient showing long neck, narrow sloping shoulders, long thorax, hyperelasticity of skin. (B) Genua valga, varicosities, pes planus. (Courtesy of DD Weaver, Indianapolis, Indiana.)

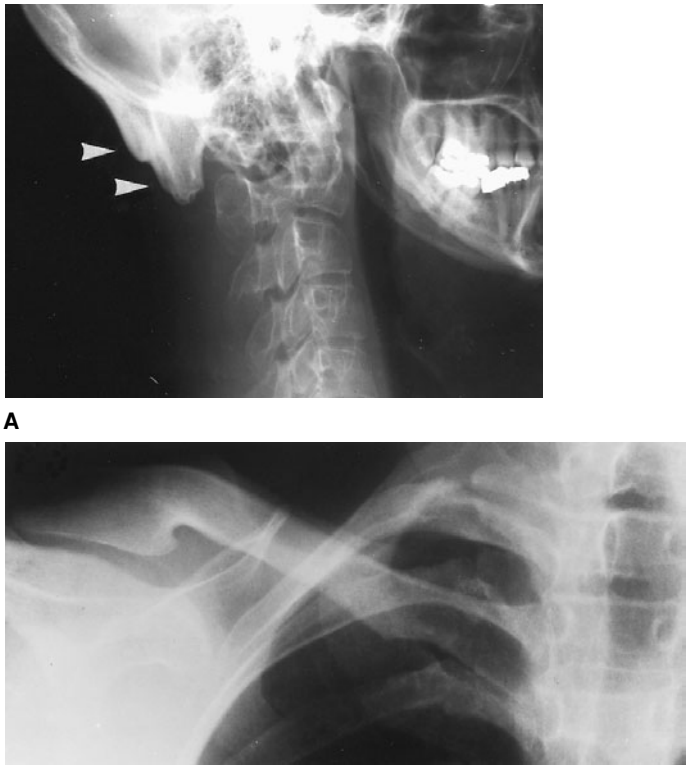

Fig. 13–16. *Occipital horn syndrome*. (A) Arrows point to occipital exostoses. Note long neck. (B) Club-shaped distal clavicles. (A,B from DJ Sartoris, Radiology 152:665, 1984.)

Patients exhibit limited extension of the narrow shoulders, elbows and knees, hypermobility of finger joints, pes planus, and genu valga in 75% (Fig. 13–15A). Pectus excavatum or carinatum has been found in 40%. Various hernias (hiatal, femoral, inguinal) have been described in about 35%. Bladder diverticula with bladder neck obstruction were found in 60%–70%. Chronic diarrhea of unknown cause has been noted in 40% (9,12,59,62,91). Borderline IQ has been documented in 40% and mental retardation has been reported (105,110).

Radiologic findings include occipital exostoses (horns) symmetrically located on each side of the foramen magnum (Fig. 13–16A). These may be palpated, are a constant feature, and may become large with age. The horns may represent ectopic bone formation within the trapezius and sternocleidomastoid aponeuroses. The clavicles are very short, with a widened medullary cavity and hammer-shaped distal extremities (Fig. 13–16B), the femora exhibit focal hyperostosis at sites of tendon and ligament insertion (Fig. 13–17A). Carpal fusion involving capitate-hamate and trapezium-trapezoid coalescence has been noted in over 50% (91) (Fig. 13–17B). Less specific are deformations of the humerus, radius, ulna, tibia, and fibula (90%), osteoporosis (70%), narrowing of rib cage (65%), dislocation of radial head (40%), mild platyspondyly, coxa valga, and flattening of the acetabular roofs. Dilated and tortuous arteries have been noted (46).

The disorder, exhibiting low serum copper and ceruloplasmin levels, is due to a defect in copper metabolism leading to lysyl oxidase deficiency and abnormal collagen (13). Allelism with *Menkes syndrome* (80) at the *MNK* gene locus was demonstrated in a definitive way by Das et al in 1995 (20). Mutations in the *MNK* gene cause defective uptake of copper and secondary deficiency of lysyl oxidase, a copper-dependent enzyme. This, in turn, results in abnormal cross-links in collagen molecules. Ronce et al (87) reported a C2055T transition in exon 8 of the *ATP7A* gene, associated with exon skipping in an occipital horn syndrome family.

Differential diagnosis. Acquired cutis laxa may follow nonspecific cutaneous inflammation, persistent urticaria, or nephrotic syndrome

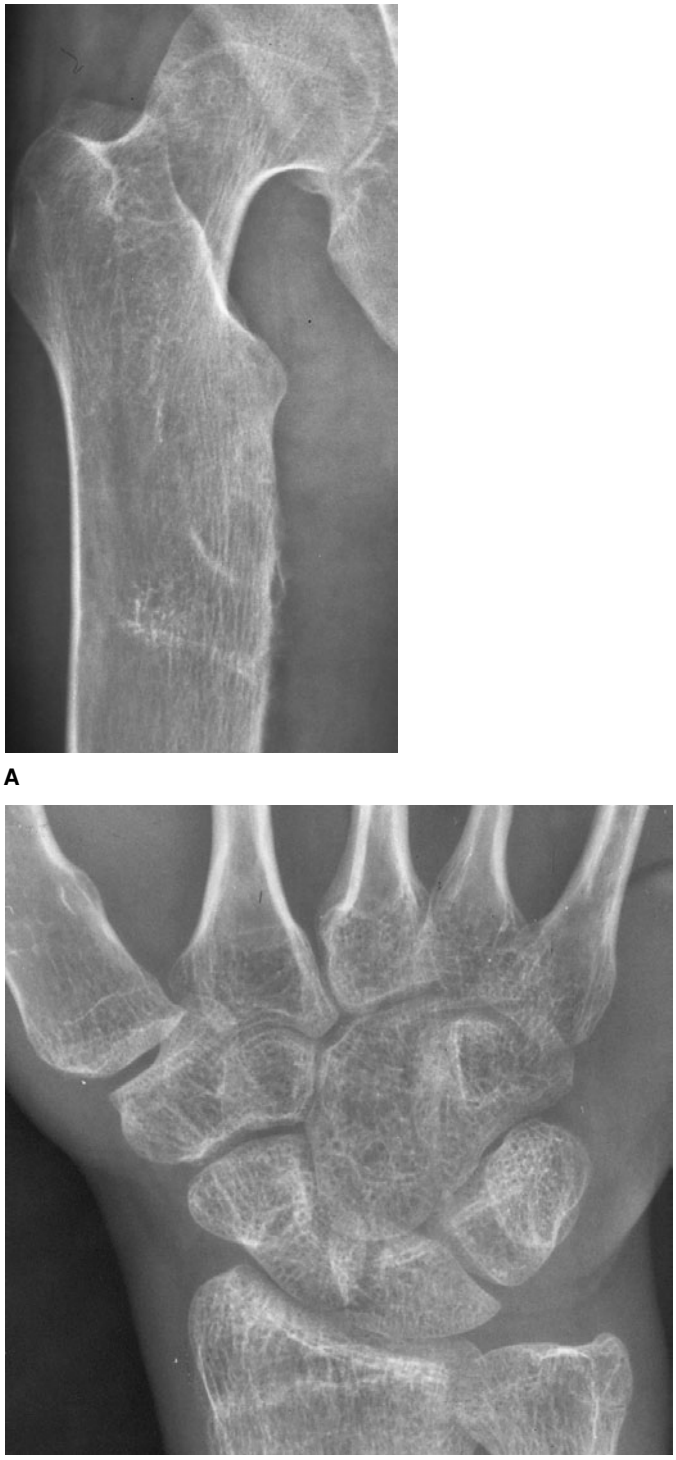

Fig. 13–17. *Occipital horn syndrome*. (A) Femur shows focal hyperostosis at site of tendon insertion. (B) Capitate-hamate and trapezium-trapezoid coalescence. (A,B from DJ Sartoris. Radiology 152:665, 1984.)

(103). Occasionally there is no history of prior skin disorder (7). Some patients have only cutaneous involvement, whereas others have internal manifestations: pulmonary emphysema with cardiovascular complications, femoral, inguinal, ventral, or diaphragmatic hernias, diverticula of intestinal tract, cystocele, rectocele, and uterine prolapse (7,49,50,60). Ruptured patellar tendons and associated multiple myeloma have been reported (15,70,95). It may also be associated with a plasma cell dyscrasia,

with immunoglobulins deposited on dermal elastic fibers (74). The reader is referred to several reviews of acquired cutis laxa (41,69,82,111,114).

Braun-Falco et al (10) were dealing with a case of prune belly. Tracheobronchiomegaly (Mounier-Kuhn syndrome) is characterized by dilatation and diverticulas of the trachea and bronchi (31). The "wrinkly" skin syndrome, a recessively inherited disorder characterized by congenital wrinkling of the skin of the chest, abdomen, and dorsa of the hands and feet, must be excluded. The palms and soles have increased numbers of wrinkles. There is generalized hypotonia with winging of the scapulae (32).

Cutis laxa of the facial skin has also been found in association with a dominantly inherited syndrome of systemic amyloidosis with corneal lattice dystrophy, cranial nerve palsy, hair loss, nephropathy, and, occasionally, cardiopathy (Meretoja syndrome) (39,73,85). It has also been seen with severe osteoporosis (89) as well as in *gerodermia osteodysplastica, De Barsy syndrome, Lenz-Majewski syndrome, Costello syndrome* (22), and *ablepharon-macrostomia syndrome* (79). A congenital generalized cutis laxa may result from chronic maternal penicillamine therapy during pregnancy. These infants may have severe pulmonary complications (66,98,111). Tsukahara et al (104) described a disorder intermediate between cutis laxa and *Ehlers-Danlos syndrome* in a mother and child. *SCARF syndrome* is a possibly X-linked recessive disorder of cutis laxa, skeletal abnormalities, craniosynostosis, psychomotor retardation, and unusual facies (58).

Bladder diverticula may also be seen in *Menkes syndrome*, prune belly sequence, *Ehlers-Danlos syndromes*, and *Williams syndrome*.

Acquired cutis laxa was described in dermatitis herpetiformis and sarcoidosis (65).

Pathology. With orcein or Weigert elastic fiber stain, absence or marked diminution of elastic fibers has been observed, especially in the papillary layer of the dermis. Degenerative changes are marked by fragmentation of elastic fibers. Some fibers are short and thin. Abnormalities of fibrillin have been reported in acquired cutis laxa (63).

Ultrastructural changes include deficiency of elastin and uneven distribution of dense, amorphous, or granular substances that produce dense bundles (42,68,74,92). The various types of cutis laxa cannot be differentiated by light or electron microscopic study.

Laboratory aids. The mechanism by which there is insufficient elastin is not known.

Olsen et al (76) found no qualitative difference between control and cutis laxa elastic mRNAs. However, quantitation of the elastin mRNA by slot blot hybridization showed markedly reduced levels. In some cases, enhanced degradation of elastin has been demonstrated (4,106). Kitano et al (57) found diminution of elastic fibers throughout the dermis, globular and unstained elastin, and relatively large amounts of the microfibrillar components of elastic fibers.

While low serum copper and increased elastase and/or decreased antielastase levels (35,38,42) have been reported, others have found normal or even elevated values (42,45). Recent evidence indicates that cutis laxa fibroblasts that express little or no elastin have normal transcriptional activity but abnormal rates of elastin mRNA degradation. This defect is substantially reversed by TGF-β through mRNA stabilization (21,115).

Khakoo et al (55) described autosomal recessive cutis laxa in boys from 2 separate families who showed deficiency of lysyl oxidase. Neither had occipital osseous projections or abnormality of copper metabolism that are characteristic of the X-linked form. In one case, the mother showed partial deficiency of lysyl oxidase; in the second case, the parents were first cousins.

Collagenase mRNA levels are increased in fibroblasts derived from patients with cutis laxa. This is due to the upregulation at the transcriptional level by endogenous activation of DNA binding of AP-1 in cutis laxa fibroblasts.

Hatamochi et al (43,44) showed that the levels of type VI collagen mRNA were increased in cutis laxa fibroblasts and the levels of α-1 (VI) and α-3 (VI) chain mRNAs increased in parallel. Increases in type VI collagen mRNAs correlated well with production levels of the corresponding proteins and suggest that this may be related to the skin changes in cutis laxa.

Acquired cutis laxa is associated with normal enzyme levels (45). Moreover, ultrastructural and biochemical observations confirmed a dramatic reduction in dermal elastin, whereas collagen content was normal (29). In generalized acquired cutis laxa associated with celiac disease, there may be evidence of immunoglobulin A deposits on the dermal elastic fibers (30).

Cutis laxa may also be associated with 7p trisomy (77).

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Cutis laxa, craniosynostosis, mental retardation, unusual facies, skeletal anomalies, and ambiguous genitalia (SCARF syndrome)

Koppe et al (1), in 1989, used the acronym SCARF for a syndrome exhibiting *S*keletal abnormalities, *C*utis laxa/craniosynostosis, *A*mbiguous genitalia, *R*etardation, and *F*acial abnormalities.

Two affected male children connected through their mother suggest X-linked recessive inheritance.

The face was characterized by multiple hair whorls, high broad nasal root, and small chin. One of the boys had ptosis, epicanthic folds, and low-set posteriorly rotated pinnae. The enamel was dysplastic (Fig. 13–18).

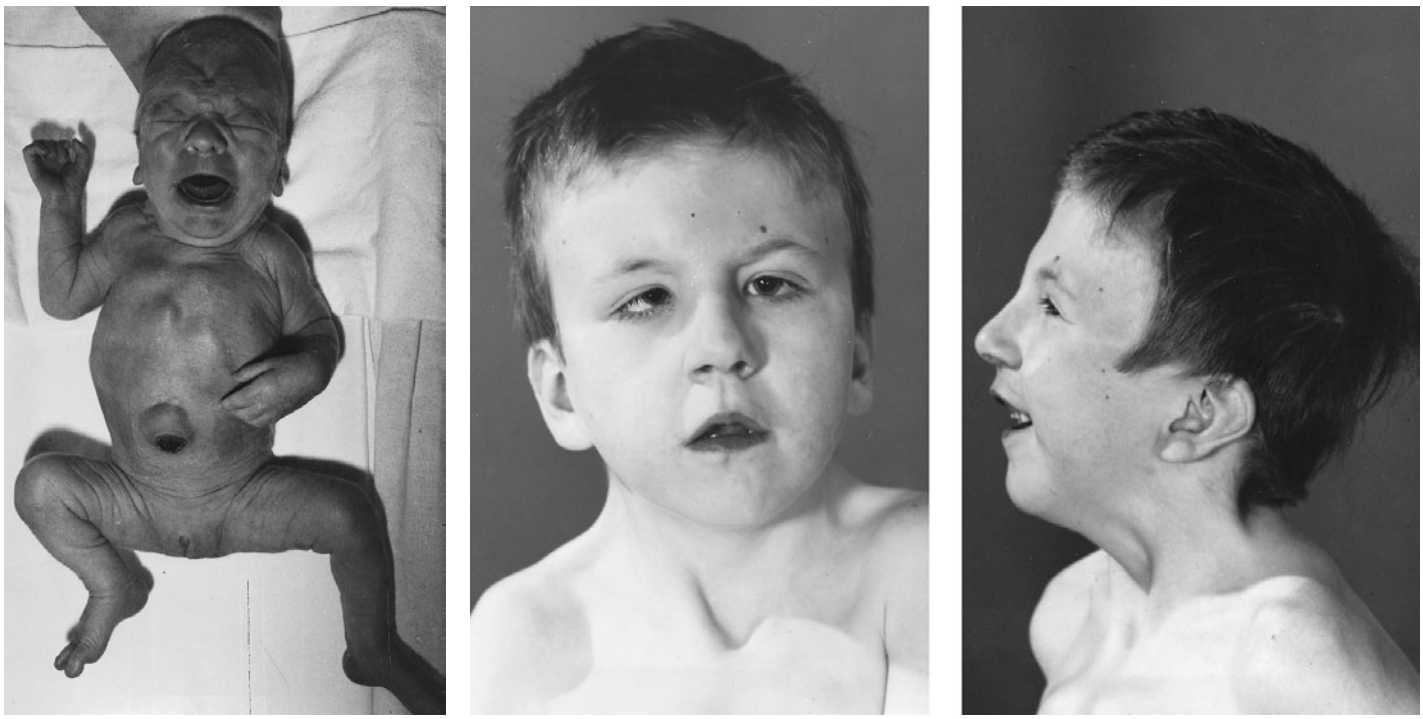
Cutis laxa was generalized and associated with excess nuchal skin, which evolved into neck webs. The nipples were widely spaced.

Musculoskeletal findings included synostosis of the lambdoidal and coronal sutures, short sternum, pectus carinatum, abnormally shaped vertebrae, abnormal modeling of long bone, and diastasis recti/umbilical hernia.

There was mild to moderate mental retardation. Micropenis and perineal hypospadias were present in both brothers.

Although reference was made regarding overlap with *Lenz-Majewski syndrome*, we do not see the resemblance.

Fig. 13–18. *SCARF syndrome*. (A) Note lax skin, pectus carinatum, umbilical hernia, ambiguous genitalia. (B,C) Child at 5 1/2 years. Note low hairline, high nasal bridge, low-set posteriorly angulated pinnae, downslanting palpebral fissures, ptosis, strabismus, and webbed neck. (Courtesy of P Kaplan, Philadelphia, Pennsylvania, and from R Koppe et al, Am J Med Genet 34:305, 1989.)



A B C

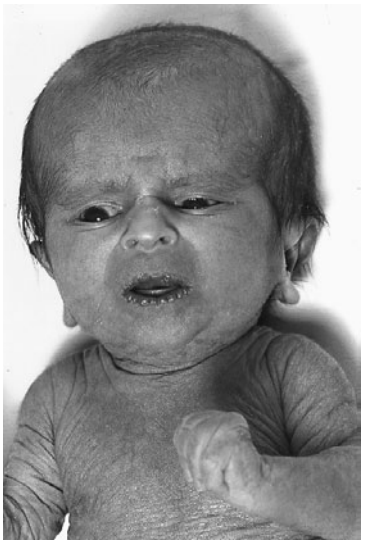


Fig. 13–19. *De Barsy syndrome*. Wizened face of 10-day-old. Note loose wrinkled skin. (From BF Pontz et al, Eur J Pediatr 145:428, 1986.)

Reference [Cutis laxa, craniosynostosis, mental retardation, unusual facies, skeletal anomalies, and ambiguous genitalia (SCARF syndrome)]

1. Koppe R et al: Ambiguous genitalia associated with skeletal abnormalities, cutis laxa, craniosynostosis, psychomotor retardation and facial abnormalities (SCARF syndrome). Am J Med Genet 34:305–312, 1989.

De Barsy syndrome

De Barsy et al (3) and others (2,4–11) described a syndrome of intrauterine growth retardation, wrinkled atrophic skin, open fontanels and sutures, corneal clouding, somatic and mental retardation, brisk deep tendon reflexes, athetoid posturing, hypermobility of small joints, and muscular hypotonia. The facies is characterized by frontal bossing in early childhood, but postnatal changes include microcephaly, prematurely aged appearance, corneal clouding, large dysplastic ears, hypertelorism, and thin lips (Figs. 13–19 to 13–23). Some patients have cataracts (10). About a dozen examples have been published (6). We are not convinced that the child noted by Bartsocas (1) has the syndrome. Inheritance is autosomal recessive (7,9,10). Possibly the child reported by Wiedemann (12) in 1969 has De Barsy syndrome or *gerodermia osteodysplastica*.

Elastic fibers are frayed and reduced in number. There appears to be defective elastin synthesis (5,6). Chemotactic migration of cultured fibroblasts is reduced, and there is impaired granulocyte function (5,6).

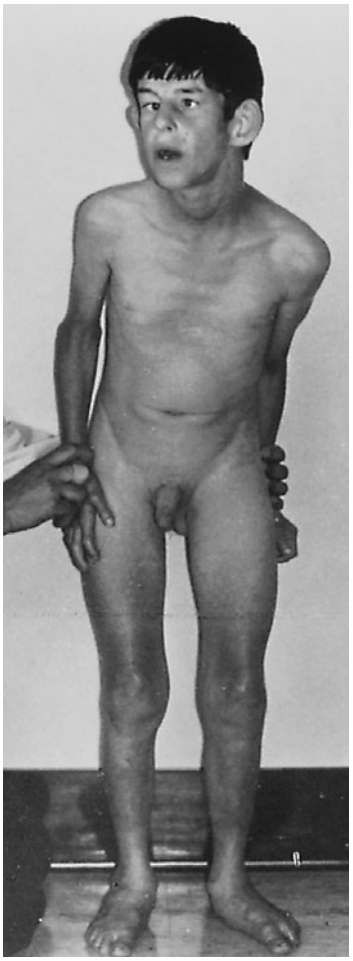


Fig. 13–21. *De Barsy syndrome*. Progeroid aspect, microcephaly, reduced subcutaneous fat, pectus excavatum, and growth retardation. (From J Kunze et al, Eur J Pediatr 144:348, 1985.)

Fig. 13–20. *De Barsy syndrome*. Microcephaly, large pinnae with poor modeling, downslanting palpebral fissures, strabismus, and right-sided cataract. (From J Kunze et al, Eur J Pediatr 144:348, 1985.)

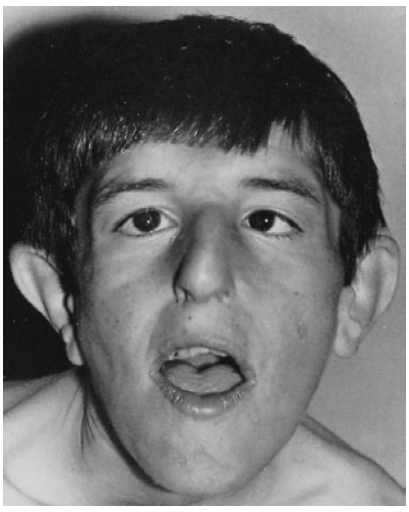
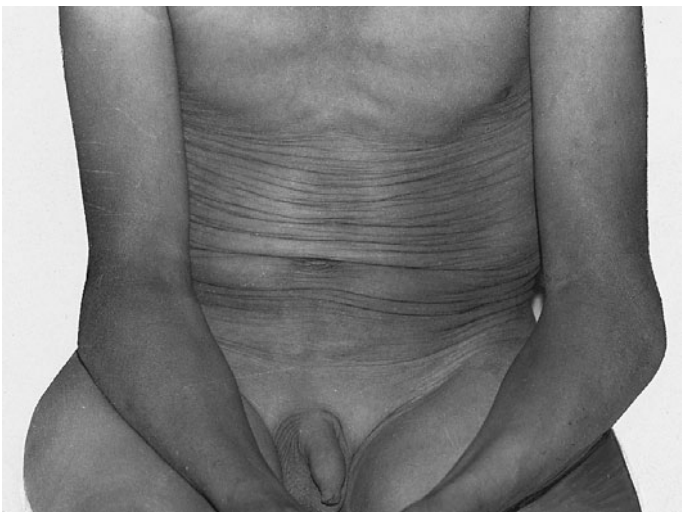


Fig. 13–22. *De Barsy syndrome*. Lax skin of abdomen. (Courtesy of F Majewski, Düsseldorf, West Germany.)



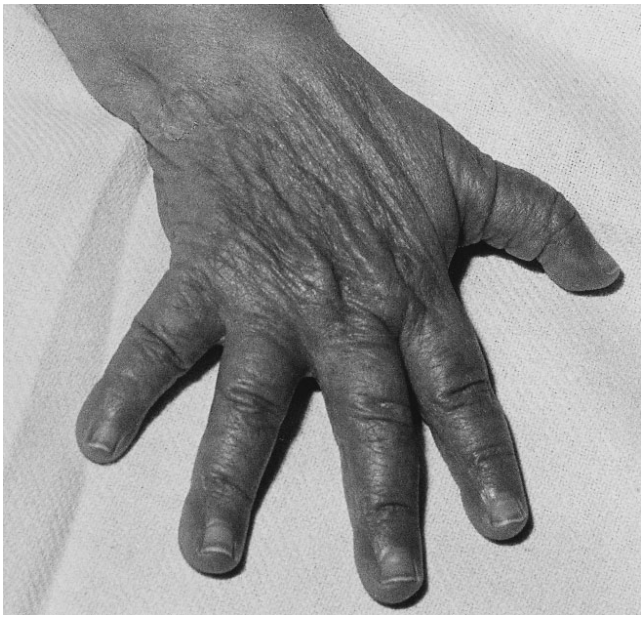


Fig. 13–23. *De Barsy syndrome*. Lax thin skin of hand. (Courtesy of F Majewski, Düsseldorf, West Germany.)

The disorder must be differentiated from *cutis laxa syndromes* and those of premature aging (acrogeria, metageria, *gerodermia osteodysplastica, Wiedemann-Rautenstrauch syndrome*).

References (De Barsy syndrome)

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Gerodermia osteodysplastica (Bamatter syndrome)

The family first reported by Bamatter et al (2), in 1949, was reviewed by the same group of investigators over a 20-year period (3,4,6–8,13,17). The disorder manifests a characteristic facies, hyperlaxity of the skin and joints, and growth retardation. Other families have been reported (1,4,5,11,12,15,16,20). Others are probable examples (18). In the interest of linguistic purity, we have changed the name from geroderma osteodysplastica to gerodermia osteodysplastica (21). About 25 examples have been reported.

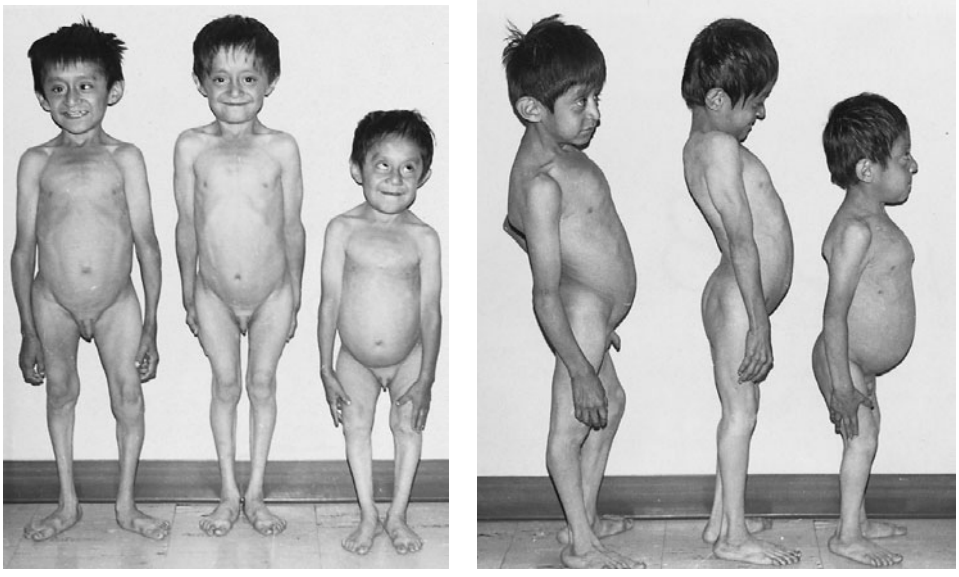
There is autosomal recessive inheritance (1,12,14,15). The disorder is undoubtedly underreported (11).

Growth retardation is below the third centile in perhaps a third of the children. Frequently, span is greater than height. There is delayed onset in walking.

Facies. Due to looseness of the skin, a sad senile appearance is imparted. The eyeballs appear sunken. The eyelids and cheeks droop. The head tends to be brachycephalic. The forehead is prominent. The nose is often jutting and fleshy. The lower lip is downturned and the midface is frequently mildly hypoplastic with relative mandibular prognathism. About half the patients exhibit malar flush (Figs. 13–24 and 13–25).

Skin. The skin is thin and creased with recoil. The subcutaneous veins are prominent. The skin is especially without turgor over the hands and feet and is easily wrinkled.

Microscopically, there is fragmentation of elastic fibers.



A B

Fig. 13–24. *Gerodermia osteodysplastica*. (A,B) Six-, seven-, and eight-year-old sibs with saggy cheeks, premature wrinkling of skin of face, abdomen, dorsum of hands and feet, stooped posture, winged scapulae, and flatfeet. (From R Lisker et al, Am J Med Genet 3:389, 1979.)

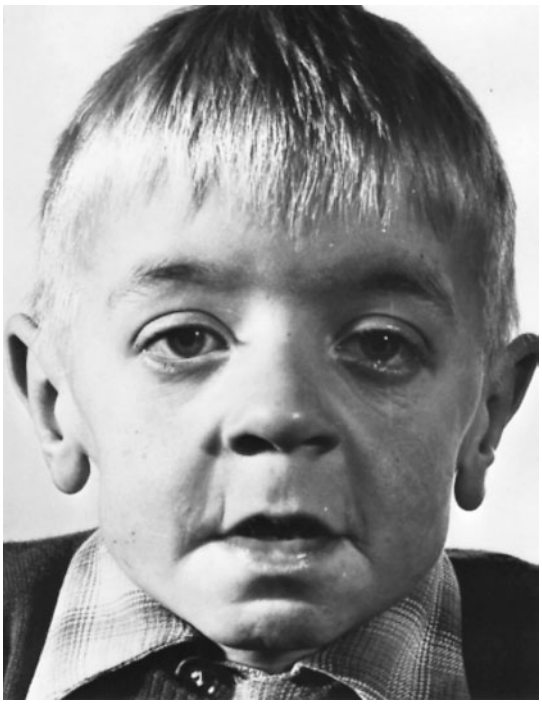


Fig. 13–25. *Gerodermia osteodysplastica*. Facies showing premature aging. (Courtesy of D Klein, Geneva, Switzerland.)

Musculoskeletal. Constant features are marked muscular hypotonia and hyperlaxity of joints (hands, feet, knees, hips), with associated hernias, flatfeet, and dislocated hips. Inguinal hernia has been found in approximately 35%. Virtually constant features are osteoporosis with resultant platyspondyly, anterior wedging, and occasionally biconcave vertebral bodies (1,7). Compression fractures may be observed within the first few years of life. Long bones tend to fracture with minimal trauma. Mild scoliosis and sternal anomalies are present in about 65%. Radiographic changes include multiple Wormian bones in the lambdoidal suture and evanescent metaphyseal pegs indenting the epiphyses of long bones, especially at the knees (9).

Oral manifestations. At least 70% have downturned lower lip. Almost constant features are malocclusion and highly arched palate. The alveolar bone is decreased in amount.

Radiographically, the mandibular lingula is funnel-shaped and molar roots extend below the inferior dental canal. Hypercementosis of maxillary incisors and mandibular molars surrounded by a radiolucent halo has been documented (15).

Differential diagnosis. Gerodermia osteodysplastica is most likely to be confused with the *cutis laxa syndromes*. Acrogeria is characterized by wrinkled and aged-appearing skin, most marked over the dorsa of the hands and feet; flatfeet; and dislocated hips. Many of these cases of acrogeria represent EDS IV. However, in gerodermia osteodysplastica, the skin is not atrophic and the superficial veins are not highly visible. Commonly associated with acrogeria are wide cranial sutures, blue sclerae, diaphyseal narrowing of long bones, and nail dysplasia. Furthermore, individuals who have acrogeria are not jowly and do not exhibit the joint hyperextensibility and the osteoporotic bony changes seen here.

The syndrome should be differentiated from *wrinkly skin syndrome* reported by Gazit et al (10). This autosomal recessively inherited disorder is characterized by wrinkled skin of the anterior chest and/or dorsal surfaces of the hands, hypotonia, kyphosis, winged scapulas, and prominent cutaneous venous pattern. There are also microcephaly, severe myopia, and chorioretinitis.

The *De Barsy syndrome*, characterized by congenital athetosis, mental retardation, severe growth retardation, and laxity of skin and ligaments, must also be excluded. *Lenz-Majewski syndrome* and *Patterson syndrome* (*pseudoleprechaunism*) have wrinkly skin as one of their components, but the phenotypes of those disorders are so distinct that discussion is not relevant.

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Wrinkly skin syndrome

Gazit et al (3), in 1973, described 3 sibs born to consanguineous Iraqi-Jewish parents. An additional 10 patients have been described (1,2,4–6). Zlotogora (8) suggested that this condition is the same as *cutis laxa with growth and developmental delay*.

Typical manifestations include low birth weight; delayed growth and development; wrinkled inelastic skin over the hands, feet, and abdomen, with an aged appearance; prominent subcutaneous truncal veins; craniofacial anomalies; microcephaly; and bilateral hip dislocation.

Nearly all of the patients have been of either Moslem (2,6) origin or Sephardic Jewish descent (3–5). In nearly all cases, there was parental consanguinity. Three patients of European origin had del(2q32) (7). The disorder in these cases went from mother to two children.

Differential diagnosis includes *pseudoxanthoma elasticum*, the *cutis laxa syndromes*, and the *Ehlers-Danlos syndromes*. In contrast to cutis laxa, the skin in wrinkly skin syndrome is hypoelastic, and there are no loose folds of skin over the face. The classic beaked nose, short columella, and long upper lip are absent in wrinkly skin syndrome.

It differs from the Ehlers-Danlos syndromes in that there are no easy bruisability, hemorrhages, ecchymoses, poor scar formation, abnormal wound healing, or hyperelasticity of the skin and joint hypermobility.

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Ehlers-Danlos syndromes

The Ehlers-Danlos syndromes (EDS) constitute a heterogeneous group of generalized connective tissue disorders. The five cardinal elements of EDS include hyperextensible doughy skin, atrophic scars, joint hypermobility, connective tissue fragility, and bruising (36). The earliest-recognized description was of a young Spaniard, George Albes, who was exhibited to the Academy of Leyden in Holland in 1657 by Van Meek'ren (2,32). The first scientific description was by Tschernogobow, a Russian dermatologist, who presented an affected 17-year-old boy to the Moscow Venereology and Dermatology Society meeting in 1892. He attributed the multisystem features to a generalized defect in formation of connective tissue (14,36).

Ehlers (17), in 1901, reported the association of hyperelastic skin, skin hemorrhages, and loose-jointedness. Danlos (13), in 1908, added cutaneous pseudotumours and fragility, and Weber and Aitken (51) included subcutaneous spherules. Terminology became especially complex during the early part of the twentieth century. The eponym Ehlers-Danlos syndrome finally emerged as the name used most commonly.

Comprehensive surveys are those of Steinmann et al (43), Beighton (3), and Pope and Burrows (36). The following aspects also have detailed coverage in different publications: molecular defects and connective tissue metabolism (7,8,10,20,24–26,29,30,37,38,40,47,48,52), ultrastructural studies of the skin (6,19,22,23), histologic and mechanical studies of the skin (21,34,44), collagen studies (1,7,12,15,18,28,30,33, 39,41,46,47,49,50), cardiovascular abnormalities (11,16,27,31), and complications of pregnancy (35,42,45).

Based on recent advances in the elucidation of the molecular mechanisms, many EDS subtypes are now well understood. The alteration of certain molecular components disrupts collagen fibril assembly, with particular anatomical distributions. Thus, the molecular composition of the skin, ligaments, tendons, cartilage, vasculature (arteries, veins, capillaries), eyes (cornea and vitreous), pleuroperitoneum, and intestinal walls may be severely weakened and disorganized (36).

Genetic, biochemical and molecular studies have defined more than 10 types of Ehlers-Danlos syndrome. Their clinical features, inheritance, and biochemical or molecular defects are summarized in Table 13–2. Whenever possible, it is essential to establish the specific type of Ehlers-Danlos syndrome because additional clinical investigations, follow-ups, and precautionary measures may be crucial for optimum care. Approximately 80% of affected individuals have type I or type II, around 10% have type III, 4% type IV, and about 6% have various other types (4). In 1998, Beighton et al (5) proposed a new, simplified classification of EDS into six major types and a seventh group comprising all the others. This classification was intended to make diagnostic efforts easier and more useful to the "generalist." For each type, major and minor criteria were defined. These may be used as a diagnostic starting point. However, for most, a more detailed approach may be necessary, based on the continuous development of molecular tests.

Before we address the specific forms of Ehlers-Danlos syndrome, let us briefly consider collagen structure (8–10).

Collagen structure and biosynthesis. Collagens, which have important structural properties, are the most abundant family of proteins in the body. Collagens are composed of molecules containing three chains (heterotrimers or homotrimers), with a triple-helical domain characterized by the repeating amino acid sequence $(Gly\text{-}X\text{-}Y)^n$. There are more than 28 genes coding for the chains that form more than 16 different types of collagen molecules. The loci of these genes are dispersed on at least 12 chromosomes (Fig. 13–26A).

Collagens are of five different types: (a) fibrillar (collagens 1,2,3,5 and 11), (b) basement-membrane, (c) fibril-associated with interrupted triple helixes, (d) network-forming, and (e) long-chain collagen of anchoring fibrils with interrupted triple helix.

Mutations of fibrillar collagen are responsible for the production of certain types of EDS. These collagens are distributed in skin, bone, tendon, arteries, cartilage, vitreous humor, placenta, chorion, and uterus. This distribution explains the pathogenesis of the clinical manifestations due to the mutations of the genes coding for these specific types of collagen (8).

The individual precursor chains of the triple helix of the collagen molecule are synthesized on membrane-bound polyribosomes. While the growing chain is being transferred into the lumen of the rough endoplasmic reticulum, certain prolyl and lysyl residues in the triple-helical domain are hydroxylated and some hydroxylysyl residues are glycosylated (Fig. 13–26B). The assembly of the three proα chains occurs through structures in the C-terminal propeptide domain of each chain. The folding of the triple-helix also occurs from the C-terminal end of the molecule. After the procollagen triple helix is secreted, N- and C-terminal propeptide extensions are cleaved by a limited proteolysis by procollagen N-proteinase and procollagen C-proteinase, which are endopeptidases and are collagen type specific (8) (Fig. 13–26C).

References (Ehlers-Danlos syndromes)

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Table 13–2. Clinical features, modes of inheritance, and biochemical defects in Ehlers-Danlos syndromes

Type	Synonym	Inheritance	Clinical features	Histology and electron microscopy	Basic biochemical or molecular defect
EDS I	Gravis type	AD	Soft, velvety, hyperextensible skin, easy bruising, "cigarette paper" scars, hypermobile joints, varicose veins, molluscoid pseudotumors	Cauliflower fibrils	COL5A1-linked in some families. Mutations include exon skips, translocation and cystein substitution
EDS II	Mitis type	AD	Similar to Ehlers-Danlos Type I, but less severe	Cauliflower fibrils	Probably allelic to EDS I
EDS III	Hypermobile type	AD	Marked large and small joint hypermobility. No cutaneous scars	Non-specific	Unknown
EDS IV	Vascular type IV A acrogeric IV B acrogeric IV C ecchymotic IV D	 AD AR AD AR	Thin, translucent skin with visible veins, marked bruising. Skin and joints have normal extensibility. Risk of arterial, intestinal, uterine rupture highest in acrogeric subtypes	Collagen depletion (Type III), variation in fiber size	COL3A1 mutations. Numerous point mutations and exon skips, rarely deletions
EDS V	X-linked type	XL	Resembles EDS II. Very rare.		Not lysyl oxidase deficient
EDS VI	Ocular type	AR	Soft, velvety, hyperextensible skin; hypermobile joints; premature scoliosis; arterial rupture in 30%; ocular fragility and keratoconus		Lysyl hydroxylase point mutations or exon skips. VIA: decreased lysyl hydroxylase levels. VIB: normal levels
EDS VII A	Arthrochalasis multiplex congenita	AD	Congenital hip dislocation, joint hypermobility, mild facial cutis laxa: Some have skin fragility and mandibular hyperplasia.	Fibrils are angular in A and B, and hieroglyphic in C	Types A and B specific exon 6 skips or deletions of COL1A1. Type C procollagen peptidase deficiency
B,C	Dermatosparaxis	AR	Severe cutis laxa		
EDS VIII	Periodontitis type	AD	Generalized periodontitis, skin similar to EDS		
EDS IX	Vacant—formerly, "Occipital horn" syndrome, now classified as X-linked type of cutis laxa				
EDS X	Fibronectin abnormality	AR/AD	Similar to EDS II. Faulty platelet aggregation		Association with fibronectin may be coincidental
Others	Progeroid form EDS type unspecified EDS type unspecified	 AD AR			

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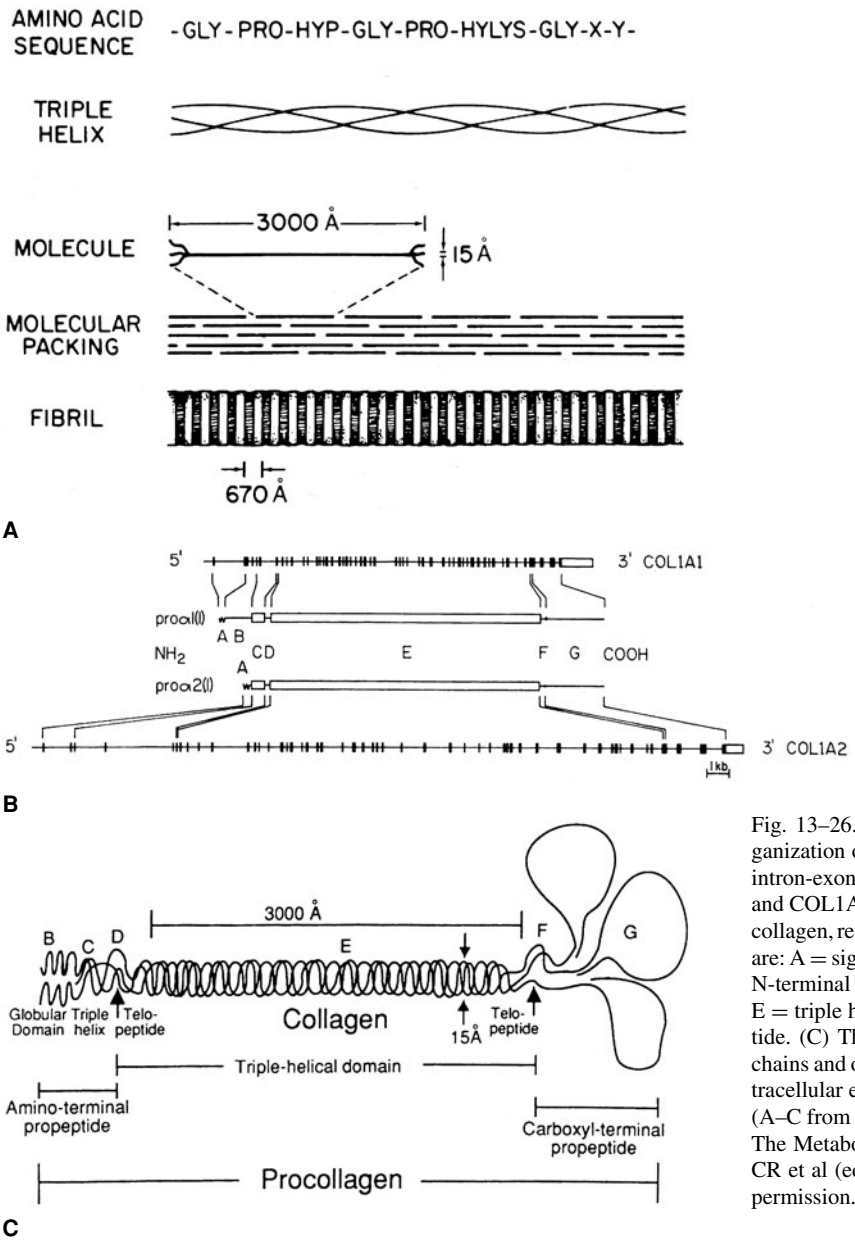

Fig. 13–26. *Ehlers-Danlos syndrome*. (A) Hierarchical structure and organization of fibrillar collagens. (B) Fibrillar collagen gene structure. The intron-exon structure of the phototype fibrillar collagen genes [COL1A1 and COL1A2, which encode the proα(I) and proα2(I) chains of type I procollagen, respectively] are presented. The domains in the polypeptide chains are: A = signal sequence; B = N-terminal propeptide globular domain; C = N-terminal propeptide triple-helical domain; D = N-terminal telopeptide; E = triple helix; F = C-terminal telopeptide; and G = C-terminal propeptide. (C) The type I procollagen molecule is composed of two pro α(1) chains and one pro α2(1) chain. Procollagen is converted to collagen by extracellular enzymatic cleavage of amino and carboxyterminal propeptides. (A–C from PH Byers, Disorders of collagen biosynthesis and structure. In: The Metabolic and Molecular Bases of Inherited Disease, 7th ed, Scriver CR et al (eds), McGraw-Hill, Inc., New York, 1995, pp 4029–4077, with permission.)

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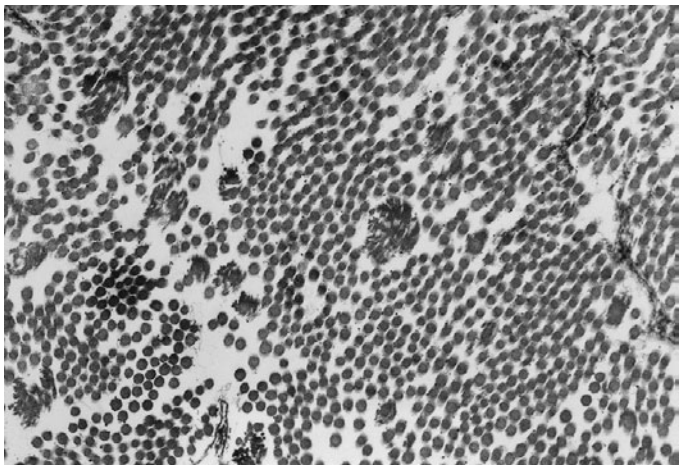

Fig. 13–27. *Ehlers-Danlos syndrome, type I.* Disorganization and so-called cauliflower fibrils. (Courtesy of K Holbrook, Athens, Georgia.)

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Ehlers-Danlos syndrome type I (severe form, EDS I) and type II (mild form, EDS II)

The clinical findings in EDS types I and II may be dramatic, with markedly soft, velvety, hyperextensible skin, impressive joint hypermobility, easy bruising, and thin, atrophic, "cigarette-paper" scars. Varicose veins are common. Birth prevalence of these two disorders is estimated to be approximately 1/10,000–20,000 (5,39). The clinical phenotypes of EDS I and II overlap substantially. They represent allelic autosomal dominant mutations with variable penetrance. Compound heterozygosity is also possible. A good general review is that of Brinckmann et al (13).

Inheritance is autosomal dominant. Mutations in the COL5A1 gene of collagen type α1(V) chains are responsible for EDS I and EDS II (16,40,47). The collagen is disorganized and forms so-called cauliflower fibrils (47) (Fig. 13–27). Several groups have reported linkage of human COL5A1 which maps to 9q34.2–q34.3 markers in families with EDS I or EDS II (50a,56). The mutations of these two conditions are therefore considered to be allelic (16,37). Several COL5A1 mutations have been reported with either EDS I or II phenotypes. In one, the COL5A1 gene is interrupted by a translocation at intron 24 (53). In the second, an exon 65 skip is found in the affected members of a three-generation family (55). In the third, there is a mutation in COL5A1, the gene encoding the proα1(V) collagen chain, segregating with EDS I in a four-generation family. The mutation causes the substitution of the most 5′ cysteine residues by a serine within a highly conserved sequence of the proα1(V) C-propeptide domain, resulting in reduction of collagen V by preventing incorporation of the mutant proα1(V) chains in the collagen V trimers (18,19). Moreover, splicing defects in COL5A1 gene were detected in a patient with EDS I and in a family with EDS II (16,49).

Mutations of the COL5A2 gene which encodes the α2(V) chain of type V collagen have also been identified in patients with EDS I (40). These mutations consist of a 7bp deletion that results in skipping of exon 27 or a single nucleotide substitution that results in skipping of exon 28 (40).

Nuytinck et al (42a) described typical EDS type 1 patients with mutations in type I collagen.

It also seems that collagen type V controls type I collagen fibril packing (11,12,14,36,41). This may explain the striking fibrillar disorganization that typifies EDS I and II. It also implies that the disorganization is a direct effect of the mutant type V collagen.

It is thought that collagen type XI regulates the thickness of collagen type II fibrils and collagen V and XI coassociate in vitreous humor. Corneal shape depends also on collagen V. This may explain why corneal or vitreous abnormalities and high myopia cosegregate with premature osteoarthritis in some EDS families (47).

Moreover, arterial fragility may be caused by COL5A2 mutations (42). This suggests that α2(V) chains and collagen type III interact analogously to α1(V) chains and type I collagen chains (47).

COL5A1 homozygotes are either exceptionally rare or are genetic lethals.

A tenascin defect has been postulated (15,22).

General features. Prematurity, due to early rupture of fetal membranes, is observed in as many as 50% of type I cases (2,52) and to a lesser degree in type II cases. In addition, there may be postpartum hemorrhage following episiotomy or lacerations, and uterine or bladder prolapse (52).

Children with types I or II EDS are often thought to have joint hypermobility as newborns, but may not come to medical attention until about one year when they are noted to be slow to walk because of poor joint stability. Susceptibility to skin tearing, forming of scars, and easy bruising become apparent. Referral for evaluation for child abuse is consequently not uncommon (43). Evidence of mitral valve prolapse by clinical criteria or by echocardiography may be present in childhood and certainly by adolescence. Early onset of joint symptoms may also occur, apparently resulting in premature osteoarthritis from mechanical stress on joints produced by excessive mobility and mild joint instability.

There is often concern that routine surgery is hazardous, but although tissue is slightly more friable than normal, careful attention to detail during surgical procedures makes the likelihood of complications minimal. Sutures are generally left in place two or three times longer than usual to ensure adequate healing. Pregnancy-related maternal and fetal morbidity may be prevented by specific measures (23,46). Life expectancy for individuals with type I or type II Ehlers-Danlos syndrome is normal (5,31,32). However, a case of acute lymphoblastic leukemia was reported in a patient with EDS II (1). Anxiety, depression, anger, and interpersonal concerns are significantly elevated in patients with EDS (38).

Skin. The skin has a velvety feel and is hyperelastic, especially over the major joints. It is thinner than normal, brittle, and fragile (27). Minimal trauma may produce gaping wounds. Healing results in pigmented, papyraceous scars. These scars are usually detected over the forehead, chin, knees, shins, and/or elbows (Figs. 13–28 and 13–29). Bruising is variable in degree. Secondary skin creases may be found over the palms (25).

Molluscoid pseudotumors may be present over the heels and major joints. Often the skin is redundant on the hands and feet (10,33). Calcified, cystlike structures, 2–10 mm in diameter, may be found subcutaneously, especially over bony prominences of the forearms and shins in about 30% (8). Varicose veins are common and acrocyanosis is frequent.

Evaluation of the mechanical properties of skin in EDS I and EDS II revealed prominent increases in the skin extensibility and elasticity (29).

Musculoskeletal system. Hyperextensibility of the joints, a weak hand clasp, and pes planus are usually present (7,20,54) (Fig. 13–30). Genu recurvatum has been noted in about 25%, and there may be recurrent joint dislocations. Talipes has been found in approximately 5%. The ulnar styloid process may be elongated. Kyphoscoliosis and thoracic asymmetry are observed in 15%–20% but usually are not severe (8,20).

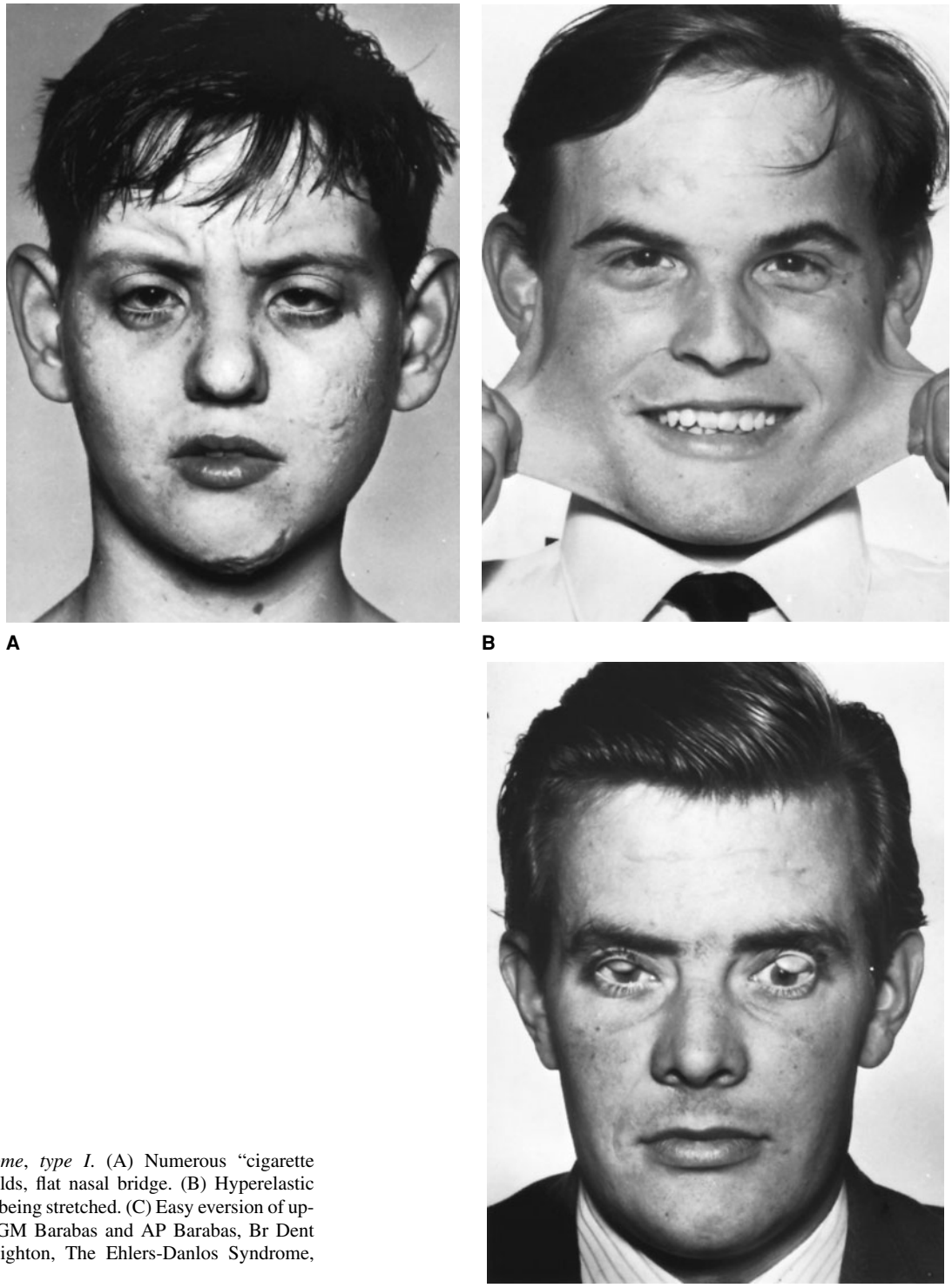


Fig. 13–28. *Ehlers-Danlos syndrome*, *type I*. (A) Numerous "cigarette paper" scars of face, epicanthal folds, flat nasal bridge. (B) Hyperelastic skin returns to normal position after being stretched. (C) Easy eversion of upper lids (Méténier sign). (A from GM Barabas and AP Barabas, Br Dent J 123:473, 1967. B,C from P Beighton, The Ehlers-Danlos Syndrome, Heinemann, London, 1970.)

Lumbar platyspondyly has been described (34). Inguinal or umbilical hernia has been found in 10%–20% (9). Soft tissue contractures have been noted (28).

Cardiovascular defects. Leier et al (35) studied 16 patients with type I EDS. Most patients had mitral valve prolapse and six had tricuspid valve prolapse. Dilatation of the aortic root or ectasia of the sinuses of Valsalva, or both, also occurred in six. However, arterial fragility is virtually unknown. Congenital heart defects included two cases of bicuspid aortic valve, one instance of pulmonic valvular stenosis, two VSDs, and one ASD.

Craniofacial features. Epicanthic folds are seen in about 25% (6,10,33). Blue sclerae are noted in less than 10% (10,20,33). Myopia and strabismus have been observed with far greater frequency than blue sclerae. Microcornea, retinal detachment, keratoconus, and angioid streaks have also been noted (44). Hyperextensibility of the skin allows the easy eversion of the upper eyelids (Méténier's sign) (5) (Fig. 13–28C). The pinnae may project outward (21).

Approximately 50% of patients can touch the nose with the tip of the tongue, an ability found in only 8%–10% of the general population (Gorlin sign) (Fig. 13–31C). The oral mucosa is fragile and easily bruised. Oral healing may be slightly retarded, since the edges of a wound draw apart, but there is no evidence of abnormal healing or excessive scar

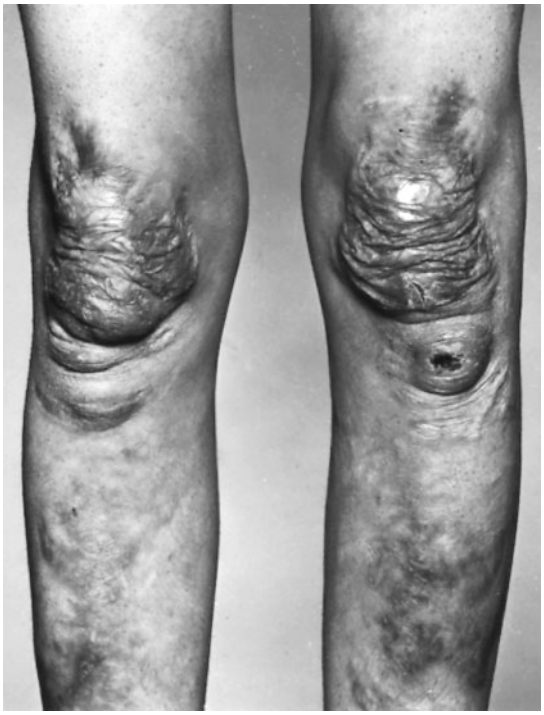
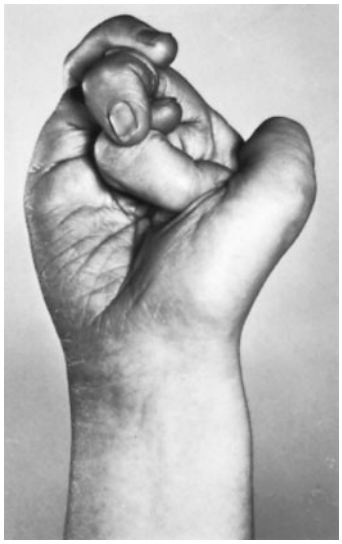


Fig. 13–29. *Ehlers-Danlos syndrome, type I.* Papyraceous scars of knees with pseudotumor below left knee. (From GM Barabas and AP Barabas, Br Dent J 123:473, 1967.)

formation in the mouth (4). The gingiva are more liable to injury, and periodontal disease has been reported at an earlier age (10,33). Recurrent subluxation of the temporomandibular joint has also been reported (7,24,39,50). The inferior labial and lingual frenula are missing.

Barabas and Barabas (4) found that premolar and molar teeth had high cusps and deep occlusal fissures. Radiographically, teeth may have stunted and deformed roots and large pulp stones in the coronal part of the pulp chamber (3,4,26,30,45,48,51) (Fig. 13–31A,B). Barabas (3) found hypoplastic areas in enamel, irregularities of amelodentinal and cementodentinal junctions, and formation of pathologic dentin, more frequently in the root than in the crown containing vascular inclusions, abnormal dentinal tubules, and many denticles. Carr and Green (17) found multiple odontogenic keratocysts in EDS II.

Fig. 13–30. *Ehlers-Danlos syndrome, type I.* Extreme joint hypermobility. (From GM Barabas and AP Barabas, Br Dent J 123:473, 1967.)



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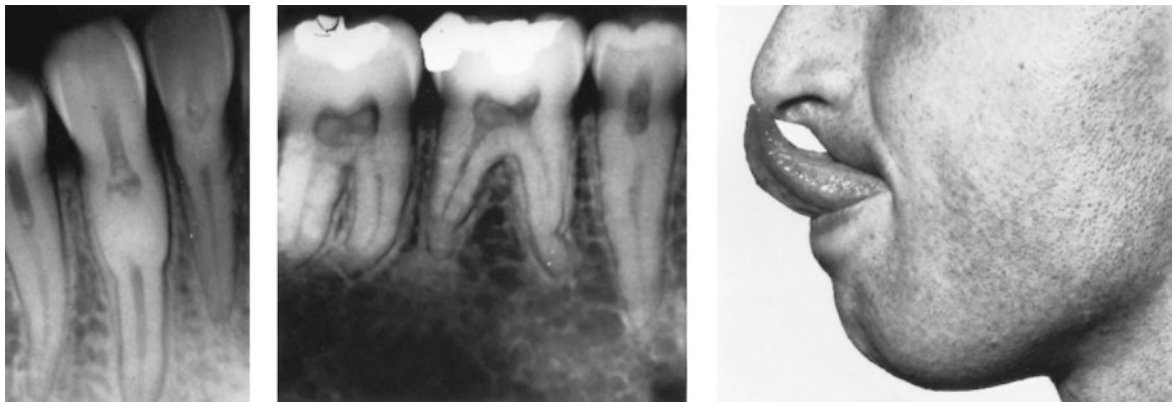

A B C

Fig. 13–31. *Ehlers-Danlos syndrome, type I.* (A,B) Stunted and deformed roots and large pulp stones in coronal portion of pulp chamber. (C) Gorlin sign. Ability to touch nose with tongue tip, present in 50% of those with Ehlers-Danlos syndrome, occurs in less than 10% of normal persons. (A,B from JJ Pindborg, Pathology of the Hard Dental Tissues, W.B. Saunders, Philadelphia, 1970. C from P Beighton, The Ehlers-Danlos Syndrome, Heinemann, London, 1970.)

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Ehlers-Danlos syndrome type III (familial hypermobility)

Ehlers-Danlos syndrome type III (familial hypermobility) is characterized by joint laxity and soft velvety hyperextensible skin. In the newborn, joint laxity is often striking, although dislocation is rare at this time. Infants may be slow to walk because of joint looseness. In the adult, the shoulder, patella, and temporomandibular joints are frequently dislocated (1–3). Major complications include joint pain, and early-onset degenerative joint disease (16). Pregnancy and delivery are usually uncomplicated (17).

Approximately 10% of Ehlers-Danlos syndrome patients have type III. EDS III has autosomal dominant inheritance. In 1994, Narcisi et al (15) identified a Gly637Ser mutation in the *COL3A1* gene in a family in which multiple members had a connective tissue disorder resembling either EDS III or familial joint instability syndrome.

Formerly, type III was known as the *benign* hypermobile variety of Ehlers-Danlos syndrome (8,9). However, there appears to be an increased risk of mitral valve prolapse as an associated complication (5,13). Mechanical properties of the skin are essentially within normal limits (7). Certain patients with clinical manifestations of EDS III may have peripheral neuropathy with brachial plexus palsy and lumbosacral plexopathy (6). Multiple supernumerary teeth have been reported (14).

Differential diagnosis includes: *Ehlers-Danlos syndrome type VII*, an autosomal dominant joint instability syndrome characterized by dislocation of the hip, patella, and elbows (10), and normal variant hypermobility found in approximately 4%–7% of the general population (4,11,12).

References [Ehlers-Danlos syndrome type III (familial hypermobility)]

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Ehlers-Danlos syndrome type IV (ecchymotic, arterial, or Sack-Barabas type)

EDS type IV, also known as the ecchymotic, arterial, or Sack-Barabas variety of Ehlers-Danlos syndrome, has the most ominous prognosis because of predilection for catastrophic bleeding from major arteries and spontaneous perforation of the gastrointestinal tract. There are low birthweight and prematurity (36). Joint hypermobility is usually limited to the digits and is evident in 30%. Skin hyperextensibility may be minimal or absent in adults, but congenitally dislocated hips are not uncommon. The skin is characteristically thin and translucent with an easily observed prominent venous network, especially apparent over the chest and abdomen. Minor trauma leads to extensive ecchymosis, resulting in scarring over bony prominences. In childhood, "battering" may be suspected (42). Other than tendon and muscle rupture, musculoskeletal and orthopedic problems do not occur in type IV. Prevalence estimates range from 1/100,000 to less than one in a million (2,3).

Heredity. Both autosomal dominant (1–3,9,35,54) and autosomal recessive (1,33,34,49) forms have been observed. Consanguinity was recorded in a family of two affected sibs reported by Sulh et al (49).

In 1979, Byers et al (5) proposed a preliminary classification of type IV with subtypes A,B,C, and D. Subtype IV A has autosomal dominant inheritance and a life expectancy of 30–50 years. Gilchrist et al (13) reported a long lived kindred. The gene maps to 2q31. Tsipouras et al (57) demonstrated further heterogeneity with different mutations affecting the stability and secretion of proα 1(III) chains of type III procollagen in two separate families, both having autosomal dominant transmission. Subtype IV B has autosomal recessive inheritance (1,33) and a life expectancy of 15–30 years. Subtype IV C is represented by a sporadic case in one family. Extreme dilatation of rough endoplasmic reticulum of dermal fibroblasts was noted (5). Subtype IV D, now thought to have autosomal recessive inheritance (49), is associated with collagen fibrils that are small in diameter but vary in size. As Byers et al (5) recognized in 1979, this classification is heuristic.

Biochemical and molecular pathology. Biochemical heterogeneity has been demonstrated and most likely results from different mutations in the same gene for type III procollagen rather than in different genes (6,39,48).

There is strong clinical, histological, biochemical, and molecular evidence that faulty collagen III causes dermal atrophy and vascular and gastrointestinal fragility (17,26,31,58). Collagen III predominates in skin, blood vessels and ligaments. It is a homotrimer of a1(III). Its deficiency causes EDS IV but may, less specifically, cause EDS III (31).

There are two general patterns of mutations. The first (group 1) exhibits poorly secreted and overhydroxylated collagen III. These are caused by either helical glycine substitutions or exon skips. Patients with such severe biochemical deficiencies have severely abnormal clinical phenotypes (31). Mutations have been found that (a) interfere with secretion of assembled molecules, (b) alter expression of one allele, or (c) lead to increased intracellular degradation of type III collagen molecules. Superti-Furga et al (50,51) described multiple exon deletion resulting in heterozygosity at the *COL3A1* locus. Various skin changes have been observed, depending on the nature of the mutation. Small collagen fibrils and a mixed population of fibril sizes may be present. In patients with defects in secretion, marked dilatation of the rough endoplasmic reticulum is found in fibroblasts (33,35,48,54).

Generally, 3′ mutations are acrogeric, whereas the phenotypes of 5′ or middle helical exon skips are harder to recognize. Unfortunately, even the latter are at risk for arterial rupture which is nevertheless much more frequent in mutations at the 3′ end (31).

The second abnormal pattern includes null alleles. In this group, there is reduced collagen type III without intracellular retention or overmodification. The residual collagen III molecules are normal and the clinical phenotype is milder (31).

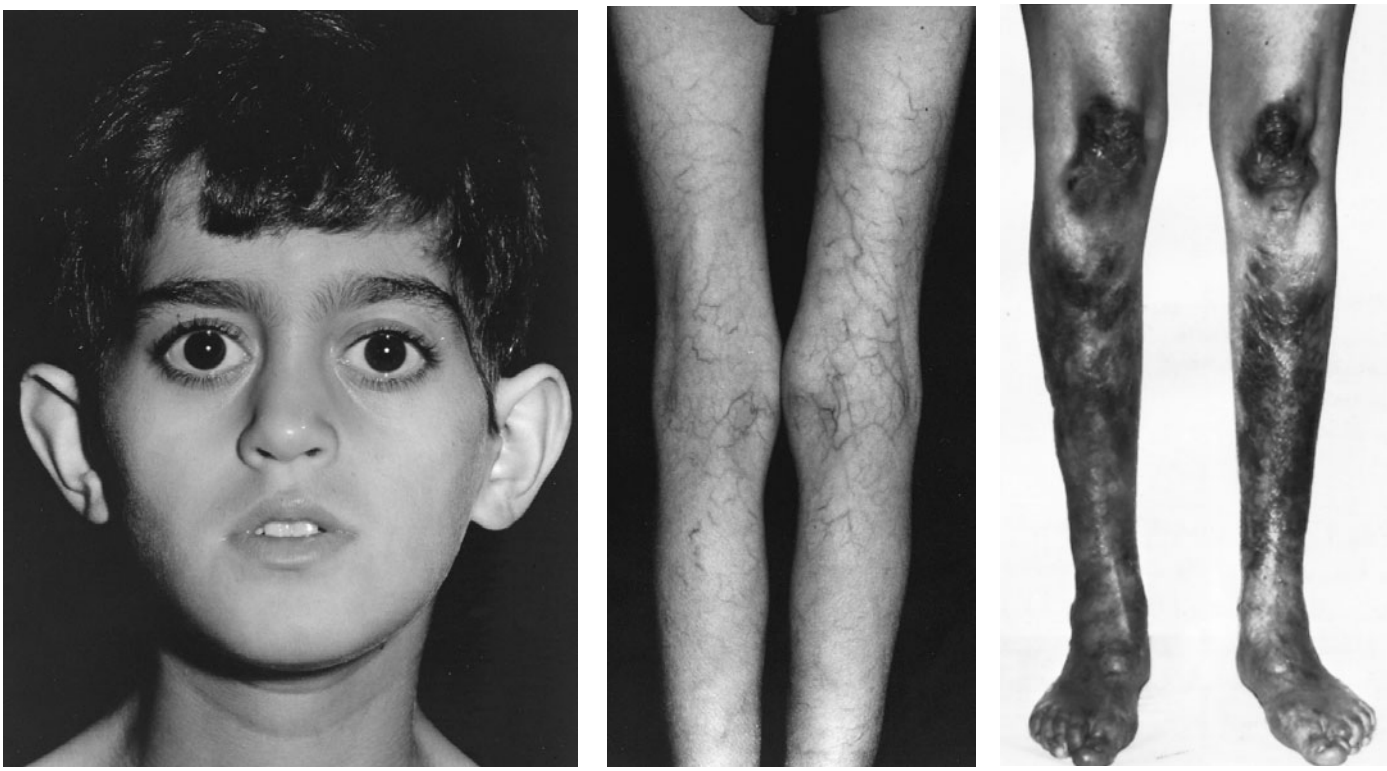
Pope et al (1996) (38) summarized 23 *COL3A1* mutations that they have analyzed. Most cause premature arterial fragility and thin skin, with EDS IV features. There are 14 glycine substitutions, eight exon skips and one small inframe deletion. Each mutation is private for the affected family. Other mutations are referred to in other studies (7,16,18,21–23,25,27,37,40,41,45,55,56).

Radioimmunoassay has revealed low levels of procollagen type III aminopropeptide in a subgroup of patients with EDS type IV (47). This is a peptide released during conversion of type III procollagen to collagen and is abnormally low in many patients with EDS IV.

Skin. The skin is thin, inextensible, and translucent (30%), showing a venous pattern over the trunk, abdomen, and extremities, and early aging. Bruising is marked, and extensive ecchymoses may follow even minor trauma in 65%. Bony prominences are covered with thin, darkly pigmented scars which differ from those observed in types I and II (Fig. 13–32C).

The facies is characterized by large-appearing prominent eyes, loss of subcutaneous connective tissue, a somewhat pinched or sharp nose, and thin lips, producing the so-called "acrogeric facies" (54) (Fig. 13–32A). The skin over the face has a parchmentlike appearance. Large varicose veins may be present (Fig. 13–32B) and the shins appear ecchymotic (Fig. 13–32C). Skin histology shows striking dermal thinning (from one-third to two-thirds of normal), collagen depletion, and elastin proliferation. Transmission electron microscopy reveals collagen fibril disorganization with irregularity and bimodal size distribution. Collagen III/I ratios seem to influence collagen fibril diameter and interactions and, if mutated or diminished, seriously impair the long-term strength and stability of arteries (31). In some cases, cells in the dermis have extremely dilated rough endoplasmic reticulum, the dermis is thin, and there is a reduced proportion of collagen although the proportion of elastic fibers appears increased. Certain mutations in *COL3A1* gene have effects on secretion, fibrillogenesis and skin architecture.

Vascular complications. Patients are at greatly increased risk for arterial aneurysm or dissection (80%), arteriovenous fistulas (20%), spontaneous rupture of colon (10%), and rupture of gravid uterus (2,3,8,9,19,43,46,52). There is early onset of varicose veins. Recurrent abdominal pain without major findings is common and may result from mural hemorrhage in the small bowel. The location of arterial hemorrhage determines the presenting symptoms in some patients (stroke, abdominal bleeding, arteriovenous, carotid-cavernous sinuses fistula, limb compartmental syndrome), whereas bowel rupture (flank pain) is the first complication in others. Removal of the distal two-thirds of the colon, the most common site of rupture, may decrease the likelihood of recurrence. Over 40% die prior to surgery. Surgical attempts at vascular repair and angiographic studies have been especially risky due to the friability of vessel walls and other tissues.



A B C

Fig. 13–32. *Ehlers-Danlos syndrome, type IV*. (A) Note prominent eyes and outstanding ears. (B) Varicosity of veins. (C) Ecchymotic type showing severe bruising following minor trauma over knees and shins. Elbows also commonly involved. Skin and joint hyperextensibility are less marked than in severe type (see Table 13–2). (A,B from HMB Sulh et al, Clin Genet 25:278, 1984; C from P Beighton, The Ehlers-Danlos Syndrome, Heinemann, London, 1970.)

Other problems. Intracranial aneurysms (44), cardiac involvement and vascular aneurysms with spontaneous coronary artery rupture and cardiac tamponade (10,12), cavitary pulmonary lesions and spontaneous pneumothoraces (11,15), ocular complications (30), atlantoaxial subluxation (14), and gingival recession may be associated with EDS IV. Life span is generally shortened. Death has been reported from 12 to 60 years, most commonly during the 20s and 30s. Causes of death include exsanguination from major artery rupture, sepsis from bowel rupture, and shock from uterine rupture (2,3). Lewkonia and Pope (19) described joint contractures and acroosteolysis.

The complications of pregnancy, in addition to vascular rupture and uterine rupture, include tearing of vaginal tissues during delivery (1,28,29,43,53). Life-threatening complications may occur in 15%–20%.

Prenatal diagnosis. Prenatal diagnosis is available for most families with EDS IV. This requires a combination of histology, electron microscopy, and type III collagen protein or *COL3A1* gene analysis. Prenatal diagnosis by amniocentesis, chorionic villus biopsy, or termination of pregnancy is potentially hazardous in affected females owing to the inherent fragility of cervical, uterine, or abdominal blood vessels (31,32,43).

References [(Ehlers-Danlos syndrome type IV (ecchymotic, arterial, or Sack-Barabas type)]

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Ehlers-Danlos syndrome type V (X-linked)

In 1968, Beighton (1) first reported this entity in two English families. Skin hyperextensibility was striking, but joint hypermobility, most evident in the fingers, was mild. Cutaneous fragility, bruising, and scarring tended to be moderate. Both spheroid and molluscoid pseudotumors were found. There was generalized musculoskeletal weakness (dorsal kyphosis, hernia, pes planus, genu valga). Intestinal obstruction and brain abscess were noted in two male sibs. Clinical features were generally similar to those affected with type II (1–9). Life span is probably normal and female carriers are asymptomatic (2). The condition is extremely rare (9).

Inheritance is X-linked recessive. In 1985, Beighton and Curtis (4) conducted a follow-up of the two families studied by Beighton (1) in 1968. In family 1, a sister of 3 affected males had an affected son.

Biochemical studies have failed to identify any abnormality. According to Steinmann et al (9), X-linked inheritance is questionable and, thus, the existence of this disorder as a distinct entity remains to be proven.

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Ehlers-Danlos syndrome VI (ocular-scoliotic type)

Pinnell et al (27), in 1972, described a form of EDS characterized by a deficiency of lysyl hydroxylase, an enzyme that modifies collagen.

Inheritance is autosomal recessive. Intermediate values of lysyl hydroxylase have been found in heterozygotes. Prenatal diagnosis is possible (9). The gene for lysyl hydroxylase has been mapped to 1p36.3, and has been cloned and sequenced (15). EDS VI may be caused by either a low level or a low activity of the enzyme (14,39). The hydroxylysine content of defective tissues varies between 5% and 50%, being

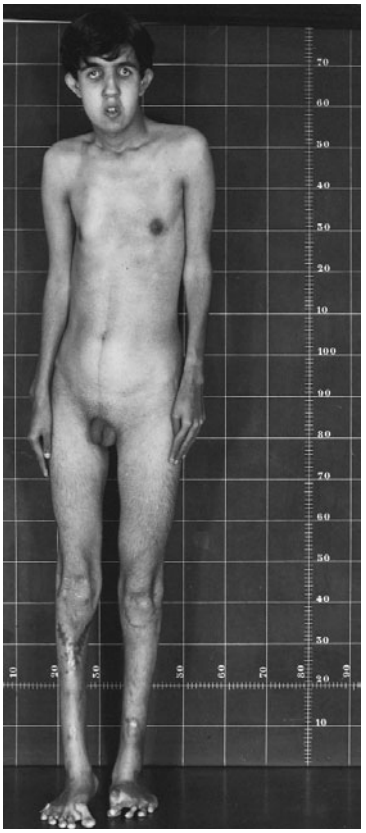

Fig. 13–33. *Ehlers-Danlos syndrome, type VI.* Note scoliosis, arachnodactyly, scarred skin, splayed feet. (From B Steinmann et al, Helv Paediatr Acta 30:255, 1975.)

lowest in skin, bone, and tendon. Mutations include partial duplications (16,17,28), homozygous or compound heterozygous exon skips (14,17), or a homozygous stop codon (19).

Many manifestations of EDS VI are similar to those of EDS I, namely moderately severe articular hypermobility, skin hyperextensibility, and connective tissue fragility. In addition, there are spinal malalignments and ocular complications. In a few persons with EDS VI, vascular and gastrointestinal catastrophes have been documented (5,32). Height is originally normal, but scoliosis develops during adolescence and is progressive. Often there is also delay in motor development (38) (Figs. 13–33 to 13–36).

EDS VI is very heterogeneous since, in a few individuals, normal lysyl hydroxylase activity has been documented (21). The latter form of the condition is designated EDS VIB to distinguish it from the classical form, EDS VIA, in which the enzyme is abnormal. Ihme et al (20) suggested three forms of EDS VI: (a) severe form, with absent hydroxylysine in skin collagen and low lysyl hydroxylase activity in skin, (b) clinically similar form but with normal skin hydroxylysine and low activity of lysyl hydroxylase in skin fibroblasts, and (c) predominantly ocular form with normal biochemical findings (40).

Both type A (9,11,22,23,27,34,36,38) and type B (21,28,30,33) patients exhibit very severe hypotonia in the newborn period, generalized loose-jointedness with dislocation, excessively stretchable soft velvety bruisable and fragile skin, and scoliosis at birth which is progressive (35,39). Ambulation may be lost in the second or third decades. Some patients may exhibit arterial rupture (39) (Figs. 13–37 to 13–41).

Epicanthic folds, blue sclerae, keratoconus, keratoglobus (Fig. 13–36A), and angioid streaks are common (8). Glaucoma (36) manifests in the third decade, with retinal detachment in the fourth. The cornea or globes may rupture following minimal trauma. Corneal diameter may be somewhat reduced (33). Moderate myopia is common, as is hearing loss.

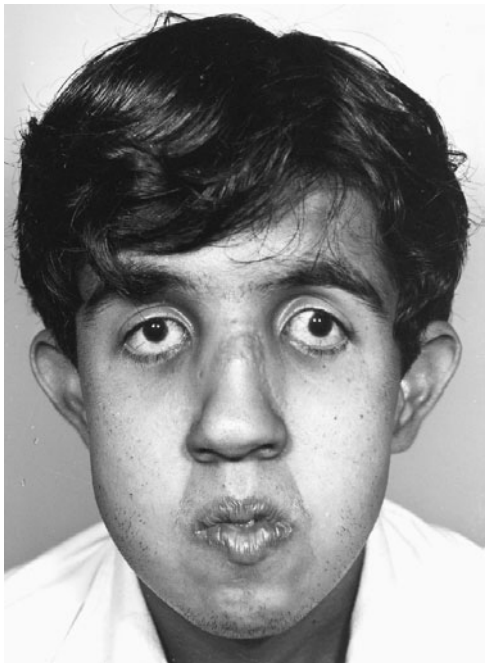

Fig. 13–34. *Ehlers-Danlos syndrome, type VI.* Microcorneae, ectropion, downward-slanting palpebral fissures, puckered mouth. (From B Steinmann et al, Helv Paediatr Acta 30:255, 1975.)

Differential diagnosis. Neonatal *Marfan syndrome, osteogenesis imperfecta, Larsen syndrome*, pseudoachondroplasia, and *cartilage-hair hypoplasia* may present with joint laxity. The autosomal recessive syndrome of pseudogliomatous blindness, osteoporosis, and mental retardation may also have retinal detachment and ligamentous laxity (25).

Brittle cornea, blue sclera, keratoglobus, keratocornea, and microcornea in various combinations have autosomal recessive inheritance with or without joint laxity, fractures, macrocephaly, hearing loss, and mild mental retardation (1–7,10,12,13,18,24,32,37) (Fig. 13–41A). Robertson (30) discovered that 50% of his patients with keratoconus had joint hypermobility (Fig. 13–41B).

Stein et al (33) and Hyams et al (18) reported Tunisian patients with red hair and suggested that this finding may be part of the syndrome. Zlotogora et al (41) noted two groups of patients with "brittle cornea syndrome." The first group was composed of 5 families of Tunisian Jewish origin. The second group consisted of 9 families that came from various ethnic backgrounds. These persons had a normal distribution of hair color. Zlotogora et al (41) suggested that the locus for the gene may be closely linked to the locus for a gene responsible for hair color, with linkage disequilibrium in Tunisian Jews. Royce et al (31) described the syndrome of brittle cornea and blue sclerae in a Syrian girl with consanguineous parents. She had red hair and joint hyperextensibility but with normal collagen lysyl hydroxylation.

Laboratory findings. Diagnosis is made by measuring total urinary hydroxylysyl and lysyl pyridinoline cross-links after hydrolysis (26). Dermal hydroxylysine estimation can also be carried out (36).

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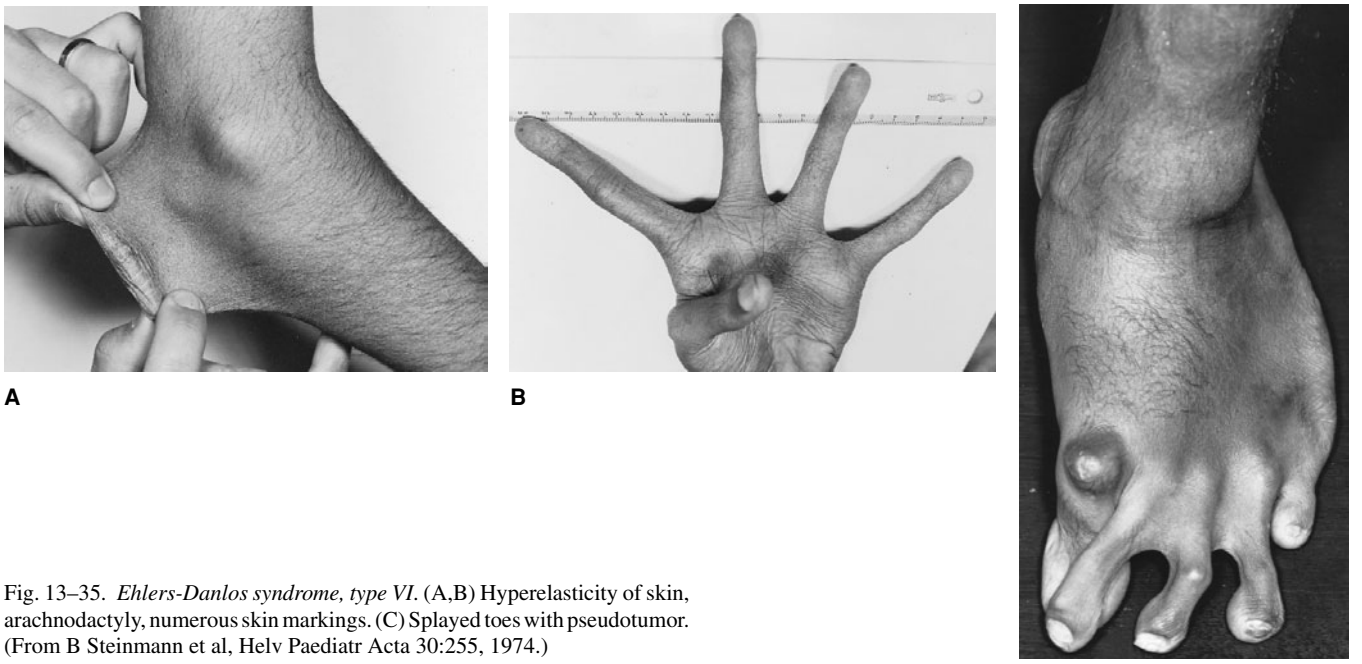

A B C

Fig. 13–35. *Ehlers-Danlos syndrome, type VI.* (A,B) Hyperelasticity of skin, arachnodactyly, numerous skin markings. (C) Splayed toes with pseudotumor. (From B Steinmann et al, Helv Paediatr Acta 30:255, 1974.)

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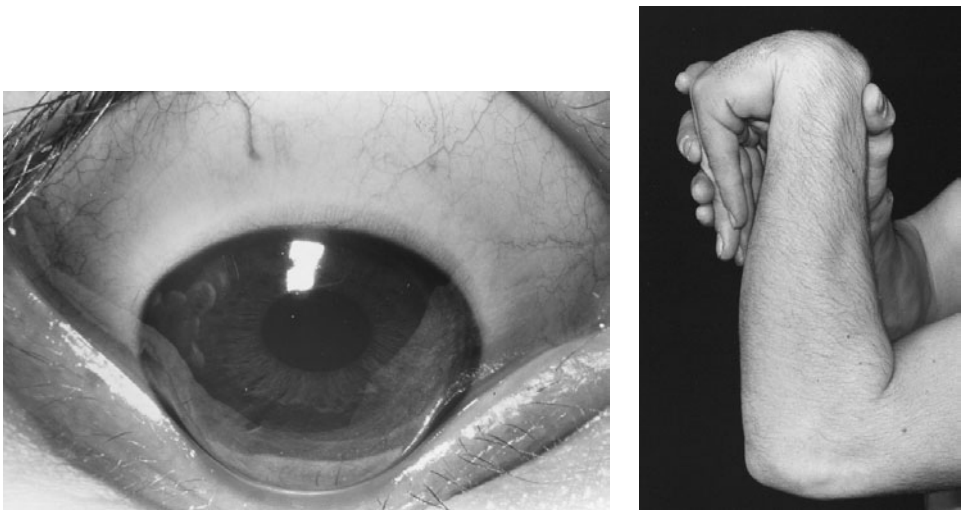

A B

Fig. 13–36. *Ehlers-Danlos syndrome, type VI.* (A) Keratoglobus. (B) Hypermobility at wrist. (A,B from AW Biglan, Am J Ophthalmol 83:225, 1979.)

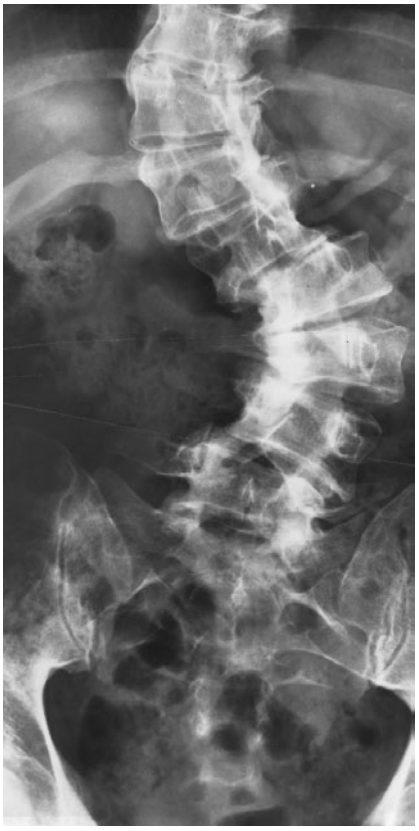

Fig. 13–37. *Ehlers-Danlos syndrome, type VIIA*. Severe scoliosis. (Courtesy of P Beighton, Cape Town, South Africa.)

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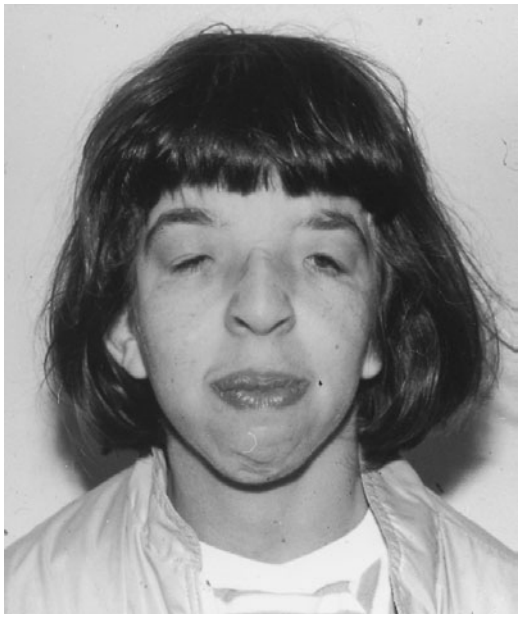
Fig. 13–38. *Ehlers-Danlos syndrome, type VIIC*. Note blepharochalasis, epicanthus, featureless philtrum, and general excess of dependent skin in 15-year-old. (B) Marked bruising and folds of excess skin around ankles. Flatfeet. (C) Note excess skin over the hand in 15-year-old. (From W Reardon et al, Clin Dysmorphol 4:1, 1995.)



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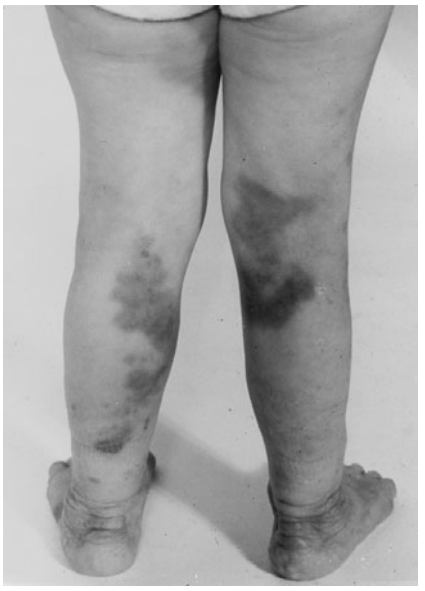

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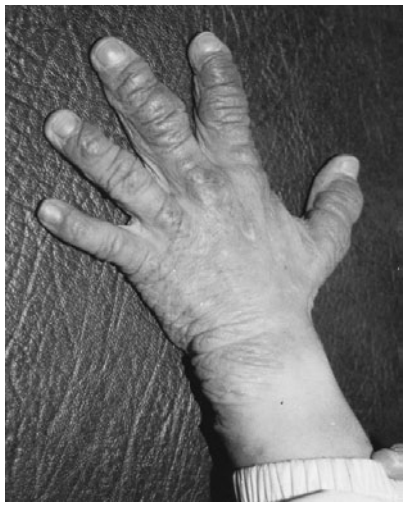

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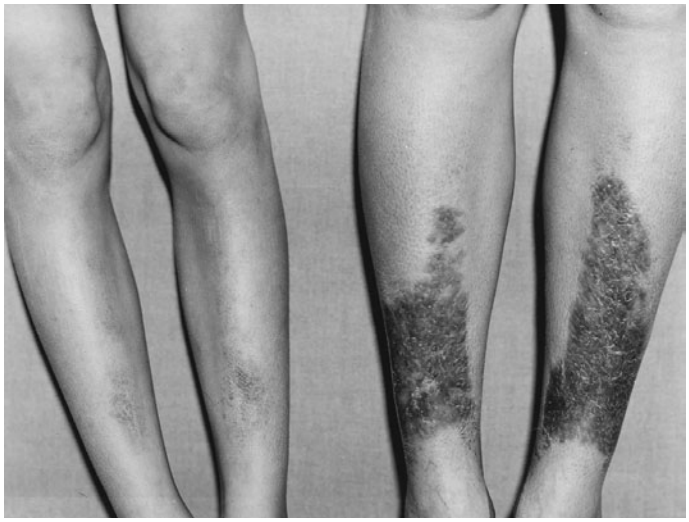

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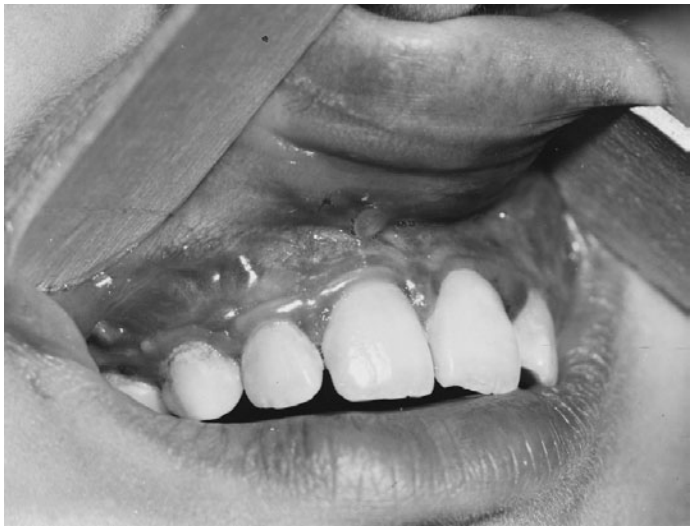

B

Fig. 13–39. *Ehlers-Danlos syndrome, type VIII.* (A) Ecchymoses of pretibial areas showing variable involvement in sibs. (B) Premature periodontal destruction.

Ehlers-Danlos syndrome type VII [autosomal dominant (arthrochalasia type congenita) (EDS VIIA and B) and autosomal recessive (dermatosparaxis type) (EDS VIIC)]

In 1973, Lichtenstein et al (18) identified a distinct type of EDS in three isolated patients who presented with severe hypermobility of joints with multiple dislocations, especially of the hips, and scoliosis which in large part accounted for the short stature (Fig. 13–37). The skin was soft, but only mild hyperelasticity and fragility of the skin were observed. The facies was characterized by epicanthic folds, depressed nasal bridge, and micrognathia. Similarly affected isolated examples had been described earlier by Hass and Hass (12). Several affected sibs in a large consanguineous kindred have also been documented (2). Later, other clinical presentations were reported (19,26,30,38) and anomalies of collagen I structure and metabolism were discovered (25). The so-called Viljoen type is a variant of EDS VIIB.

Classification. There are two distinctive phenotypes of EDS VII, one overlapping with EDS I/II and the other with congenital cutis laxa (3,25). The former is mild, affecting mostly the joints. It exhibits autosomal dominant inheritance. The latter is severe, affects primarily the skin, and is autosomal recessive.

The autosomal dominant group is further divided into EDS VIIA and EDS VIIB. This subdivision is based on abnormal type I procollagen maturation, that is failure to remove the amino-terminal propeptide. In type VIIA the proα(1) (COL1A1) chain is affected, and in type B it is the proα2(1) (COL1A2) chain (7,9,10,27,31). Type VIIC is caused by mutations in procollagen 1 N-proteinase (8). Hood et al (16) demonstrated markedly variable clinical expression in individuals with the same structural mutation. Collagen fibril morphology is only marginally abnormal. The fibers are angular in transverse section rather than forming cauliflowers (25).

The autosomal recessive form is termed EDS VIIC. Its clinical manifestations (Fig. 13–38) (11,21,28,30,38) include late closure of anterior fontanel, hypertrichosis, large-appearing eyes, blue sclerae, thickened eyelids, prolapsed upper lip mucosa, easy bruising, predisposition to fractures, soft velvety hyperextensible skin which sags, suggesting *cutis laxa*, large fontanels with wide sagittal and metopic sutures, micrognathia, and umbilical hernia (22,30,38). It is caused by deficiency of procollagen N-peptidase (19) due to homozygosity or compound heterozygosity of mutant alleles. Electron microscopic examination of the skin shows collagen sheets rather than fibrils, and characteristic distortions resembling hieroglyphics (30,38). The basement membrane is defective with an apparent paucity or focal absence of type IV collagen and laminin (23,28).

Biochemical and molecular pathology. EDS VII thus results from two distinct but related mechanisms of faulty collagen type I metabolism. Either there is a structural abnormality at the protease cleavage site [proα1(I)-EDS VIIA or proα2(I) EDS VIIB, respectively] or a defect in the protease (EDS VIIC) (15,19,25,30).

Collagen type I is a heterotrimer with two α1(I) and one α2(I) chains and loss of either the pNa1 or pNa2 peptidase cleavage sites may cause EDS VIIA or EDS VIIB, respectively (5,9,24,26).

The faulty conversion of procollagen to collagen in EDS VII was described by Lichtenstein et al (18), Steinmann et al (31), and Cole et al (6,7). Until the end of 1997 (1), the total number of individuals reported with this condition has been 16. All of them, except one, have mutations in the splice-junction sequences of the COL1A1 gene (three individuals) or the COL1A2 gene (12 individuals). These affect the splice donor site of COL1A2 (14,17,20,32–38), the last nucleotide of the exon in the COL1A2 gene (37), the splice-acceptor site of the COL1A2 gene (4), or the last nucleotide of exon 6 in the COL1A1 gene (8,35).

Differential diagnosis. EDS VII and *osteogenesis imperfecta* (OI) overlap clinically and biochemically (13,29). In EDS VII, cutaneous fragility and ligamentous laxity predominate, while in OI, the bone fragility is the most striking finding (25). EDS VIIC resembles *Ascher syndrome*.

References (Ehlers-Danlos syndrome type VII [autosomal dominant (arthrochalasia type congenita) (EDS VIIA and B) and autosomal recessive (dermatosparaxis type) (EDS VIIC)])

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Fig. 13–40. *Ehlers-Danlos syndrome, type Beasley-Cohen*. (A–D) Narrow face with midface deficiency, small eyes, hypermobility of joints, and hyperelasticity of skin.

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Fig. 13–41. *Familial generalized articular hypermobility*. Should not be confused with Ehlers-Danlos syndrome. Proposita is an acrobatic dancer. (From P Beighton et al, J Bone Joint Surg Br 52:145, 1970.)

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Ehlers-Danlos syndrome type VIII (periodontal type)

In 1972, McKusick (13) first identified a form of EDS characterized by periodontal disease, scarring of pretibial skin unaccompanied by joint hypermobility, and hyperextensibility of skin. Stewart et al (21), in 1977, and later others (2,3,5,9,15), reported kindreds with marfanoid habitus, unusual facies, severe skin fragility and bruisability, and evidence of visceral involvement (duodenal rupture), moderate or marked skin stretchability, or normal facies and body habitus with only slight joint hypermobility. Other examples are less certain (1,4,8,12,17). Hartsfield et al (6,7) questioned the existence of this type since they found periodontitis in type IV, and Lapière and Nusgens (10) found reduced type III collagen in type VIII. The case of Müsebeck et al (14) is not documented and may be type IV. However, a large comprehensive study is needed.

The onset of skin fragility is noted in childhood. Ecchymoses following slight trauma resolve except for the pretibial areas. These heal with tender yellow-brown atrophic wrinkled scars as necrobiosis lipoidica diabeticorum or venous stasis (Fig. 13–39A). DDAVP may be used to treat hemorrhagic symptoms (22).

Histology of the skin lesions shows a granulomatous collagen degeneration resembling necrobiosis lipoidica diabeticorum (11).

The periodontal disease appears after puberty and the permanent teeth are usually lost by the third decade (Fig. 13–39B). There is collagen degradation as judged by gingival resorption and cutaneous inflammation (16,18,19). Leukodystrophy may also be associated with EDS VIII (20).

Inheritance is autosomal dominant.

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Ehlers-Danlos syndrome type X (fibronectin defect)

Arneson et al (2), in 1980, described four sibs affected with joint hyperextensibility, easy bruising, thin hyperextensible skin, and with "fish-mouth scarring," but with normal texture. The parents were unaffected. The clinical presentation of these patients resembles that of EDS II and III. Narrow pelvis (4) and mitral valve prolapse (2,4) were also noted.

A platelet aggregation deficit resulted in petechiae. The common link to joint hypermobility and platelet malfunction was thought to be defective fibronectin and the addition of affinity-purified normal human fibronectin restored aggregation.

Only one family with this phenotype has been reported. A variety of clotting abnormalities (1,7) as well as defective platelet size and function (3,5,6) have been described in other EDS families.

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Other types of Ehlers-Danlos syndrome

Since Ehlers-Danlos syndrome (EDS) is a very heterogeneous condition, some patients cannot be included in the present general classification. However, they must be mentioned for additional information, and to encourage further reports and better delineation.

Hernández et al (5) described a variant of EDS, the progeroid form, in two unrelated males where, in addition to joint and skin hyperextensibility, increased bruisability, hernia, and papyraceous scars, the patients had mental retardation, wrinkled facies, short stature, fine curly hair, scant eyebrows and lashes, telecanthus, prominent pinnae, periodontitis, winged scapulae, cryptorchidism, multiple nevi, and varicose veins. In both patients, paternal age was increased, suggesting de novo dominant mutation. A third case was described in 1981 (6), stressing the progeroid facial appearance and mental retardation; and two more patients were reported in 1986, with histopathologic ultrastructural studies (7).

Kresse et al (9), in 1987, reported a 4-year-9-month-old boy with features of both Ehlers-Danlos syndrome and progeria. The child had delayed mental development, short stature, osteopenia, defective deciduous teeth, loose but elastic skin, delayed wound healing with thin, atrophic scars, scanty scalp hair, hypotonic muscles and hypermobile joints. Quentin et al (10) demonstrated that fibroblasts from this patient had a deficiency in galactosyltransferase that catalyzes the second glycosyl transfer reaction in the assembly of the dermatan sulfate chain. There was an unsubstituted xylose residue in the glycosaminoglycan-free core protein secreted by the patient's fibroblasts.

In 1982, Friedman and Harrod (3) described a seemingly dominant condition in mother and son. They presented with large hernias, positional foot deformities, severe scoliosis, mild joint hypermobility, periodontitis, aortic rupture, and allergy problems (eczematoid dermatitis and asthma). Both had facial asymmetry, prominent nasal bridge, and small jaw. The mother had "cigarette paper" scars over her legs.

Conditions suggesting autosomal recessive inheritance have also been reported. In 1979, Beasley and Cohen (1) described two sibs with a "new" and presumably autosomal recessive form of EDS. The parents were consanguineous. The patients had hyperelasticity of the skin of the hands, very mild scarring, generalized hyperextensibility of the joints, dislocation of the hips, and decreased muscle mass (Fig. 13–40).

Shohet et al (11), in 1987, reported two unrelated patients with minor signs of EDS but with severe aortic change. One of the patients had a similarly affected sister and brother.

Hamada et al (4) reported four unrelated patients with soft-tissue contractures and moderate joint hypermobility, skin hyperelasticity, and skin fragility.

Carter and Sweetnam (2) reported dominant inheritance in several families that suffered from recurrent dislocation of joints. Horton et al (8) described a large family in which many members had joint laxity, most also having congenital hip dislocation. It was the recommendation of a workshop convened in Berlin in 1986 by Beighton that the Ehlers-Danlos designation be used for joint hypermobility with skin changes, leaving this as a separate category. Thus, familial isolated generalized articular hypermobility (Fig. 13–41) should not be confused with Ehlers-Danlos syndrome.

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Dyskeratosis congenita (Zinsser-Engman-Cole syndrome, Scoggins type, autosomal recessive type)

Dyskeratosis congenita (DC) is characterized by reticular skin hyperpigmentation, nail dystrophy, lacrimal duct obstruction, leukoplakia of mucous membranes, bone marrow hypofunction, and predisposition to malignancy. It was first described by Zinsser in 1906 (66). The second report was in 1926 by Engman (22), who was not aware of Zinsser's earlier publication. Cole et al (9), in 1930, further delineated the condition and brought it to the attention of dermatologists. The syndrome has been seen in all races (55). Excellent reviews have been published by Sirinavin and Trowbridge (55), Womer et al (62), and Rodermund et al (53).

Dyskeratosis congenita is a heterogeneous condition, but most cases (90% are males) are compatible with X-linked recessive inheritance (Zinsser-Engman-Cole syndrome) (7,11,12,14,20,30,53,55,56,63). The gene has been assigned to Xq28 (3,12,36). It has been reported in monozygotic twins (8).

Scoggins et al (54), in 1971, described a black family with autosomal dominant inheritance (dyskeratosis congenita, Scoggins type). Three generations were affected with male-to-male transmission. Tchou and Kohn (59), in 1982, also suggested the existence of an autosomal dominant form.

Juneja et al (32) and others (7,21,41,57) described an autosomal recessive form in a brother and sister.

In 1995, Drachtman and Alter (20) analyzed the clinical manifestations of dyskeratosis congenita according to mode of inheritance. They classified all sporadic male cases and families with multiple male cases as X-linked recessive and families with affected male and female members in consecutive generations as autosomal dominant. All sporadic female cases, including those where both male and female sibs were affected and those with parental consanguinity in only one generation, were classified

Table 13–3. Findings in dyskeratosis congenita

Findings	Percent
Growth	
Hypasthenic build	48
Performance	
Subnormal intelligence	42
Skin	
Hyperpigmentation	100
Atrophy	93
Hyperhidrosis (palms and soles)	89
Hyperkeratosis (palms and soles)	72
Bullous eruptions	78
Acrocyanosis	55
Hair	
Alopecia	51
Nails	
Dystrophy	98
Mucosa	
Leukoplakia	87
Hematopoietic	
Anemia	52
Leukopenia and/or thrombocytopenia	49
Other	
Epiphora	78
Dysphagia	59
Small testes, small penis[a]	40

[a] Percentage adjusted for male sex.
(Based on C Sirinavin and AA Trowbridge, J Med Genet 12:339, 1975.)

as autosomal recessive. They noted variation in the clinical phenotype with the mode of inheritance. The X-linked recessive and autosomal recessive cases had a higher incidence of nail dystrophy, cutaneous manifestations, and leukoplakia, with a median age of diagnosis of around 15 years. Autosomal dominant cases had milder clinical manifestations, with a median age at diagnosis of 28 years and the median survival of more than 50 years. However, it is not yet clear whether the autosomal recessive and dominant forms represent separate genetic loci. Moreover, the sporadic female cases categorized in the autosomal recessive group may be carriers of the X-linked recessive form.

In 1998, Heiss et al (31) described a novel gene in Xq28, *DKC1*, which is responsible for X-linked dyskeratosis congenita. They identified six different mutations. Dyskerin, the protein coded for by *DKC1*, is multifunctional and possibly involved in rRNA biosynthesis, ribosomal subunit assembly, and/or centromere/microtubule binding (38,42). Hoyeraal-Hreidarsson syndrome is allelic (64).

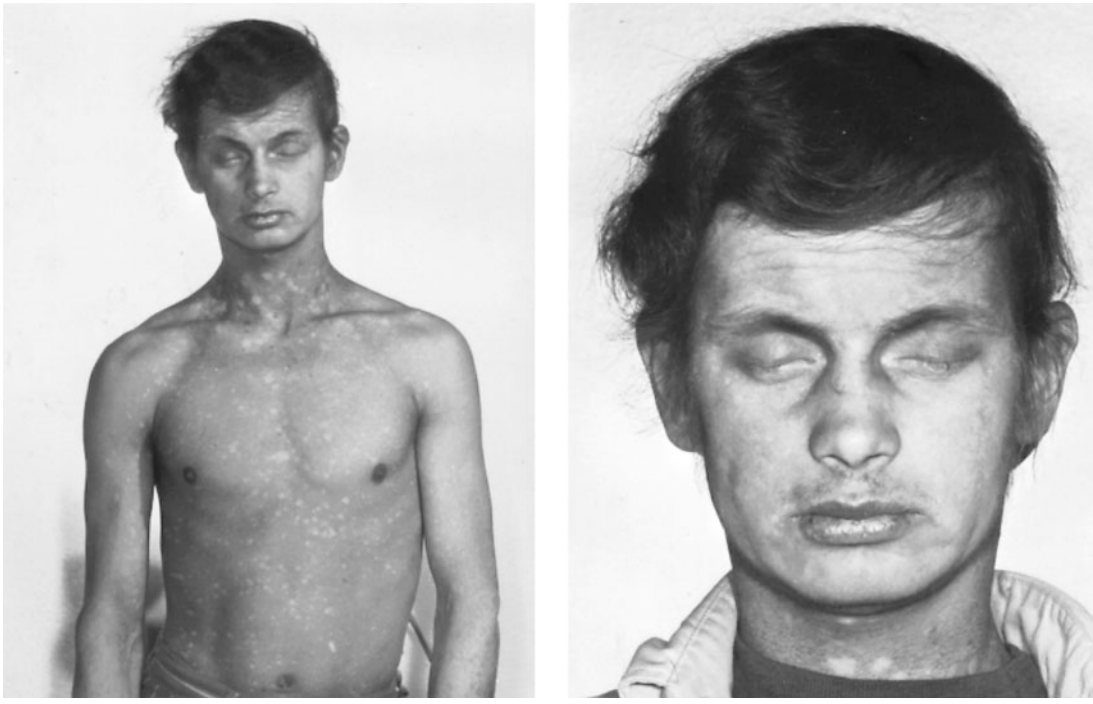
Highly skewed X inactivation was observed in white blood cells, cultured skin fibroblasts, and buccal mucosa from female carriers of DC (16). The skewed X inactivation was reported by other investigators as well (23,60). Ferraris et al (23) hypothesized that, at least in some DC families, the selective pressure in the cells of carriers may be strong enough to result in negative selection of cells expressing the mutant alleles, resulting in extreme skewing of X-chromosome inactivation in cells of hematopoietic descent.

General aspects. Dyskeratosis congenita is a misnomer, since the syndrome is neither dyskeratotic nor congenital. Oral lesions are characterized by a decreased number of keratinosomes associated with decreased epithelial turnover. As a rule, cutaneous manifestations of the disorder are not present during infancy.

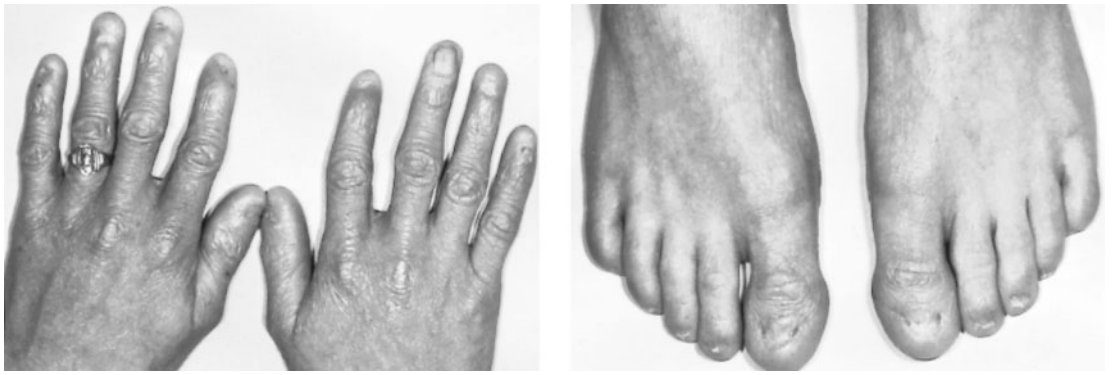
The clinical features are summarized in Table 13–3. Findings in hemizygous males are usually manifest at 5–10 years. Skin, nail, and mucosal changes appear during the first decade. Patients are usually frail and have generalized growth retardation. Hematopoietic manifestations appear in about 50% and develop during the second and third decades. Neoplasms may evolve over the third, fourth, or fifth decades. Mean age at death is about 25 years, usually from infections (50%), gastrointestinal bleeding (20%), or malignancy (30%).

Skin and its appendages. The most prominent skin changes closely resemble those found in poikiloderma vasculare atrophicans, involving especially the face, neck, upper arms, and chest and appearing around 8–9 years of age. A prominent reticulated hyperpigmentation of the skin is present, usually described as gunmetal in color (Fig. 13–42). Microscopy

Fig. 13–42. *Dyskeratosis congenita*. (A) Whitish, irregular atrophic areas, increased pigmentation, and telangiectasia, producing appearance that resembles poikiloderma vasculare atrophicans. (B) Sparse scalp hair, blepharitis due to absence of lacrimal puncta.



A **B**



A B

Fig. 13–43. *Dyskeratosis congenita.* (A,B) Note shriveled, shrunken appearance of nails.

reveals atrophy of the epidermis and subcutaneous tissues, accompanied by capillary hyperplasia. Melanin pigment is heavily deposited in macrophages, especially near blood vessels. Characteristically, no inflammatory exudate is evident (10,13,26–29,50,55). Cutaneous macular amyloidosis has been noted in one instance (41), a Blaschko line pattern in another (4).

Hyperhidrosis of the palms and soles, but with generalized hypohidrosis elsewhere, has been described in about 90%, and palmar and plantar keratoses have occurred in approximately 70%. Cutaneous bullae are noted in 25%. Acrocyanosis of the hands and feet has been reported in about 55% (10,13,22,25–29,50,55,62).

Nail dystrophy, initially longitudinal ridging and splitting (Fig. 13–43), found in 98%, is not of the same degree in all digits, and fingernails tend to be more severely affected than toenails (55). Nail changes are usually seen by 10 years of age. They become progressively dystrophic and are often lost.

The hair is thin and lusterless in 50%. Sparse body hair in some cases is related to hypogonadism. Eyelashes and eyebrows may be absent (50,55).

Dokal et al (19) found that skin fibroblasts in primary cultures were abnormal both in morphology (polygonal cell shape, ballooning, and dendritelike projections) and in rate of growth (with a doubling time around twice that of normal). No significant difference from the normal was found in fibroblast survival after using 4 clastogens and gamma radiation.

Mucosal manifestations. Leukoplakia, a feature in 87%, can occur on any mucosa, but most commonly affects the oral mucosa prior to puberty (44).

Crops of vesicles and bullae appear on the oral mucosa. They are recurrent and essentially painless. Because of moisture and maceration, they rupture early, leaving ulcerated areas, with epithelial tags along the margin. After several attacks, the mucosa becomes atrophic and the tongue loses its papillae and appears smooth. Under ultraviolet light, the normal orange fluorescence of the tongue is absent. Eventually, the mucosa becomes thickened, fissured, and white (Fig. 13–44). Mucosal atrophy or stenosis has been described in the mouth, esophagus, anus, urethra, and vagina (7,26,27,33,46,55,58,64,65).

Eyes and ears. Chronic blepharitis, ectropion (9,13,22,27,47,50) and profuse tearing due to keratinization with obstruction of the lacrimal points (80%) (27,46,49) around puberty have been described. Rare ophthalmologic findings, such as congenital cataracts, are reviewed by Womer et al (62). Thinning of the eardrum, malformation of the middle ear, and sensorineural hearing deficit have been reported (11,13).

Gastrointestinal features. Although not often emphasized, many patients have gastrointestinal problems. Abdominal pain, vomiting and dysphagia, occurring in about 60%, may result from esophageal strictures or diverticula (60%). Severe diarrhea, sometimes bloody because of mucosal ulcerations, has been noted. Liver disease is relatively common, and hepatic cirrhosis has been recorded (5,7,13,27,57,62).

Hematologic manifestations. Two serious complications of dyskeratosis congenita are anemia and cancer (44). With progressive pancytopenia, the age of onset and the rapidity of progression are variable, but the mean age of onset is about 15 years. A decline in the platelet count usually occurs first, followed by progressive anemia and, later, granulocytopenia. (7,9,17,27,32,55,56,62).

Bone marrow failure has been reported in approximately 50% of cases of dyskeratosis congenita (6,18,39,40) and is the principal cause of early mortality (36). It increases to more than 80% by age 30 years (37). In some patients, symptoms related to aplastic anemia may precede the diagnosis of DC (24). Friedland et al (25) considered the disorder to be a stem cell defect. Following in vitro clonogenic assays, as well as long-term bone marrow culture studies, Marsh et al (43) suggested also that the symptoms of aplastic anemia in DC may be due to a defect at the level of the hematopoietic stem cell.

In 1997, Vulliamy et al (60) found that in families with X-linked DC, the hematopoiesis of heterozygous female cells expressing the normal DC allele had a growth advantage over the cells that express the mutant allele.

It has also been noted that splenomegaly occurs in 45% and hepatomegaly in 15% of patients, although they are not sites of extramedullary hematopoiesis.

Reichel et al (51) found reports of 15 cases of elevated fetal hemoglobin in association with dyskeratosis congenita and added another case.

Fig. 13–44. *Dyskeratosis congenita.* Thick white plaques of labial and lingual mucosa.

Immunologic manifestations. A wide range of immunoglobulin abnormalities may occur, including decreased IgG and IgM with normal IgA, normal IgG and IgA with slightly decreased IgM, and increased IgG. Abnormalities of cell-mediated immunity have also been noted (28,59). Autopsies have revealed a number of findings, including lymphoid depletion with absence of the primary germinal follicles and occasionally fibrosis of lymph nodes. The high frequency of opportunistic infections is further evidence of abnormal immune function (48,55,62).

Neoplasia. Malignancy occurs in about 17%, the mean age being about 30 years. Carcinoma of the oral mucosa has been recorded at least six times. Other tumors have included carcinomas of the nasopharynx, esophagus, rectum, cervix, and vagina (34). Squamous cell carcinoma of the hand, adenocarcinoma of pancreas, and Hodgkin's disease have also been reported (8–10,12,13,26,50,55,62). Tchou and Kohn (59) noted an increased rate of cancer in unaffected sibs. It has been suggested that p53 expression is a good marker to predict premalignant change in skin keratoses (46).

Central nervous system. Mental deficiency occurs in about 40% and is mild to moderate in degree. Schizophrenia has also been reported (13,27,55).

Other findings. Small testes and small penis have been observed in about 40% of males. Rarely, hypopituitarism, enlarged thyroid, and secondary hypogonadism have been recorded (55).

A variety of skeletal anomalies have been documented including joint deformities, incomplete closure of vertebral arches, and other minor skeletal anomalies (56). Radiolucencies in the shafts of long bones with coarse trabeculation in the metaphyses have been reported (55,62). Osteoporosis, bone fragility, and aseptic necrosis of the hip have been encountered, usually but not always attributable to steroid therapy (62). Intracranial calcifications were reported by several authors.

The teeth are subject to early decay (50,55), periodontal disease (13,65), and malformation and malposition (13,50). These changes, with rare exception, have never been well documented and merit further investigation.

Differential diagnosis. Differential diagnosis includes Fanconi syndrome, *Rothmund-Thomson syndrome, Bloom syndrome, xeroderma pigmentosum* and *focal dermal hypoplasia*. Similarities and differences between dyskeratosis congenita and Fanconi syndrome have been discussed by a number of authors (55,57). An allelic variant called Hoyeraal-Hreidarsson syndrome consists of infant lethality, intrauterine growth retardation, mental retardation, cerebellar hypoplasia, pancytopenia, and oral mucosal lesions (64).

Laboratory findings. Chromosomal breakage has been reported by several authors (7,30,35,48). These findings have been questioned and most karyotypes have been normal (11,62). Pai et al (49) showed that fibroblasts, peripheral blood lymphocytes, and transformed lymphoblasts of six DC patients and an obligate DC heterozygote showed more chromatid breaks than controls exposed to bleomycin during the G2 phase of the cell cycle. Unsynchronized DC fibroblasts also showed decreased survival following bleomycin treatment. Lymphocytes from DC patients, when treated with bleomycin for the final 24 hours of culture showed more chromatid and chromosome damage than normal. Ning et al (45) found that the mean number of chromosome breaks per cell in bleomycin-treated lymphocytes was higher in patients with DC and in obligatory heterozygotes than in normals. However, unequivocal heterozygote detection was not possible because of overlapping values.

De Bauche et al (15) reported increased frequency of chromatid breaks and chromatid gaps after X-radiation during the G-2 phase of the cell cycle. Bone marrow metaphases and fibroblasts from some patients showed numerous unbalanced chromosomal rearrangements (dicentrics, tricentrics, and translocations) in the absence of any clastogenic agents. A higher rate of chromosomal rearrangements was found in the older patients (19).

References [Dyskeratosis congenita (Zinsser-Engman-Cole syndrome, Scoggins type, autosomal recessive type)]

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Dyskeratosis benigna intraepithelialis mucosae et cutis hereditaria

In 1977, From et al (1) described a father and son with a hereditary syndrome that affected the skin, oral mucosa, and bulbar conjunctiva.

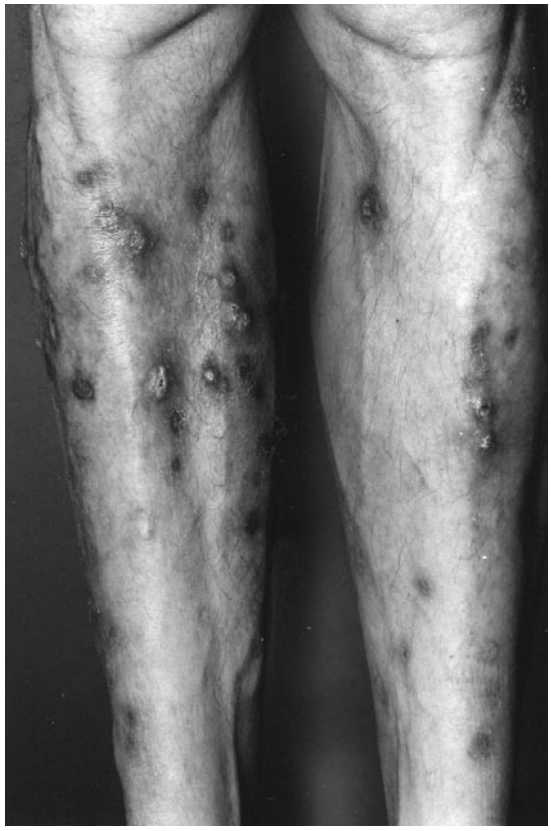


Fig. 13–45. *Dyskeratosis benigna intraepithelialis mucosae et cutis hereditaria*. Skins showing brownish papules with keratotic plugs. (From E From et al, J Cutan Pathol 5:105, 1978.)

The disorder was characterized by recurrent nonseasonal conjunctivitis, epiphora, and photophobia. Suppurating, red or brown, papular eruptions with central keratotic plugs (not greater than 10 mm in diameter) were found on the scrotum, buttocks, and body, the majority being on the lower limbs (Figs. 13–45 and 13–46).

Trauma-provoked papular lesions and Koebner phenomenon were also noted. Verrucalike lesions were described on palmar and plantar surfaces of the hands. Leukoplakic lesions were seen on the buccal mucosa. Total tooth loss (both primary and permanent) at an early age due to edematous hypertrophic gingivitis was noted (Fig. 13–47).

Pathologic findings in mucous membrane epithelium and epidermis included moderate to severe simple hyperplasia, acantholysis (with no "corps ronds"), moderate hyperortho- and/or hyperparakeratosis, and benign dyskeratosis characterized by pronounced single cell keratinization. No true dysplasia was found (Fig. 13–48). Gingival biopsy showed focal intraepithelial microabscesses and spongiform edema.

The syndrome is distinguished from *Papillon-Lefèvre syndrome* and *dyskeratosis congenita*.

Reference (Dyskeratosis benigna intraepithelialis mucosae et cutis hereditaria)

1. From E et al: Dyskeratosis benigna intraepithelialis et cutis hereditaria. A report of this disorder in father and son. J Cutan Pathol 5:105–115, 1978.

Pachyonychia congenita (Jadassohn-Lewandowsky syndrome, Jackson-Lawler syndrome)

Although sketchy earlier reports exist (31), Jadassohn and Lewandowsky (29), in 1910, described a patient with a syndrome of dystrophic fingernails and toenails, palmoplantar keratosis and hyperhidrosis, follicular keratosis, and oral leukokeratosis. In 1951–1952, Jackson and

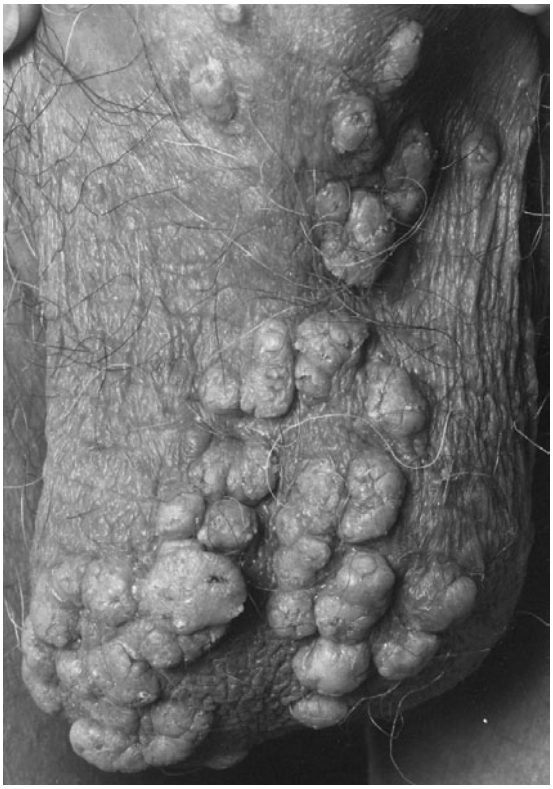
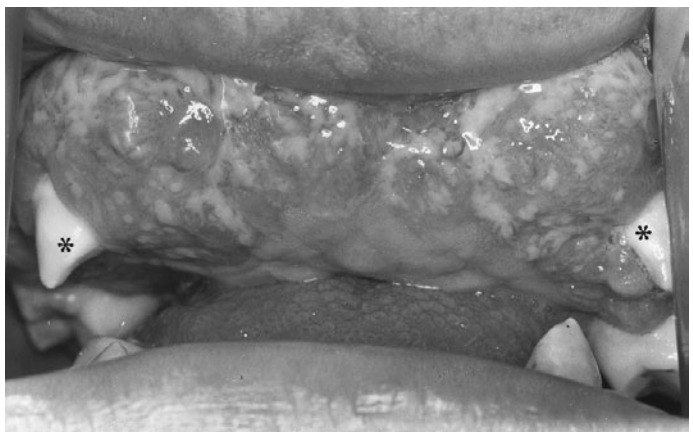


Fig. 13–46. *Dyskeratosis benigna intraepithelialis mucosae et cutis hereditaria*. Hyperkeratotic papules of scrotum. (From E From et al, J Cutan Pathol 5:105, 1978.)

Lawler (28) reported a family with pachyonychia congenita, palmoplantar hyperkeratosis, hyperhidrosis, and follicular keratosis. However, oral leukokeratosis was not observed. In addition, their patients had cutaneous cysts and natal teeth. Corneal dystrophy was found to be an exclusive feature of this type. Some had recurrent flexural infections. Kindreds with characteristics shared by both syndromes have been reported (4,50), suggesting that the differences originally observed represented variability of expression. The opposite point of view, that of separating the disorder into four subtypes, was expressed by Feinstein et al (19) in 1988. Since the publication of all of these reports, mutations at different keratin loci have been identified for the variants described by Jadassohn and Lewandowsky (type 1) (29) and Jackson and Lawler (type 2) (28). However, because

Fig. 13–47. *Dyskeratosis benigna intraepithelialis mucosae et cutis hereditaria*. Marked hypertrophic gingivitis at 2.5 years. (From E From et al, J Cutan Pathol 5:105, 1978.)



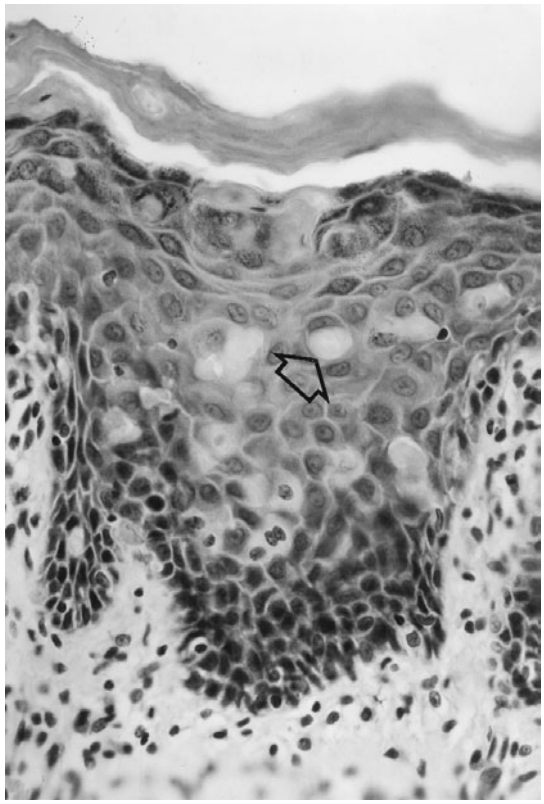


Fig. 13–48. *Dyskeratosis benigna intraepithelialis mucosae et cutis hereditaria*. Photomicrograph of buccal white lesion showing hyperparakeratosis and numerous dyskeratotic cells (arrow). (From E From et al, J Cutan Pathol 5:105, 1978.)

of the significant overlap in the clinical manifestations, the two disorders will be presented together.

Pachyonychia congenita has a frequency of about 0.7/100,000 population (20), with a 9:5 male predilection (38). At least 350 cases have been reported. An excellent statistical study is that of Kansky et al (31).

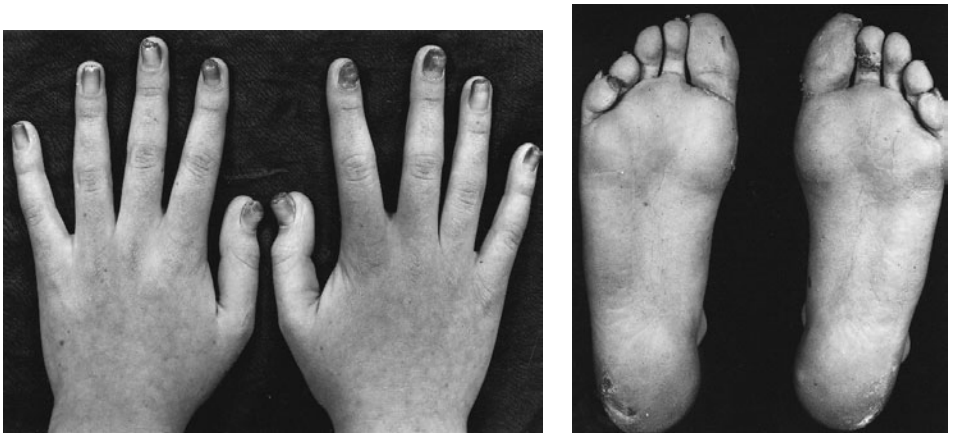
Heredity and molecular genetics. Pachyonychia congenita of both types 1 and 2 has autosomal dominant inheritance. An autosomal recessive form was suggested but has not been definitively confirmed (11,24, 47).

Mutations associated with pachyonychia congenita were identified in different keratin genes. Those involving the *KRT6A* gene at 12q13 and the *KRT16* gene at 17q12–q21 were found to cause pachyonychia congenita type 1 (3,7,21,37,52). Mutations of the *KRT17* gene at 17q12–q21 were associated with pachyonychia congenita type 2 (21,37,41,48). We have no information on gene localization for types 3 and 4 which, in addition to nail changes, include cheilitis, corneal dystrophy, and cataracts. Type 4 exhibits hearing loss and mental retardation (33a).

KRT16 and *KRT17* gene mutations may also produce phenotypes with little or no nail changes. *KRT16* mutations may present as focal non-epidermolytic palmoplantar keratoderma and *KRT17* mutations can result in a phenotype resembling steatocystoma multiplex (15).

Skin and skin appendages. At birth (14,23,53) or soon after (54), fingernails and toenails become thickened, tubular, and hard (Fig. 13–49A). Their undersurfaces fill with a horny, yellow-brown material that causes the nail to project upward from the nail bed at the free edge. Pachyonychia congenita has also been reported in the absence of other syndrome abnormalities (10).

Hyperhidrosis of the palms and soles nearly always occurs, but the rest of the skin is dry and may be described as ichthyotic. Palmar and plantar hyperkeratoses are noted in 40%–65% during the first few years of life.



A B

Fig. 13–49. *Pachyonychia congenita*. (A) Note thickening and elevation of fingernails at free edge in 13-year-old female. (B) Note ruptured blisters of toes and heels. Often there is severe hyperkeratosis of soles. (From ADM Jackson and SD Lawler, Ann Eugen 16:141, 1951.)

During warm weather, bullae appear on the feet, especially on the plantar surfaces of the toes and heels and along the sides (2,51). They burst, may become infected, are very painful, and often make walking difficult (3,33,45,53) (Fig. 13–49B). Diffuse hyperkeratosis of the perineum has also been described (8,14).

During the first few years of life, pinhead-sized follicular papules appear over the elbows, knees, popliteal areas, and buttocks (2,51). In the center of each papule, a horny plug is seen. Verrucous lesions may also occur in the same areas. The skin is thickened because of acanthosis and parakeratosis, especially about the pilosebaceous apparatus. Follicles and sweat pores are dilated and plugged with imperfectly cornified and partly degenerated horny material (2). The hair may be dry (10) and twisted (59), and alopecia has been reported (32,38). Cornoid lamellae have been described in a patient in whom oral leukokeratosis was not well documented (44,58).

Electron microscopic studies of involved skin from the knee (52) show increased number and thickness of tonofibrils, an increased number of desmosomes throughout the epidermis, intracellular and extracellular edema, and large, abnormal keratohyaline granules. These findings are consistent with a defect in keratinization. Similar findings were reported by Thormann and Kobayasi (54). Ultrastructural findings have also been described by Thomas et al (53). Eruptive villus cysts, especially of the head, neck, and upper chest, appear around puberty (5,6, 16,18,22,28,33,38,39,46,56,57,60) (Fig. 13–50). Most reports do not adequately describe the histology of the skin cysts. However, Hodes and Norins (26) and Velasquez and Bustamante (56) determined that their patients had steatocystomas, whereas Clementi et al (13), Chapman (10), and Soderquist and Reed (49) determined that the cysts in their patients were epidermal inclusion cysts.

Laryngologic and esophageal abnormalities. Hoarse voice and thickening of the posterior commissure of the larynx have been noted (1,13,14,28,33,38,62). Patients may have multiple, white exophytic lesions involving the ventricles, true cords, subglottis, and interarytenoid area (13,23). Hagemann and Vogel (25) reported dysphagia due to esophageal involvement.

Oral manifestations. White patches are observed on the dorsum and lateral borders of the tongue (3,17,23,32,35,50,55,61). The buccal mucosa at the interdental line, the gingiva, and palate can also be involved (10,17,23,35,61,63) (Fig. 13–51). These lesions may be present as early as the first decade.

On microscopic examination, the oral mucosa is characterized by hyperparakeratosis, acanthosis, and generalized intracellular vacuolization of the epithelial cells (4,63).

Natal teeth are frequently present (4,5,8,26,28,42,45,49,56).

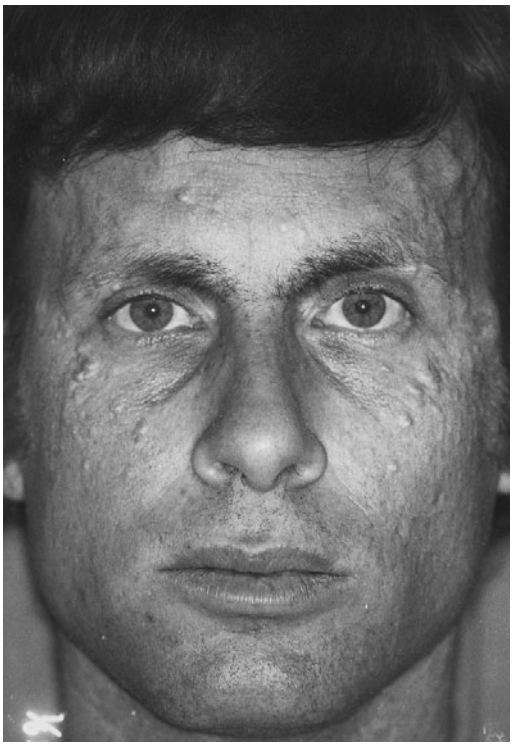
Differential diagnosis. Late onset of the nail disease has been described by several authors and designated as pachyonychia congenita tarda (9,27,34,40,43).

Haber and Rose (24) reported two male sibs with bullae on hands and feet, oral leukokeratosis, leukonychia of fingernails, onycholysis of fingernails and toenails with slight elevation by subungual debris, keratoderma of palms and soles, and hyperkeratotic papules on dorsa of fingers and toes. There were no skin cysts, and natal teeth were not mentioned. Parents were normal but consanguineous. Although this disorder might be autosomal recessive, X-linked inheritance cannot be excluded.

Chong-Hai and Rajagopolan (11) reported a child born to consanguineous parents and presenting with the nail abnormalities of pachyonychia congenita, palmar and plantar hyperhidrosis, blistering of feet, follicular keratoses, epidermal cysts, and oral leukokeratosis. Autosomal recessive inheritance was suggested, but a new dominant mutation cannot be excluded.

Tidman et al (55) have also described a variant with cutaneous amyloidosis and hyperpigmentation. This dominant form is associated with diffuse rippled pigmentation of the neck, axillae, waist, buttocks, and

Fig. 13–50. *Pachyonychia congenita*. Multiple cysts of skin. (Courtesy of RM Goodman, Tel Aviv, Israel.)



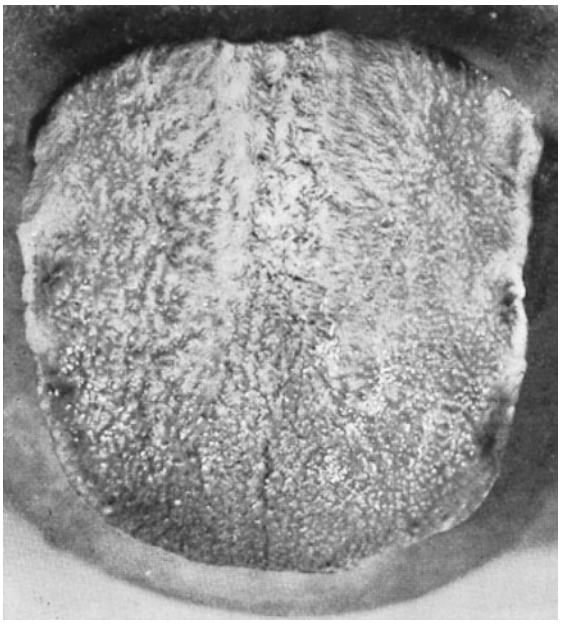


Fig. 13–51. *Pachyonychia congenita*. Thickening of oral mucosa, especially that of tongue and buccal mucosa.

thighs that fades with age. Histologic and ultrastructural examination of the hyperpigmented skin has revealed pigmentary incontinence and deposition of amyloid within the papillary dermis.

In pachyonychia congenita, the nail changes are distinctive. However, the oral leukokeratosis is nonspecific and is also seen in *dyskeratosis congenita, hereditary benign intraepithelial dyskeratosis*, white sponge nevus (30), and *leukoplakia, tylosis and esophageal carcinoma*. Other clinical findings serve to distinguish these disorders from pachyonychia congenita. Patients with *endocrine-candidiasis syndrome* also have diffuse white lesions of the oral mucous membranes.

The frequency of natal teeth unassociated with other abnormalities has been estimated to range from 1:700 to 1:30,000 (average 1 per 3000) white newborns (12,33). However, natal teeth occur in 1 in 28 Native Americans of Athabascan origin (44). Natal teeth may also be found in *Ellis–van Creveld syndrome, Hallermann-Streiff syndrome*, and *Wiedemann-Rautenstrauch syndrome*. McDonald and Reed (36) reported a kindred in which natal teeth and steatocystoma multiplex were inherited as a dominant condition.

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Hereditary benign intraepithelial dyskeratosis (Witkop-Von Sallmann syndrome)

Hereditary benign intraepithelial dyskeratosis (HBID) was described in a North Carolina triracial isolate (white-black-Indian) in 1960 by Witkop et al (9) and by Von Sallmann and Paton (6). The patients reported by Yanoff (10) had already been included in the study by Witkop et al (9). The chief components are plaques of the bulbar conjunctiva and oral mucosal thickenings clinically similar to white folded hypertrophy.

The syndrome has autosomal dominant inheritance with complete penetrance (9). The gene maps to 4q35 where there is a duplicated region (1,1a).

Eyes. About the limbus, both nasally and temporally, there are foamy gelatinous plaques, more superficial than pterygia, on a hyperemic bulbar conjunctiva (Fig. 13–52). The eye lesion is usually noted within the first year of life (5,6). There is vernal exacerbation with shedding in the summer or fall.

The dyskeratotic process may involve the cornea, producing blindness from shedding and resultant vascularization of this structure (3). Photophobia and itching of the eyes, especially in children, is common.

Oral manifestations. The oral mucosal thickenings are asymptomatic. They appear as soft white folds and plaques, resembling white sponge nevus (11,12). Though the thickenings appear at birth, they are

Fig. 13–52. *Hereditary benign intraepithelial dyskeratosis*. Superficial gelatinous plaques on hyperemic bulbar conjunctiva involving limbus and cornea. (Courtesy of CJ Witkop Jr, Minneapolis, Minnesota.)

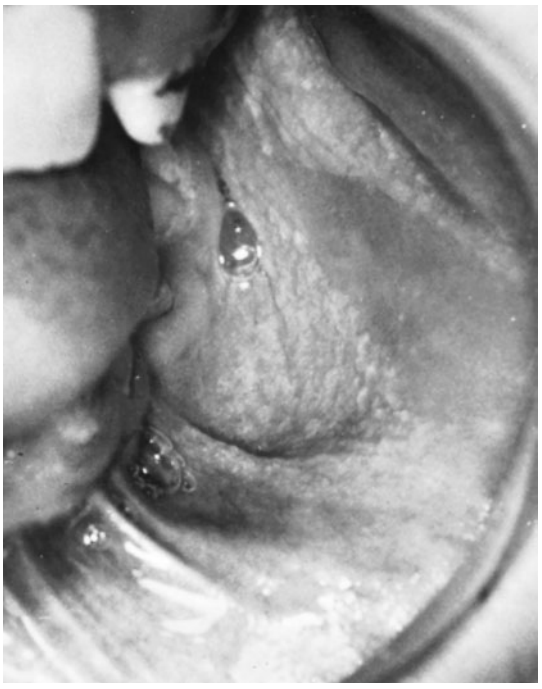
mild, increasing in severity to about 15 years of age. There is no tendency for the plaques to undergo malignant degeneration (Fig. 13–53).

Differential diagnosis. White sponge nevus and oral lesions of pachyonychia congenita bear a distinct clinical resemblance to those of HBID.

Laboratory aids. Tissue sections of buccal or conjunctival scrapings treated with Giemsa stain are characteristic (Fig. 13–54). Acanthosis, vacuolization of the stratum spinosum, and intraepithelial dyskeratosis characterized by waxy eosinophilic cells called "tobacco cells" and "cell-within-a-cell" pattern are noted. These latter changes are especially evident in Papanicolaou-stained smears (2,6) (Fig. 13–55).

Witkop and Gorlin (8) found similarities in oral smears from HBID and keratosis follicularis (Darier-White disease). The grains of the latter

Fig. 13–53. *Hereditary benign intraepithelial dyskeratosis*. Leukokeratosis of buccal mucosa. (Courtesy of CJ Witkop Jr, Minneapolis, Minnesota.)



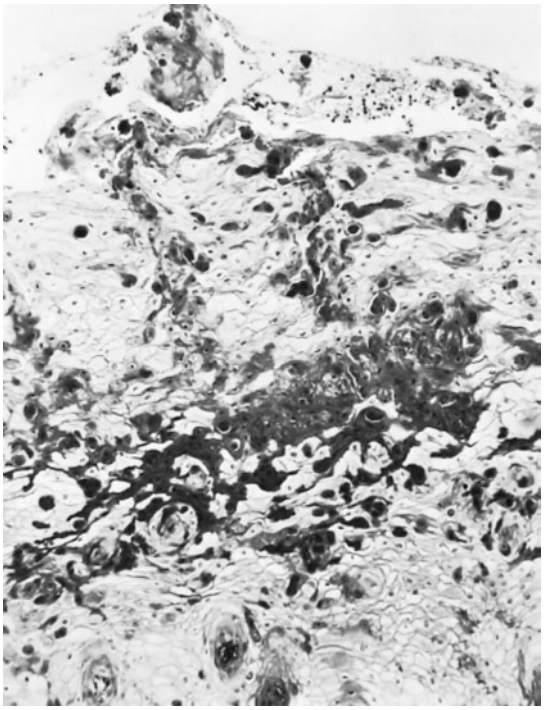


Fig. 13–54. *Hereditary benign intraepithelial dyskeratosis*. Section of buccal mucosa demonstrating dyskeratotic eosinophilic cells in acanthotic epithelium (Giemsa stain). (Courtesy of CJ Witkop Jr, Minneapolis, Minnesota.)

resemble the "tobacco cells" of the former, and the corps ronds of the latter resemble the "cell-within-a-cell" body seen in the syndrome under discussion. However, the "cell within a cell" is far more common in oral smears of HBID, and, in addition, one rarely sees the small blue parabasilar cells so often noted in keratosis follicularis. Witkop (7) pointed out that patients receiving methotrexate and 5-fluorouracil also exhibit the "cell-within-a-cell" phenomenon in exfoliated buccal cells.

Ultrastructural studies have revealed numerous vesicular bodies in immature dyskeratotic cells, and the disappearance of cellular interdigitations and desmosomes in mature dyskeratotic cells (4).

Fig. 13–55. *Hereditary benign intraepithelial dyskeratosis*. "Cell-within-a-cell" phenomenon, Papanicolaou smear. (Courtesy of CJ Witkop Jr, Minneapolis, Minnesota.)

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Leukoplakia, tylosis, and esophageal carcinoma (Clarke–Howel-Evans syndrome)

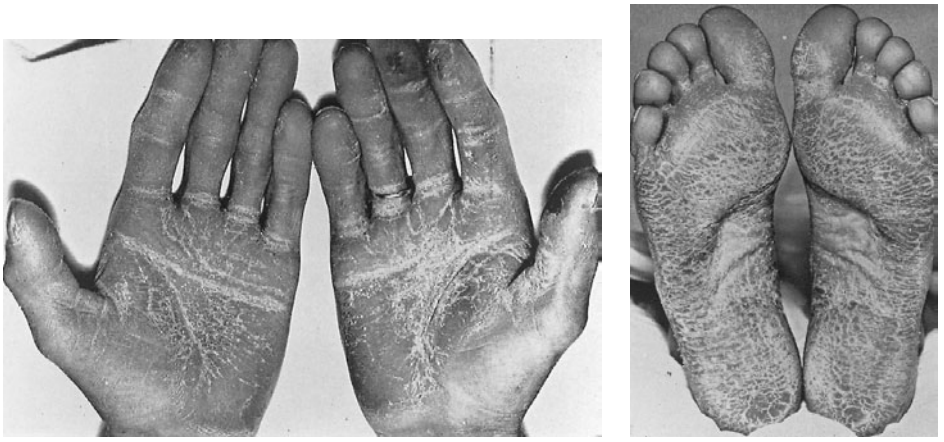
In 1954 Clarke and McConnell (1) and, later, Clarke et al (2,3) and Howel-Evans et al (7) reported the association of hyperkeratosis of palms and soles (tylosis) and carcinoma of esophagus in two families. Subsequently, Tyldesley and Hughes (21) and Tyldesley (20) reexamined members of these two kindreds and found, in addition, oral leukoplakia. Several other kindreds with this constellation of abnormalities have been reported (4,5,10–14,17,18).

Inheritance is autosomal dominant. The gene has been mapped to 17q24 (6,9,12,19). Ruhrberg et al (15) proposed that the chromosomal localization of the human envoplakin gene (*EVPL*) to the region of the tylosis-esophageal cancer gene at 17q25 raises the possibility that loss of envoplakin function could be responsible for this condition. Envoplakin is a membrane-associated precursor of the epidermal cornified envelope. It is considered to link desmosomes and keratin filaments to the cornified envelope.

Skin. The age of onset of palmar and plantar hyperkeratosis is usually during the second decade of life (7), although onset between 1 and 5 years of age has been suggested (5) (Fig. 13–56). The tylosis is diffuse, may be yellow, and is sometimes associated with hyperhidrosis. In some women, the feet alone have been reported to be affected (5,7). Ritter and Petersen (14) and others (4) also described hyperkeratotic nodules on the distal and proximal interphalangeal joints and hyperpigmentation and hyperkeratosis on the upper parts of the arms.

Gastrointestinal tract. Squamous cell carcinoma of the esophagus develops in 95% of individuals by age 65. The age of onset may be as early as the fourth decade (7). Although the lower third of the esophagus is the most common site, the lesion may originate in the middle or upper third (7) (Fig. 13–57).

Oral manifestations. Clinical leukoplakia develops on the buccal mucosa (12,17) (Fig. 13–58) as early as 4 years of age as a diffuse gray-white lesion. On microscopic examination, parakeratosis, spongiosis of the superficial layer of the epithelium, and acanthosis are noted; no atypia



A B

Fig. 13–56. *Leukoplakia, tylosis, and esophageal carcinoma*. (A) Palmar hyperkeratosis. (B) Plantar hyperkeratosis. (A,B from W Howel-Evans et al, Q J Med 27:413, 1958.)

is seen. In older patients, lesions are smaller and more discrete; however, more diffuse regions may also be found. Ultrastructural studies demonstrate intranuclear electron-dense particles, similar to those found in nuclei of epithelium from the esophageal carcinomas (22).

Differential diagnosis. Many syndromes have associated hyperkeratosis of palms and soles. These include *hyperkeratosis palmoplantaris and periodontoclasia in childhood (Papillon-Lefèvre syndrome)* and *hyperkeratosis palmoplantaris and attached gingival hyperkeratosis*. Yesudian et al (23) reported a large kindred in which tylosis was present at birth. Inheritance was autosomal dominant. The tylosis was not associated with hyperhidrosis. Three members developed squamous cell carcinoma of the tylotic skin in the third decade of life; one of these three also developed squamous carcinoma of the lower end of the esophagus at age 40. The oral cavity was not described. The *Schöpf syndrome*, in addition to palmoplantar keratosis, has small cysts of marginal eyelids, hypotrichosis, and onychodystrophy; hypodontia was reported but not well documented. Shine and Allison (17) reported a family with onset of hyperkeratosis of the palms and soles at adolescence; there was no associated hyperhidrosis. Dysphagia had been noted since infancy. The proband developed esophageal carcinoma at the site of an esophageal stricture. Inheritance was autosomal dominant. Tylosis has been associated with bronchogenic carcinoma (16).

White lesions of the oral mucous membranes, similar to those seen in this syndrome, are also found in white sponge nevus (8), *hereditary benign intraepithelial dyskeratosis, pachyonychia congenita*, and *dyskeratosis congenita*.

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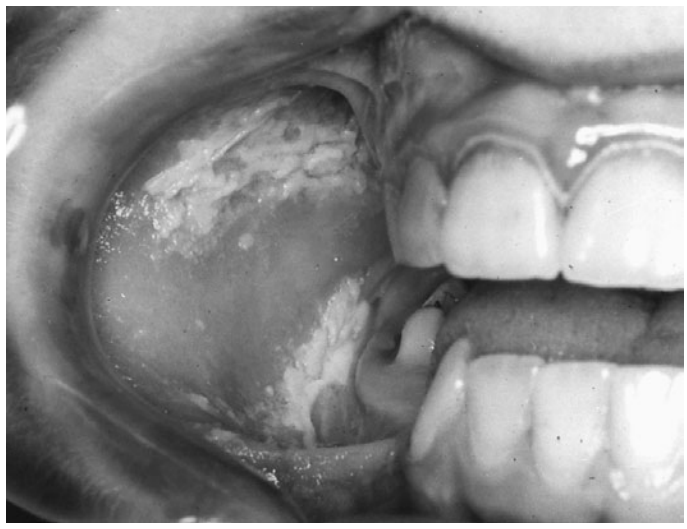
Fig. 13–57. *Leukoplakia, tylosis, and esophageal carcinoma*. Esophageal carcinoma. (Courtesy of PS Harper, Cardiff, Wales.)

Fig. 13–58. *Leukoplakia, tylosis, and esophageal carcinoma*. Focal lesions of leukoplakia on the buccal mucosa.



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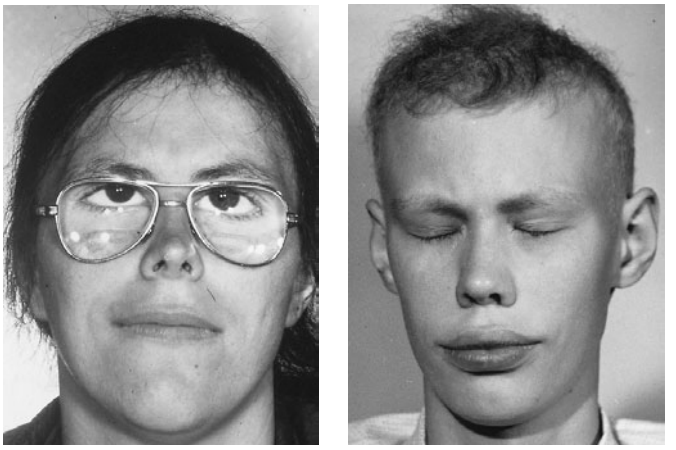
Mucoepithelial dysplasia syndrome (Witkop syndrome)

Witkop et al (4,6–9), from 1978 to 1982, described an autosomal dominantly inherited syndrome that involved the skin and various mucous membranes, eyes, and lungs.

Other families have also been reported (1–3,5), and RJ Gorlin has seen another kindred.

The disorder is heralded in infancy by severe tearing and photophobia. Corneal vascularization, development of a pannus, nystagmus, and cataracts first appear at 4–6 years of age, leading to blindness before puberty (Fig. 13–59). The oral, nasal, vaginal, urethral, anal, and bladder mucosae are fiery red (Fig. 13–60). Red erosive or granular periorificial mucosal lesions, noted by the end of the first year, tend to persist. The skin of the trunk and extremities (but not the hands and feet) is rough (follicular keratosis), and the scalp hair is scant (nonscarring alopecia). Patients often complain of easy burning on sun exposure.



A B

Fig. 13–59. *Mucoepithelial dysplasia syndrome*. (A,B) Sparse scalp hair, strabismus, photophobia, and cataracts. (Courtesy of CJ Witkop Jr, Minneapolis, Minnesota.)

Chronic rhinorrhea, upper respiratory tract infections, pneumonia, diarrhea, bladder infections with pyuria, and/or hematuria are common findings. Spontaneous pneumothorax is frequent in males, eventuating in terminal fibrocystic-type lung disease, cor pulmonale, and death in the third and fourth decades.

Mucosal biopsies show dyshesion, lack of keratinization, and dyskeratosis. Mucosal PAP smears principally exhibit numerous basal and parabasal cells (lack of epithelial maturation), nuclear atypia, and cytoplasmic vacuolization (Fig. 13–61). Ultrastructural changes suggest desmosomal and gap junction defects.

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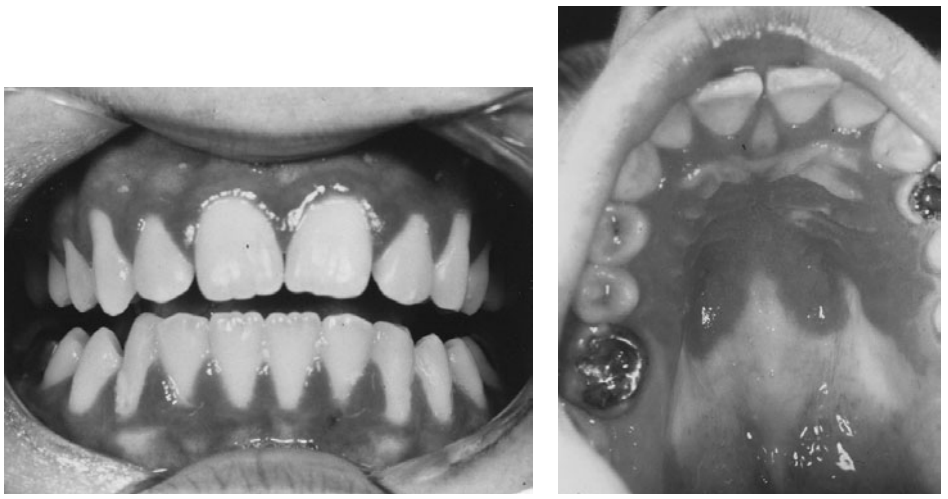

A B

Fig. 13–60. *Mucoepithelial dysplasia syndrome*. (A) Fiery red gingival mucosa involving both free and attached gingiva. (B) Anterior palate involvement.

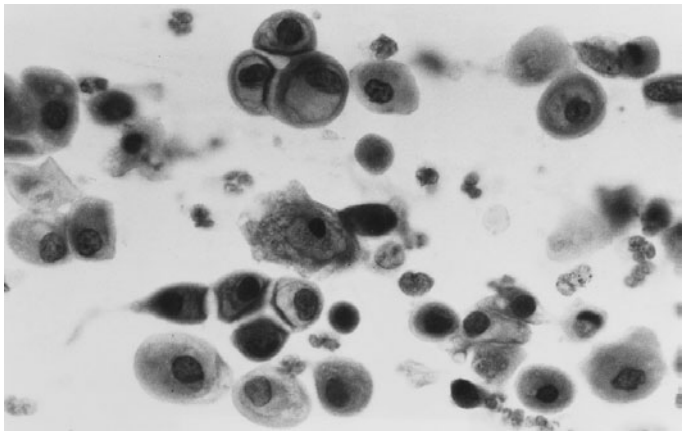

Fig. 13–61. *Mucoepithelial dysplasia syndrome*. Exfoliated cell smears show numerous immature epithelial cells, perinuclear vacuoles, and strand-shaped inclusions. Small dark cells are dyskeratotic cells that are orangeophilic. (Courtesy of CJ Witkop Jr, Minneapolis, Minnesota.)

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Hypohidrotic ectodermal dysplasia

The syndrome is characterized chiefly by hypohidrosis, hypotrichosis, and hypodontia. Charles Darwin (23) cited Wedderburn as having found the disorder in an Indian from the subcontinent. Thurnam (109), in 1848, also described the condition. According to Perabo et al (79), it may have been recorded as early as 1792 by Danz. Christ (13), in 1913, further defined it as a "congenital ectodermal defect," and Weech (119), in 1929, impressed by the depression of sweat gland function, coined the term "anhidrotic ectodermal dysplasia." We believe that "hypohidrotic" is more accurate a term. The frequency of occurrence is between 1/10,000 and 1/100,000 births (15,20). A most comprehensive survey is that of Airenne (2). A good discussion of classification is that of Pinheiro and Freire-Maia (83).

The syndrome usually (vide infra) has X-linked inheritance (17,41). The *EDA1* gene has been mapped to Xq12–q13.1 (31,122,123). There are apparently 12 exons. The gene isolated by positional cloning (53) codes ectodysplasia A, a transmembrane protein, with deletion mutations in collagenous repeats (8,46,53). Only a small percent of affected males can be detected by direct mutational analysis (31). A new splice form of the *EDA1* gene now permits diagnosis of nearly all cases (69). Males have full expression of the disorder. About one-third of female carriers exhibit no clinical changes (12a). Another one-third have minor expression, such as hypodontia, and the other one-third express the condition to a less severe degree than males. The teeth of carrier females may be deficient in number and/or have conical crown form. They may have reduction in body and scalp hair, and eczema. Sweating occurs in a patchy distribution, consistent with lyonization (17,80,82,84). About 80% of carriers have difficulty in nursing. Sofaer (99,100) suggested that 1 in 500 females with hypodontia in the permanent dentition and 1 in 50 with hypodontia in the deciduous dentition may be carriers for hypohidrotic ectodermal dysplasia. A remarkable report describes the disorder in monozygotic quadruplets (26).

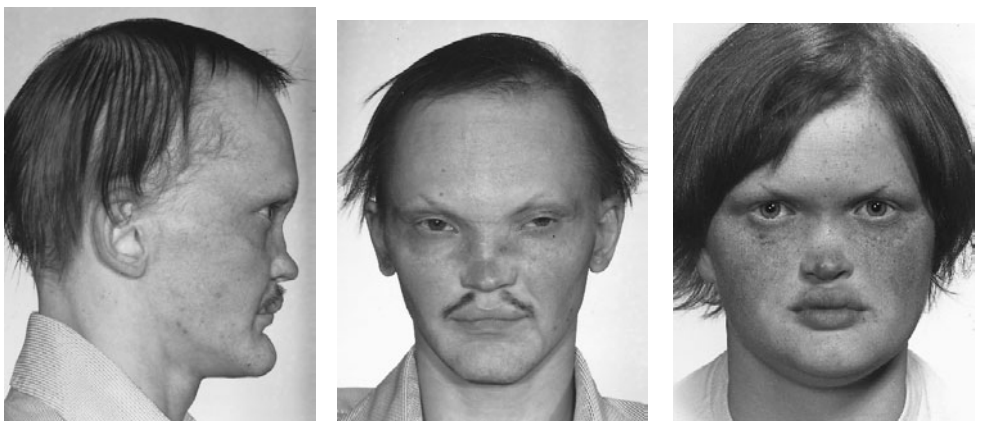
There have been a number of females with full expression of the syndrome. Some of these had balanced X/autosomal translocations, the break point being in the Xq12–Xq13.1 region (58,62,86). Other female examples clearly represent genetic heterogeneity. Passarge et al (77,78) reported a large consanguineous kindred with affected males and females. Gorlin et al (41), in 1970, reviewed all published examples of affected females and suggested the existence of an autosomal recessive form that could not be distinguished on clinical grounds from the X-linked form. For examples published prior to 1970, the reader is referred to Gorlin et al (41). Many additional autosomal recessive examples have been documented (3,7,22,28,49,51,54,56,68,72a,76,78,88,104,107,108,110,117); however, the first definitive molecular proof of an autosomal recessive form was not presented until 1997 by Munoz et al (71). The autosomal recessive and dominant forms map to 2q11–q13 (6,47,51,70,71).

Hypohidrotic ectodermal dysplasia has also been seen in Holstein-Friesian cattle (95).

Facies. Frontal bossing, usually marked, and depressed nasal bridge give added emphasis to the small size of the face. There are often fine linear wrinkles and pigmentation about the eyes (98). Due to absence of teeth, and resulting reduced vertical height, the lips are protuberant. The pinnae are often outstanding (79) (Fig. 13–62).

Cephalometric and anthropometric studies of hemizygotes and heterozygotes have shown a small lower facial height and depth, small palatal and cranial base widths, small malar bones, small calvarial height, prominent forehead, depressed nasal bridge, and high-set orbits (10).

Skin and skin appendages. A hallmark of this disorder is hypohidrosis. Because other physical features of this syndrome are not so apparent in the first year, the child may present with a "fever of unknown origin." Inability to sweat, because eccrine sweat glands are severely



A B C

Fig. 13–62. *Hypohidrotic ectodermal dysplasia*. (A,B) X-linked recessive form. Face is characterized by frontal bossing, depressed nasal bridge, thin hair, and periorbital increased pigmentation. (C) Female with autosomal recessive form. Note sparse hair and fine linear wrinkling around eyes. (From EC Passarge et al, Humangenetik 3:181, 1966.)

reduced in number, results in intolerance to heat, with severe incapacitation and hyperpyrexia after only mild exertion. The disorder is hypohidrotic rather than anhidrotic. Bizarre heat loss has been documented (89). The skin has been somewhat scaly or eczematous.

The skin is soft and thin. Dryness is often severe, because sebaceous glands are absent (52). Eczema is seen in 65%, especially during the early years of life (17). The body is usually devoid of lanugo hair. After puberty, the mustache and beard are described as normal, although axillary and pubic hair are frequently scant (65). Scalp hair is often blond, fine, stiff, and short. The eyelashes and, especially, the eyebrows are scanty or often missing. Female heterozygotes often exhibit sparse scalp hair, spotty sweating, random reduction in sweat pores, and a mosaic, patchy distribution of body hair (80). Happle and Frosch (43) noted that the hypohidrosis in heterozygotes follows Blaschko lines.

Nails are usually normal, but rarely may be spoon-shaped (119). Mammary glands may occasionally be aplastic or hypoplastic (65,75,112), and nipples may be rudimentary (65,75). Congenital absence of nipples in a putative heterozygote has been reported (12). There has been a report of sebaceous gland hyperplasia (74). Dermatoglyphic alterations have been described (87,116).

Eyes. Lacrimal gland function has been reported diminished in a few cases (60,67) and increased in others (81). There are no meibomian glands and, frequently, punctate epithelial keratopathy has been found (27). Congenital glaucoma has been noted in some patients (48,93); this association may have been coincidental or the patients may have had a syndrome different from hypohidrotic ectodermal dysplasia.

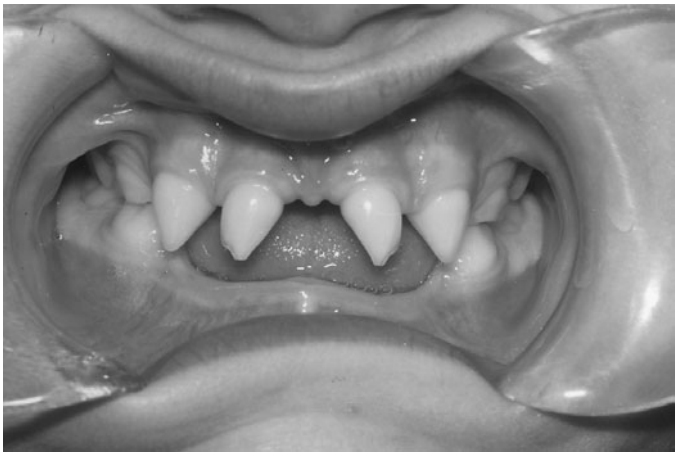
Otolaryngologic manifestations. Mucous glands in portions of the respiratory tract have been described as absent by some investigators (25). Pharyngeal and laryngeal mucosa may be atrophic, resulting in dysphonia (27,79,98). On laryngologic examination, breathy voice quality has been noted. Vocal folds appeared to close completely, although they are dry. Abnormal voice quality on spectrographic analysis has also been documented (19). Atrophy of the nasal mucosa associated with severe crusting and a fetid secretion (ozena) is frequent (27,60,79). These crusts may obstruct the nasal passages and make feeding difficult. Scintigraphic studies (63) have suggested an inflammatory process in the parotid glands.

Other findings. Several reports have noted that about 65% exhibit allergic disorders, especially eczema and asthma (17,98,113). Although rare, death may occur in infancy due to respiratory infection or hyperpyrexia (25). The latter may be accompanied by seizures. Pinheiro and Freire-Maia (81) noted deviation of some of the terminal phalanges of the hands and feet.

Oral manifestations. In hemizygotes, the most striking oral abnormality is absence of most deciduous and permanent teeth. Maxillary central incisors and canines usually have a conical crown form (Fig. 13–63). Frequently one or more molars may be present. More rarely, one or both jaws may be edentulous (94). Female heterozygotes exhibit reduction in numbers of teeth and smaller crown size than hemizygous males (20,63). Taurodontism is frequent (20). Because so many teeth are congenitally missing in hemizygous males, vertical dimension is reduced, and the lips are protuberant. The vermilion border is indistinct and pseudorhagades may be present (20,112).

The alveolar processes do not develop in the absence of teeth and, hence, are missing in those areas (30,94). Cephalometric studies have been limited in number (59,72,94) but have indicated that apart from defective alveolar growth, jaw and facial development is essentially normal. However, Ward and Bixler (118), employing cephalometric analysis in 16 affected individuals, found pronounced size reduction, compared to controls, in anteroposterior dimensions of the lower two-thirds of the face, in facial height, and in the size of the ears, nose, and mouth.

A few investigators have stated that the oral mucosa appears dry or that salivary secretion is diminished (30,37,98). Aplasia of intraoral mucous glands has been noted on microscopic examination (30).



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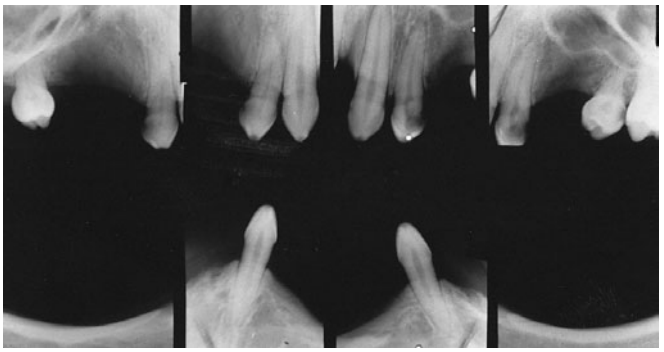

B

Fig. 13–63. *Hypohidrotic ectodermal dysplasia*. (A) Hypodontia and conical crown tooth form in 14-year-old female. No other stigmata present; possible carrier of trait. (B) Dental radiographs showing hypodontia and conical form of tooth crowns.

Differential diagnosis. Freire-Maia and Pinheiro (33) have provided a comprehensive discussion of differential diagnosis. Although the physiognomy in hypohidrotic ectodermal dysplasia is distinctive, several features resemble those of other disorders. The nasal deformity and linear perioral scarring may suggest congenital syphilis. Conical or tapered teeth, as well as congenitally missing teeth, may be found in individuals who have no other abnormalities (isolated hypodontia, oligodontia); in many cases, this condition may be familial (29,32,36,98,106). Hypodontia or oligodontia with dominant inheritance has been mapped to 4p16 (114) and to 14q12–q13 (103) and recessive hypodontia to 16q12.1 (1). Absence of all permanent teeth may be inherited as an autosomal recessive trait (42). Conical teeth are also found in *acrodental dysostosis* (21). Congenital absence of numerous teeth as well as conical teeth may be seen in *Ellis-van Creveld syndrome, Hay-Wells syndrome, Rieger syndrome, Witkop tooth-nail syndrome*, Fried tooth and nail syndrome, and *incontinentia pigmenti*; however, other abnormalities should serve to distinguish these disorders from hypohidrotic ectodermal dysplasia.

A complex ectodermal dysplasia with autosomal recessive inheritance consists of melanoleukoderma with hypodontia, hypotrichosis, retarded growth, and mental retardation (8).

In the trichodental syndrome (92), an autosomal dominant disorder, patients have fine scalp hair that grows slowly, and sparse eyebrows distally; males have a high anterior hairline. Several teeth are congenitally absent, although not as many as in hypohidrotic ectodermal dysplasia. The nails are presumably normal, and no abnormalities in sweating have been described. Pinheiro et al (83) reported a mother and two children with sparse, thin, and brittle scalp hair from birth, scanty axillary and pubic hair, sparse eyebrows and eyelashes, mild palmoplantar keratosis,

multiple congenitally absent deciduous and permanent teeth, conically shaped maxillary central incisors, café-au-lait spots, and mildly dystrophic toenails. M Pierpont and R Gorlin (personal communication, 1998) have seen such a family. Two kindreds with autosomal dominant hypohidrotic ectodermal dysplasia have been described (5,49). Autosomal recessive hypotrichosis, pili torti, hypoplasia of teeth, and cutaneous syndactyly of hands and feet was reported by Wiedemann et al (120). The parents were consanguineous.

Aswegan et al (5) reported a six-generation family of 38 individuals with autosomal dominant hypohidrotic ectodermal dysplasia. The disorder maps to 2q11–q13 (5). The skin was smooth, dry, and thin. Scalp and body hair were thin and slow-growing. Eyebrows and eyelashes were sparse and sweating was decreased. Some deciduous and permanent teeth did not develop or erupted late or had conical crown form. Nails tended to be slow growing and split. The facies was not abnormal. It is possible that the family reported by Jorgenson et al (49) had still a different condition.

The reader is also referred to a paper by Solomon and Keuer (101) for a discussion of the ectodermal dysplasias.

Cole et al (18) reported sisters with alopecia, small conical teeth, hypoplastic nails, hypohidrosis, mottled skin, lamellar cataracts, and mental retardation. Freire-Maia and Pinheiro (33) called the disorder tricho-odonto-onycho-hypohidrotic ectodermal dysplasia and suggested autosomal dominant inheritance. *ANOTHER syndrome* consists of hypohidrotic ectodermal dysplasia, freckling, enteropathy, onychodystrophy, atopy, and hypothyroidism. There is pulmonary and upper respiratory infection due to a ciliary defect. However, normal facies and dentition are noted. Zadik et al (121) reported the combination of hypothyroidism, sparse hair, unusual facies, hypohidrosis, oligodontia, and dermoid cysts. One should exclude the recessive syndrome of *cleft palate, congenital hypothyroidism, and spiked hair*. Tuffli and Laxova (111) reported a mother and son with hypohidrosis, scalp defect at the vertex, hypoplastic nipples, onychodysplasia, and possible abnormalities of dentition; in addition, the mother was unable to lactate.

Teeth often do not erupt in *cleidocranial dysplasia* and never in *GAPO syndrome*. Shokeir (97) described a family in which failure of most permanent teeth to erupt was inherited as an autosomal dominant disorder.

Autosomal dominant hidrotic ectodermal dysplasia (*Clouston syndrome*) is characterized by normal sweat and sebaceous gland function, sparse hair, severe nail dystrophy, palmar and plantar hyperkeratosis, skin hyperpigmentation, especially over the joints, and normal teeth. Another dominantly inherited hidrotic ectodermal dysplasia is characterized by sensorineural hearing impairment, polydactyly, syndactyly, nail dystrophy, and teeth that have conical crowns (61,90). The patients described by Mannkopf and Hanney (66) as having ectodermal dysplasia were of several types. Their case 7 had *focal dermal hypoplasia*. Patients possibly similarly involved are those described by Šalamon and Milicevic (91) and Friederich and Seitz (35).

An apparently hidrotic form has been described with breast aplasia (29a). A patient that defies classification was seen by RJG. She had extremely sparse body and scalp hair, including eyelashes and eyebrows. Nails and breasts were deficient and enamel was missing from the teeth.

Anhidrosis and middle-life-onset-neurolabyrinthitis has been described as an autosomal dominant disorder (45). Isolated anhidrosis may have autosomal recessive inheritance (64). Dominantly inherited hypohidrosis and hyperpigmentation with hyperkeratosis (*Naegli syndrome*) is a recognized disorder (102). Isolated amastia may be inherited as a dominant trait (40). A number of patients with so-called autosomal recessive HED undoubtedly represent still other disorders (18,56).

Laboratory aids. The dental radiograph is invaluable in determining whether teeth are congenitally absent, or whether they are present but unerupted.

Decreased sweating may be demonstrated by the starch-iodine method (Minor test) (16,30), by pilocarpine iontophoresis (80), by the use of agar plates containing silver nitrate and potassium chromate (39), by altered electrical resistance of the skin (56), or by the use of *o*-phthalaldialdehyde in xylene (116) (Fig. 13–64). Sweat pore counting may be carried out by direct observation or by use of silicone rubber (Fig. 13–65) or cellulose acetate (44,50,57,73,80,115,116). Happle and Frosch (43) suggested that the entire back be tested using the starch-iodine method, the areas of hypohidrosis following Blaschko lines.

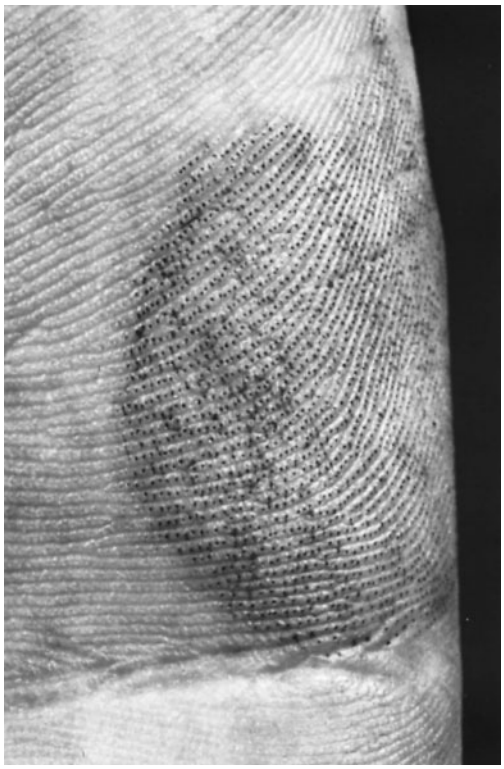

Fig. 13–64. *Hypohidrotic ectodermal dysplasia*. Sweating demonstrated by use of *o*-phthalaldialdehyde. (From J Verbov, Br J Dermatol 83:341, 1970.)

Frias and Smith (34) advocated counting sweat pores per linear centimeter, the normal number decreasing from about 40 in infancy to 20 in old age. Carrier mothers had fewer sweat pores, a finding confirmed by Verbov (116) and Settineri et al (96). Although few sweat pores or intradermal eccrine glands or ducts are found in male hemizygotes with the X-linked form, it has been stated that a significantly decreased number are noted in both affected males and females with the autosomal recessive type (77). Heterozygotes with the autosomal recessive form have somewhat reduced pore counts (55,77). Identification of functioning sweat pores in carriers can be done by thermography (14).

Davis and Solomon (24) described some degree of cellular immunodeficiency in hypohidrotic ectodermal dysplasia. IgA has been normal in serum and saliva (98).

Hypohidrotic ectodermal dysplasia has been diagnosed prenatally by biopsy on fetoscopy (4,11,38) and by molecular means using flanking genes (105).

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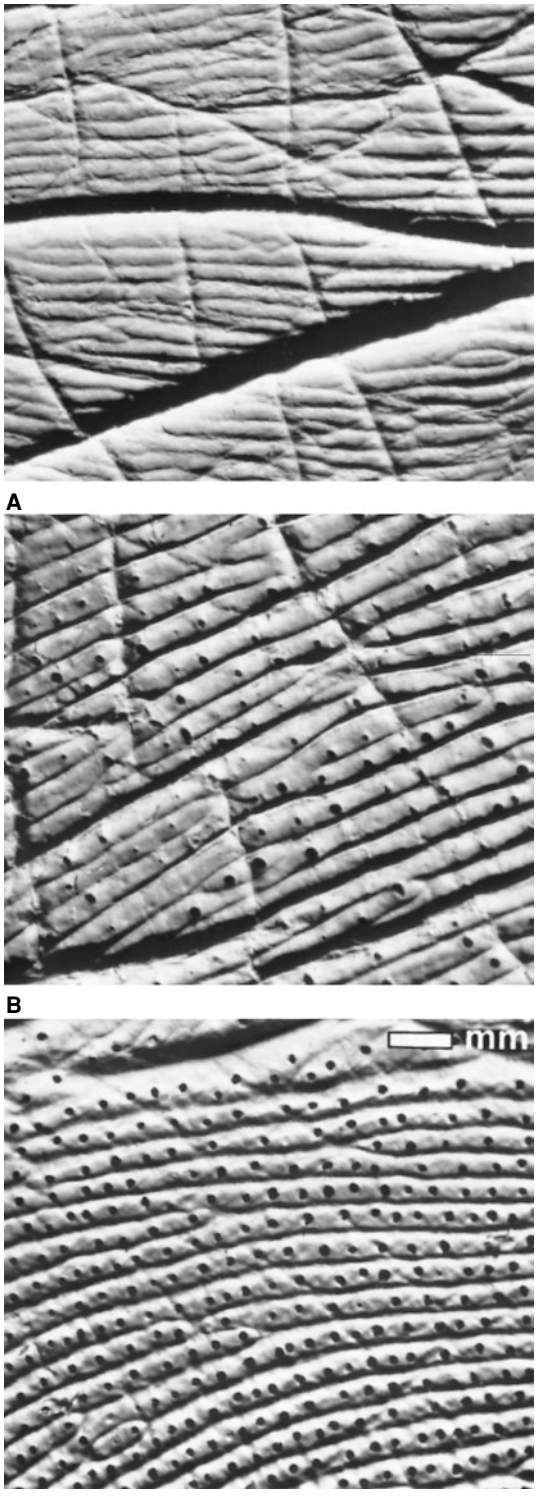

Fig. 13–65. *Hypohidrotic ectodermal dysplasia*. Sweating using silicone rubber technique. (A) Affected male. (B) Female heterozygote. (C) Normal individual. (From J Verbov, Br J Dermatol 83:341, 1970.)

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Hypohidrotic ectodermal dysplasia and central nervous system malformations

Soekarman and Fryns (2), in 1993, described a male with hypohidrotic ectodermal dysplasia, internal hydrocephalus, partial hypoplasia of the cerebellum, cleft palate, and severe mental retardation. The anterior fontanelle was widely patent. Fryns et al (1), in 1989, reported a somewhat similar condition (vide infra).

References (Hypohidrotic ectodermal dysplasia and central nervous system malformations)

1. Fryns JP et al: Hypohidrotic ectodermal dysplasia, primary hypothyroidism, and agenesis of the corpus callosum. J Med Genet 26:520–521, 1989.
2. Soekarman D, Fryns JP: Hypohidrotic ectodermal dysplasia, central nervous system manifestation, and distinct facial features: Confirmation of a distinct entity? J Med Genet 30:245–247, 1993.

Hypohidrotic ectodermal dysplasia, hypothyroidism, and agenesis of corpus callosum

Fryns et al (2), in 1989, described a male with unusual facies, hypohidrotic ectodermal dysplasia, hypothyroidism, frequent respiratory and eye infections, and agenesis of the corpus callosum. Severe mental retardation and enlarged head were evident. An ectopic thyroid was found at the foramen cecum. In 1993, Soekarman and Fryns (4) reported another male with similar findings. In addition, he had cleft palate, cerebellar hypoplasia, and dacryocystitis and suffered from recurrent respiratory infections. Devriendt et al (1), in 1996, noted another male with severe mental retardation, macrocephaly, agenesis of corpus callosum, cerebellar hypoplasia, and similar face. The mother was mildly affected. The facies was characterized by relative macrocephaly, frontal bossing, low nasal bridge, hypertelorism, downslanting palpebral fissures, sparse scalp hair, and eyebrows and lashes. The teeth were small and sometimes with conical crowns. The anterior fontanel is late in closing. One patient had trichorrhexis nodosa (3).

Inheritance may be X-linked or, possibly, autosomal dominant. All but one are males, and a mother was mildly affected in one case (1).

References (Hypohidrotic ectodermal dysplasia, hypothyroidism, and agenesis of corpus callosum)

1. Devriendt K et al: Mental retardation, distinct craniofacial dysmorphism, and central nervous system malformation: Confirmation of a syndrome. J Med Genet 33:224–226, 1996.
2. Fryns JP et al: Hypohidrotic ectodermal dysplasia, primary hypothyroidism, and agenesis of the corpus callosum. J Med Genet 26:520–521, 1989.
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Hypohidrotic ectodermal dysplasia, hypothyroidism, and ciliary dyskinesia (ANOTHER syndrome)

Pabst et al (3), Morris et al (2), and Pike et al (4) reported sibs with hypohidrotic ectodermal dysplasia, hypothyroidism developing in childhood, enteropathy, nail dystrophy, freckling (urticaria-like skin pigmentation), and atopy. The hair, wispy at birth, became lost. Pulmonary and upper respiratory infection due to a ciliary defect was found (3). Eyelashes and teeth were normal. This combination was called ANOTHER syndrome (*A*lopecia, *N*ail dysplasia, *O*phthalmic complication, *T*hyroid dysfunction, *H*ypohidrosis, *E*yelids and *E*nteropathy, and *R*espiratory tract infections) (4).

Inheritance appears to be autosomal recessive.

One must exclude *cleft palate, congenital hypothyroidism, and spiky hair* (1). This autosomal recessive disorder was also seen with choanal atresia and bifid epiglottis. Probably unrelated is the syndrome of congenital hypothyroidism, cleft palate, subpalpebral dermoid cysts, dacryostenosis, and oligodontia (5). Probably also unrelated is the recessive syndrome of *hypohidrotic ectodermal dysplasia, hypothyroidism, and agenesis of the corpus callosum*.

References [Hypohidrotic ectodermal dysplasia, hypothyroidism, and ciliary dyskinesia (ANOTHER syndrome)]

1. Bamforth JS et al: Congenital hypothyroidism, spiky hair, and cleft palate. J Med Genet 26:49–51, 1989.
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4. Pike MG et al: A distinctive type of hyphidrotic ectodermal dysplasia featuring hypothyroidism. J Pediatr 108:109–111, 1986.
5. Zadik Z et al: Case report 112: Dermoid cysts, hypothyroidism, cleft palate, and hypodontia. J Clin Dysmorphol 1(4):24–25, 1983.

Hypohidrotic ectodermal dysplasia, unusual facies, cataracts, and mental and motor retardation

Freire-Maia et al (1), in 1975, reported a girl with trichodysplasia (dry brittle hair, absent eyebrows and lashes, hypohidrosis, and absent body hair), frontal bossing, depressed nasal bridge, normal teeth, follicular keratosis of skin, hyper- and hypochromic skin pigmentation, and nuclear cataracts. Psychomotor retardation and growth retardation were evident.

Reference (Hypohidrotic ectodermal dysplasia, unusual facies, cataracts, and mental and motor retardation)

1. Freire-Maia N et al: A syndrome of hypohidrotic ectodermal dysplasia with normal teeth, peculiar facies, pigmentary disturbances, growth retardation, bilateral nuclear cataract, and other signs. J Med Genet 12:308–310, 1975.

Ectodermal dysplasia and cleft lip/palate (Margarita Island syndrome)

Abramovitz-Ackerman et al (1) described a disorder seen in 27 patients from seven families from Margarita Island off the coast of Venezuela.

Hair is sparse, short, and brittle. Eyebrows and lower eyelashes are scant. There is complete alopecia by adulthood (2).

Over 90% had corkscrew hair and follicular plugging of the scalp. Seventy-five percent had keratosis pilaris, xerosis, and eczema. Palmoplantar keratoderma (100%), cutaneous syndactyly (65%), and nail dysplasia (60%) were seen. Sweating was normal.

Malar hypoplasia, anteverted pinnae, cleft lip/palate (65%) with broad or flat philtrum and dental abnormalities were also frequent.

Inheritance is autosomal recessive. The frequency on the island is 1 per 2,000. The gene has been mapped to 11p23 (3).

There is distinct resemblance to *Zlotogora-Oğur syndrome*. They are allelic (4).

References [Ectodermal dysplasia and cleft lip/palate (Margarita Island syndrome)]

1. Abramovitz-Ackerman W et al: Cutaneous findings in a new syndrome of autosomal recessive ectodermal dysplasia with corkscrew hairs. J Am Acad Dermatol 27:917–921, 1992.
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3. Suzuki K et al: Linkage disequilibrium mapping of the gene for Margarita Island ectodermal dysplasia (ED4) to 11q23. Am J Hum Genet 63:1102–1107, 1998.
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"Pure" hair-nail-type ectodermal dysplasias

"Pure" ectodermal dysplasias are developmental disorders affecting only tissues of ectodermal origin. Three different pure ectodermal dysplasias involving only hair and nails have been described to date (1,3,7,8).

The first of these three pure ectodermal dysplasias is known as "pili torti and onychodysplasia," an autosomal recessive disorder (3). This condition presents with congenital onychodystrophy and severe hypotrichosis, nearly resulting in atrichia universalis. The hair is brittle. On scanning electron microscopy, it shows twisting.

The second pure ectodermal dysplasia affecting nails and hair is an autosomal dominant condition described as "hair-nail dysplasia" (7). This condition is characterized by varying degrees of hypotrichosis with thin, fragile, slow-growing, sparse hair and nail dystrophy with short, fragile, spoon-shaped nail plates. Hypotrichosis involves the whole body. The scanning electron microscopy reveals "stretched monilethrix hairs."

The third type has congenital nail dystrophy, hypotrichosis in frontotemporal regions of the scalp, associated with folliculitis decalvans of the nape of the neck. It has been reported in a woman and her son, suggesting autosomal dominant inheritance (1). In this condition, irregular scleroatrophic patches lacking hair and follicles are present at the vertex of the scalp and nape. These are associated with follicular pustules at the periphery. The nail abnormalities are observed on all the digits. They exhibit micronychia, onychorrhexis, and a triangular shape of the nail plate resulting in a hypoplastic and dystrophic appearance. The main finding in the toenails is micronychia and onychorrhexis (1). Scanning electron microscopy of hairs demonstrated abnormal hair shafts with longitudinal grooves and constrictions, resulting in a "branch of dry wood" appearance. Twisting along the longitudinal axis of the shaft was observed, and hair casts were noted. There was also an abnormally increased density in cuticular cells.

The differential diagnosis comprises the "onychotrichodysplasia and chronic neutropenia" syndrome, an autosomal recessive ectodermal dysplasia with congenital hypotrichosis, trichorrhexis nodosa, and nail dystrophy (6,9). Other previously described disorders should also be considered (2,4,5).

References ("Pure" hair-nail–type ectodermal dysplasias)

1. Barbareschi M et al: Family with "pure" hair-nail ectodermal dysplasia. Am J Med Genet 72:91–93, 1997.
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4. Christianson AL, Fourie S: Family with autosomal dominant hidrotic ectodermal dysplasia: A previously unrecognized syndrome? Am J Med Genet 63: 549–553, 1996.
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6. Hernández A et al: Autosomal recessive onychotrichodysplasia, chronic neutropenia and mental retardation. Clin Genet 15:147–152, 1979.
7. Pinheiro M, Freire-Maia N: Hair-nail dysplasia—a new pure autosomal dominant ectodermal dysplasia. Clin Genet 41:296–198, 1992.
8. Pinheiro M et al: New cases of dermoodontodysplasia? Am J Med Genet 36:161–166, 1990.
9. Verhage J et al: A patient with onychotrichodysplasia, neutropenia and normal intelligence. Clin Genet 31:374–378, 1987.

Ectodermal dysplasia and cerebellar ataxia

Klingmüller and Kirchhof (3) reported four males affected with what appears to be typical hypohidrotic ectodermal dysplasia, but, in addition, they exhibited cerebellar ataxia, probably independently inherited.

Georgmaneanu et al (2) described a female with progressive spinocerebellar ataxia, curly thin short dense hair exhibiting monilethrix and a somewhat unusual facies (hypertelorism, flattened nose with wide base, prominent nostrils, large mouth, thick lips, and small, widely spaced teeth). Rushton and Genel (4) described male and female sibs with ataxia due to olivopontocerebellar degeneration, mental retardation, hearing loss, hypogonadotrophic hypogonadism, short stature, and widely spaced teeth with conical crown form. Baraitser et al (1) reported two brothers with cerebellar ataxia and an ectodermal dysplasia characterized by sparse thin hair, deep-set eyes, triangular face, pes cavus, dysarthria, normal intelligence, inguinal hernia, and oligodontia.

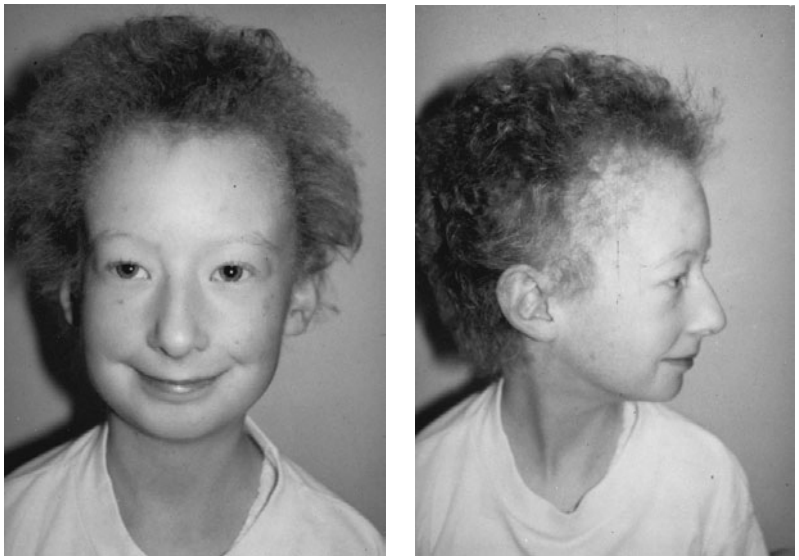
Although grouped and compared by Baraitser et al (1), we see little resemblance among these families.

References (Ectodermal dysplasia and cerebellar ataxia)

1. Baraitser M et al: Cerebellar ataxia and ectodermal dysplasia in brothers. J Med Genet 30:515–517, 1993.
2. Georgmaneanu M et al: Spinocerebellare Ataxie assoziiert mit Monilethrix, eigenartigen Gesichtszügen und Zahnanomalie. Monatsschr Kinderheilkd 124: 647–649, 1976.
3. Klingmüller G, Kirchhof JK: Über die erbliche ektodermale Dysplasie mit Anhidrosis und cerebellarer Heredoataxie im Sinne einer Friedreichschen Erkrankung. Hautarzt 5:351–357, 1954.
4. Rushton AR, Genel M: Hereditary ectodermal dysplasia, olivopontocerebellar degeneration, short stature, and hypogonadism. J Med Genet 18:335–339, 1981.

Ectodermal dysplasia and arthrogryposis

Coté et al (2), in a brief note, described a syndrome of arthrogryposis and ectodermal dysplasia. Several additional examples (1,3,5) have been added. We suspect that the case described by Parker et al (4) has the same disorder.



A B

Fig. 13–66. *Ectodermal dysplasia and arthrogryposis*. (A,B) Note thin sparse hair which exhibits pili torti. (Courtesy of ID Young, Nottingham, England.)

Stature has been below the 3rd centile. Generalized arthrogryposis has been a nearly consistent feature. Kyphoscoliosis has also been noted (1,5). Dilated cardiomyopathy was documented once (4).

The skin is thin and bruises easily (2,5). Some patients have hypohidrosis (3,5). The nails break longitudinally (2,5). The hair may be thin and sparse with pili torti (1–3) (Fig. 13–66). The teeth may be reduced in number (5) and have amelogenesis imperfecta (2,5).

Inheritance is autosomal recessive, there being affected sibs and parental consanguinity (5).

References (Ectodermal dysplasia and arthrogryposis)

1. Alves AFP et al: An autosomal recessive ectodermal dysplasia syndrome of hypotrichosis, onychodysplasia, hyperkeratosis, kyphoscoliosis and other manifestations. Am J Med Genet 10:213–218, 1981.
2. Coté GB et al: Arthrogryposis and ectodermal dysplasia. Hum Hered 32: 71–72, 1982.
3. Ladda RL et al: Ectodermal dysplasia with arthrogryposis and cleft lip and palate: A new combination. Am J Hum Genet 45:A51, 1989.
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5. Stoll C et al: Arthrogryposis, ectodermal dysplasia, and other anomalies in two sisters. Genet Couns 3:35–39, 1992.

Ectodermal dysplasia, syndactyly, and mental retardation

Ilyina et al (1) noted a female with mild mental retardation, aplasia cutis congenita of scalp, large palpebral fissures, broad nasal bridge, open mouth, dysmorphic pinnae, syndactyly of fingers 3–4/toes 2–3, and severe onychogryposis. The hair was short and stiff with sparse eyebrows. There was some resemblance to *Margarita Island syndrome*.

Reference (Ectodermal dysplasia, syndactyly, and mental retardation)

1. Ilyina HG et al: "New" ectodermal dysplasia with mental retardation and syndactyly. Am J Med Genet 58:345–347, 1995.

Ectodermal dysplasia, lipoatrophic diabetes, and acrorenal field defect (AREDYLD syndrome)

Pinheiro et al (2), in 1983, employed a best-forgotten acronym, AREDYLD, to report a syndrome of lipoatrophic diabetes, ectodermal dysplasia (generalized hypotrichosis, natal teeth, dysplastic deciduous teeth, absent permanent dentition, aplasia/hypoplasia of breasts, and mild hypoplasia of renal calyx) in a female. The fifth metacarpal was markedly short in one hand. Other anomalies included hepatosplenomegaly, hypoplasia of labia minora, enlarged clitoris, bowing of tibia, and mild scoliosis. Breslau-Siderius (1) reported a female with ectodermal dysplasia, lipoatrophy, diabetes mellitus, and amastia. Mesiodens and oligodontia were also found. There was also decreased sweating.

Parental consanguinity was found in one case (2), but both were isolated female patients.

References [Ectodermal dysplasia, lipoatrophic diabetes, and acrorenal field defect (AREDYLD syndrome)]

1. Breslau-Siderius EJ et al: Ectodermal dysplasia, lipoatrophy, diabetes mellitus, and amastia: A second case of the AREDYLD syndrome. Am J Med Genet 44:374–377, 1992.
2. Pinheiro et al: AREDYLD: A syndrome combining an acrorenal field defect, ectodermal dysplasia, lipoatrophic diabetes, and other manifestations. Am J Med Genet 16:29–33, 1983.

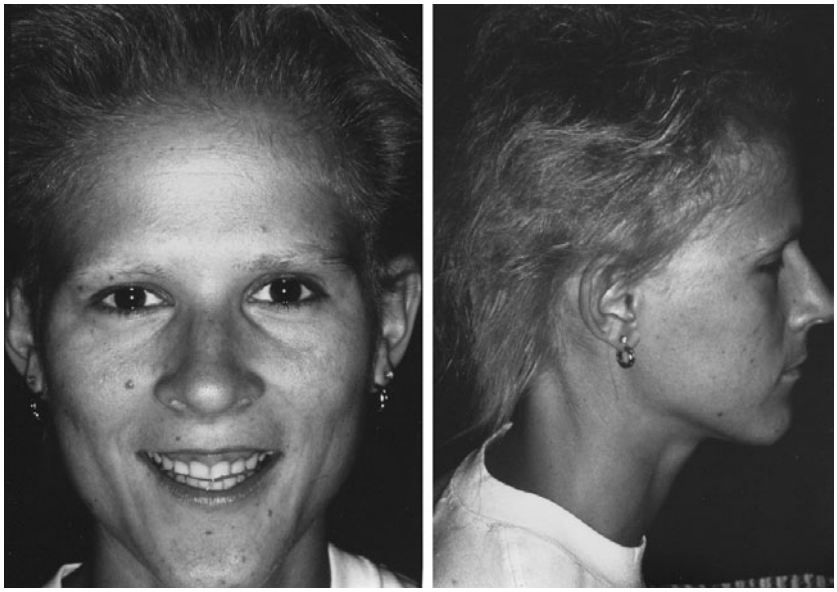
Hidrotic ectodermal dysplasia (Clouston syndrome)

Jacobsen (9), in 1928, first reported a family with atrophic nails, sparse, absent, or downy hair, and rough scaly skin. Clouston (2), in 1929, found that the patient belonged to a large French Canadian kindred. There are many subsequent reports of this and other families (3–5,7, 10,12,14,17,19–21). Rajagopalan and Tay (17) described a large Chinese kindred. See Fraser and Der Kaloustian (3a) for history.

Inheritance is autosomal dominant. Expression is variable, dysplastic nails being the most common feature. The gene has been mapped to 13q11–q12.1 (11,11a,16).

Body hair, in general, is fine, brittle, or sparse, and scalp, axillary, and pubic hair is often absent. Females are often completely bald, while males are more variable, hair loss ranging from focal alopecia to total balding (Fig. 13–67). Palmoplantar hyperkeratosis (keratoderma) is often present. The extensor surface of the finger joints may occasionally be hyperpigmented. Sweating is normal. The nails are thick, discolored, and hyperconvex with onycholysis (Fig. 13–68). The fingers may be clubbed. Ultrastructural studies of hair showed disorganizations of hair fibrils with loss of cuticular cortex (3). The teeth are normal (7).

Halal et al (6) reported autosomal recessive inheritance of similarly affected individuals who also had mental retardation. Turnpenny et al (18) described autosomal dominant inheritance of hidrotic ectodermal dysplasia affecting the skin and hair. However, oligodontia, natal teeth, and acanthosis nigricans were also present. Nail dystrophy was mild.

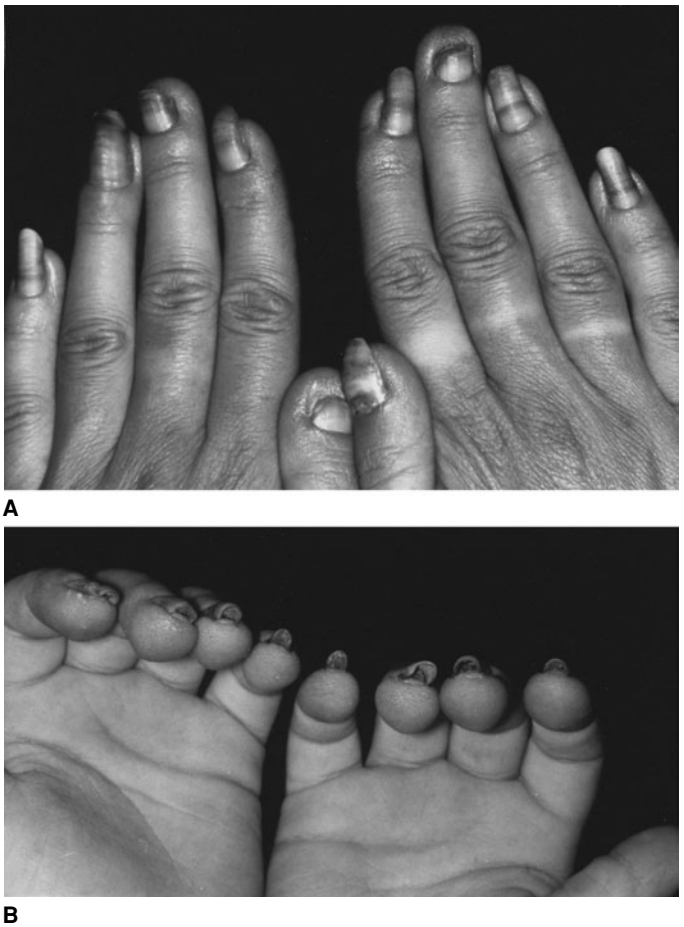


A B

Fig. 13–67. *Hidrotic ectodermal dysplasia* (*Clouston syndrome*). (A,B) Sparse eyebrows and scalp hair, normal dentition. (From SJ Hassed et al, Am J Med Genet 61:274, 1996.)

Christianson and Fourie (1) reported an autosomal dominant syndrome resembling Clouston syndrome, but there was absence of hyperkeratosis of the palms and soles and no skin abnormalities. Hazen et al (8) reported a hidrotic ectodermal dysplasia in which there were premature cortical cataracts and angular cheilitis. We suspect an *endocrine candidosis syndrome*. Pinheiro and Freire-Maia (15) described an autosomal dominant hidrotic ectodermal dysplasia characterized by hypotrichosis but mildly dystrophic nails. Mégarbané et al (13) reported a large kindred with autosomal recessively inherited hidrotic ectodermal dysplasia characterized by marked oligodontia, fine hair, and dystrophic nails.

Fig. 13–68. *Hidrotic ectodermal dysplasia* (*Clouston syndrome*). (A) Dystrophic nails of proposita. (B) Dystrophic nails of daughter of proposita. (From SJ Hassed et al, Am J Med Genet 61:274, 1996.)



A

B

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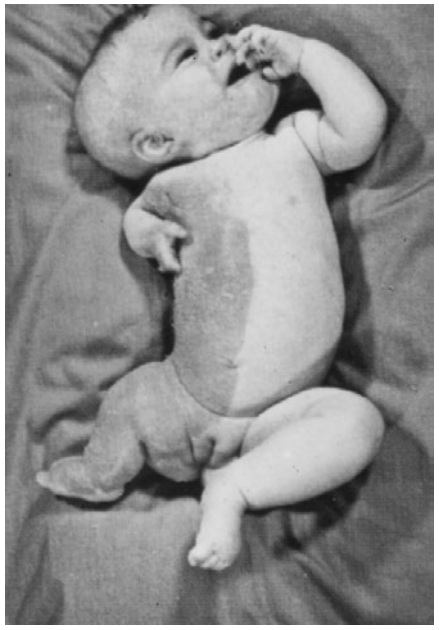

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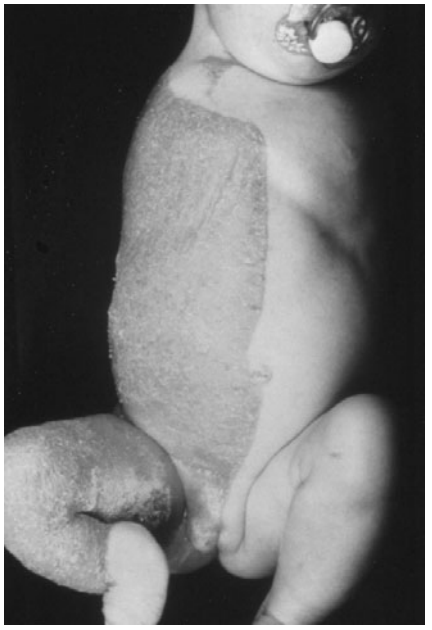

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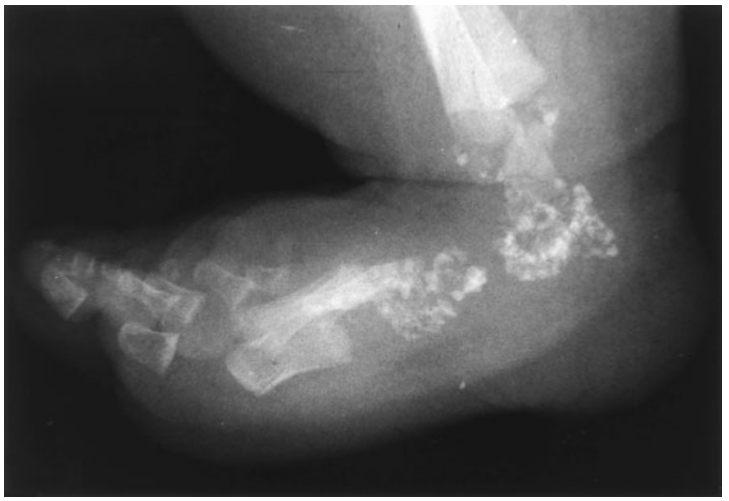

C

Fig. 13–69. *CHILD syndrome*. (A,B) Infant showing hypotrophy of right side, sharply limited by midline. (C) Severe chondrodysplasia punctata as part of CHILD syndrome. (A,B from R Happle, J Am Acad Dermatol 23:763, 1990. C courtesy of D Grange, St. Louis, Missouri.)

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CHILD syndrome

Zellweger and Uehlinger (25) appear to be the first to describe an "osteochondromatosis with nevus ichthyosiformis" that was unilateral. Happle et al (12) coined the term CHILD syndrome to represent *C*ongenital *H*emidysplasia, *I*chthyosiform erythroderma, and *L*imb *D*efects.

About 35 examples have been described (1–25), all but two (16,25) being females. Happle et al (10,14,164) postulated that the disorder is X-linked dominant, lethal in the male, and that survival depends on the child being a mosaic (9). Mother-to-child transmission has been noted (14). Affected sibs have been reported (6). Grange et al (7) have shown a deficiency of 3β-hydroxysteroid-$\triangle^8$,$\triangle^7$-isomerase in patients with CHILD syndrome. This makes CHILD syndrome and X-linked chondrodysplasia punctata to be allelic. Mutations in NSDHL, the gene that encodes the X-linked component of sterol-4-demethylase complex, have been demonstrated (19). Happle et al (16a) believe that diagnosis in the case of Grange et al (8) was incorrect and that there is only the NSDHL gene involved.

Skin. Erythematous scaly plaques are present at birth unilaterally and sharply demarcated by the midline. The plaques may extend with age. The plaques follow the lines of Blaschko (Fig. 13–69). The ichthyosiform nevus has a predilection for body folds. The lesions may also disappear with age.

Nails. There is suprabasal staining of basal layer keratin (AE1) (4,17,18). Presumably, the basal cells fail to switch to produce a more differential keratin. Involucrin-positive cells are greatly increased.

Extremities. There is ipsilateral shortening of one or both limbs. Hypoplasia of long bones is most common, but one can also find syndactyly, polydactyly, scoliosis, contractures, and hypoplasia/aplasia of hand or foot (3,21).

Punctate epiphyseal calcification may be found in the involved limbs.

Other findings. Malformed kidney has been described (3,22).

Diagnosis. Moss and Burn (20) suggested that CHILD syndrome was the same as ILVEN syndrome. This was vigorously denied by Happle (12), who, we believe, convincingly argued that they are a distinctly different form of nevus (*I*nflammatory *L*inear *V*errucous *E*pidermal *N*evus).

References (CHILD syndrome)

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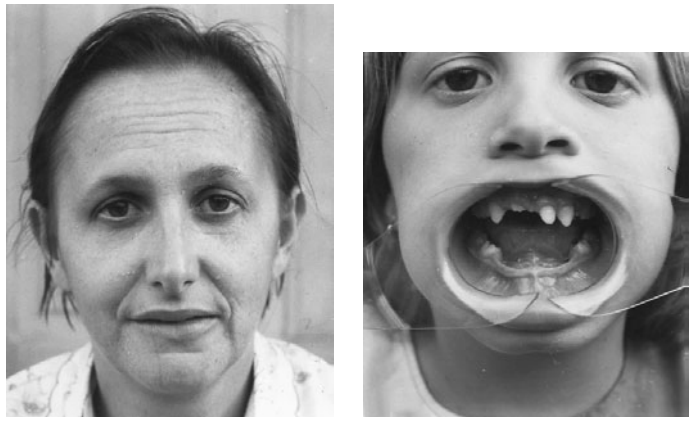
Hair-nail-skin-teeth dysplasias (dermo-odonto-dysplasia, pilo-dento-ungular dysplasia, odonto-onycho-dermal dysplasia, odonto-onychial dysplasia, tricho-dermo-dysplasia with dental alterations)

There are an inordinately large number of rare disorders involving dysplasia of hair, nails, skin appendages, and teeth in binary, ternary, or quaternary combination (1,2,4–10). These have been dealt with exhaustively by Freire-Maia and Pinheiro (3). Only a few can be briefly described here (2,5–10).



A B

Fig. 13–70. *Tricho-dermo-dysplasia with dental alterations*. (A) Hypotrichosis of scalp, sparse lateral eyebrows. (B) Severe oligodontia in daughter of woman seen in A. (From M Pinheiro et al, Clin Genet 29:332, 1986.)

Pinheiro et al (6) reported sibs with hair loss ranging from almost total alopecia involving scalp, eyebrows, lashes, and axillary and pubic hair to less severe involvement: finger and toenail dystrophy, palmoplantar hyperkeratosis, supernumerary nipples, and enamel hypoplasia (Fig. 13–70). All had short stature, and two sibs had a frontoparietal skull defect. Autosomal recessive inheritance was suggested. The disorder was termed *tricho-dermo dysplasia with dental alterations*.

We are not entirely convinced that the disorder is different from *odonto-onycho-dysplasia* with alopecia also reported by Pinheiro et al (7), except for greater severity in the latter. They described sisters with probably consanguineous parents. At birth, both sibs had sparse scalp hair that soon fell out. The sparse body hair distribution was similar to that noted in *tricho-odonto-onychial dysplasia*. Hypodontia, microdontia, and enamel hypoplasia were found (Fig. 13–71).

Pinheiro et al (8) described an autosomal dominant disorder with trichodysplasia, hypodontia, onychodysplasia, and bilateral inward deflection of the fourth toes. The disorder was termed *tricho-dermo-dysplasia*. A four-component disorder was titled *tricho-odonto-onycho-dermal syndrome* (5).

Pinheiro and Freire-Maia (4) reported a four-generation autosomal dominantly inherited syndrome termed *dermo-odonto-dysplasia*. Thin, fragile, or brittle finger and toe nails, palmoplantar xeroderma, oligodontia, and/or microdontia with persistence of deciduous teeth were found (Fig. 13–72A,B). The hair was dry and the beard and axillary and pubic hair were slow growing. There was variable expressivity. Differentiation must be made from the *Witkop tooth-nail syndrome*.

Fadhil et al (2) described two families with a syndrome of hyperkeratosis of palms and soles with hyperhidrosis in these areas; somewhat scaly dry skin, erythema, and telangiectasia over the nose and malar areas; and peg-shaped maxillary central incisors. The term chosen was *odonto-onycho-dermal dysplasia*. Inheritance appears to be autosomal recessive (Fig. 13–72C–F).

References [Hair-nail-skin-teeth dysplasias (dermo-odonto-dysplasia, pilo-dento-ungular dysplasia, odonto-onycho-dermal dysplasia, odonto-onychial dysplasia, tricho-dermo-dysplasia with dental alterations)]

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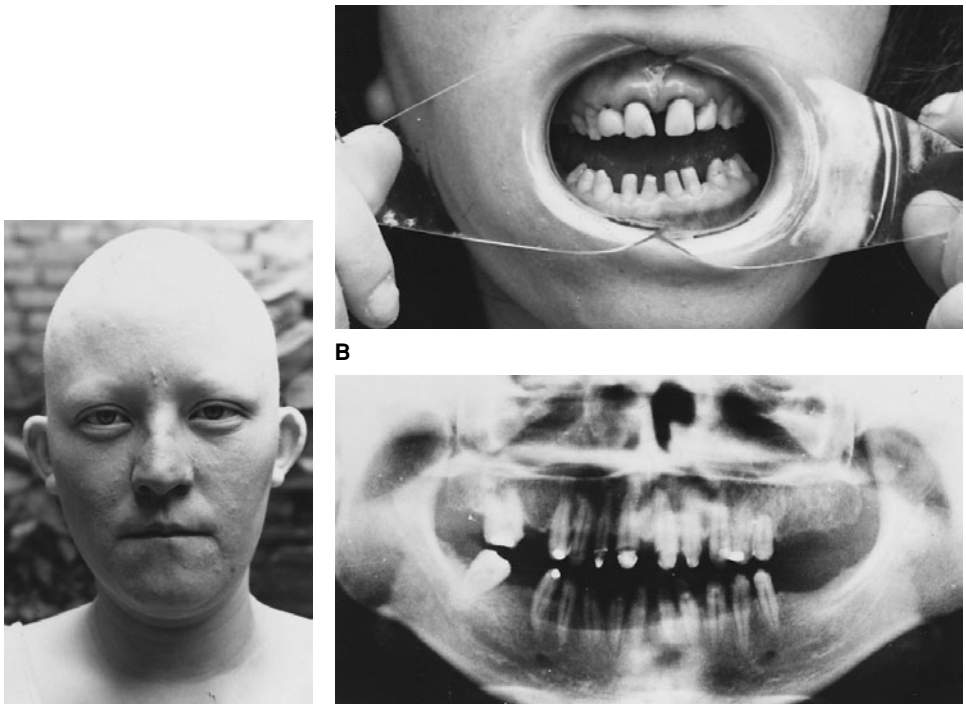

Fig. 13–71. *Odonto-onycho-dysplasia with alopecia*. (A) Total alopecia. (B,C) Oligodontia. (Courtesy of M Pinheiro et al, Curtitiba, Brazil.)

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Incontinentia pigmenti (Bloch-Sulzberger syndrome)

Incontinentia pigmenti (IP) is a disturbance of skin pigmentation sometimes associated with malformation of the eye, teeth, skeleton and other systems. Although it may have been first noticed by Garrod (17) in 1906, credit is usually given to Bardach (2), Bloch (5), and Sulzberger (63) for clearly defining it in the 1920s. Major features include vesicular, verrucous, and pigmented macular lesions of the skin. At least 900 cases have been reported. There are several good surveys (10,33).

A sporadic pigmentary disorder associated with X/autosome translocation involving Xp11.21 has been termed IP1 (4,18,20,26,29). Linkage studies suggest that the classic disorder (IP2) maps to Xq28 (54,55,58). There are some large pedigrees (13,60,72). Frequency has been estimated to be 1:40,000 females (9). Sybert (63) stated that IP1 is not incontinentia pigmenti, but is an "X-autosome translocation associated with pigmentary abnormality."

The syndrome is X-linked dominant and essentially lethal in males (10,32,35,45). In a personal communication, RI Kelley (Jan. 2000) indicated that familial and nonfamilial forms have different forms of sterol defects: familial-sterol demethylase deficiency; sporadic-sterol isomerase deficiency). The gene for IP2 is called *NEMO*. It encodes the gamma subunit of the IKK complex in the NF-kB pathway. Male patients with *NEMO* mutations present with osteopetrosis, lymphedema, hypohidrotic ectodermal dysplasia, and immune deficiency (37,58a). Two to three percent of IP patients are males (7,9,37,42,68,77) with phenotypes identical to those of affected females (3). A number of authors (16,42,44,46,47,70) reported males with IP and XXY Klinefelter syndrome, and Scheurle (53), in a 1999 survey of 49 affected males, found that 5 had Klinefelter syndrome. To explain affected males with normal male karyotype, it has been suggested that only part of the male cells carries the mutated X. This form of mosaicism can result from a genetic error (half chromatid mutation) during gametogenesis (35). Others have disputed this (24,25). A half-chromatid back-mutation is an alternative hypothesis to explain the occurrence of affected males (34). Early somatic mutation in embryogenesis is another possibility, as is unstable premutation (69). There have been a few examples of male-to-female transmission (14,59).

Kirchman et al (32) reported 2 paternally related half sisters with incontinentia pigmenti. The father was clinically normal, with a 46,XY normal karyotype. Following confirmation of paternity, X-inactivation studies indicated that the paternal X chromosome was preferentially inactivated in each girl, implying that the father was a gonadal mosaic for the IP mutation.

Harris et al (23) reported evidence of extensive skewed X inactivation in blood from 35% of IP patients. This frequency of skewed inactivation was seen in both familial and sporadic cases. Wieacker et al (71) demonstrated that inactivation of the X chromosome carrying the IP gene has a proliferative advantage in the cell population. Migeon et al (40) found that cells that express the mutated allele are eliminated from skin fibroblast cultures and, to varying degrees, from hematopoietic tissues. Harris et al (23) presented arguments against cell selection during early embryogenesis as the explanation for the observed skewed inactivation. Parrish et al (43) reported completely skewed patterns of X-inactivation in the peripheral blood leukocytes of 98% of affected females. They also reported that new mutations were twice as common in paternal X chromosomes as in those of maternal origin.

Skin. Cutaneous abnormalities serve as a basis for the four clinical stages of the condition. However, all stages need not necessarily occur, and several stages may overlap. The first stage present at or soon after birth is characterized by linear or grouped vesicles on the extremities or trunk, sparing the face. By the end of the first month, the vesicles may disappear, recur, or be replaced by irregularly distributed violaceous papules and inflammatory lesions. The first stage clears by four months. This is accompanied by massive infiltration of eosinophils into the epidermis and marked peripheral leukocytosis with up to 65% eosinophils. The second

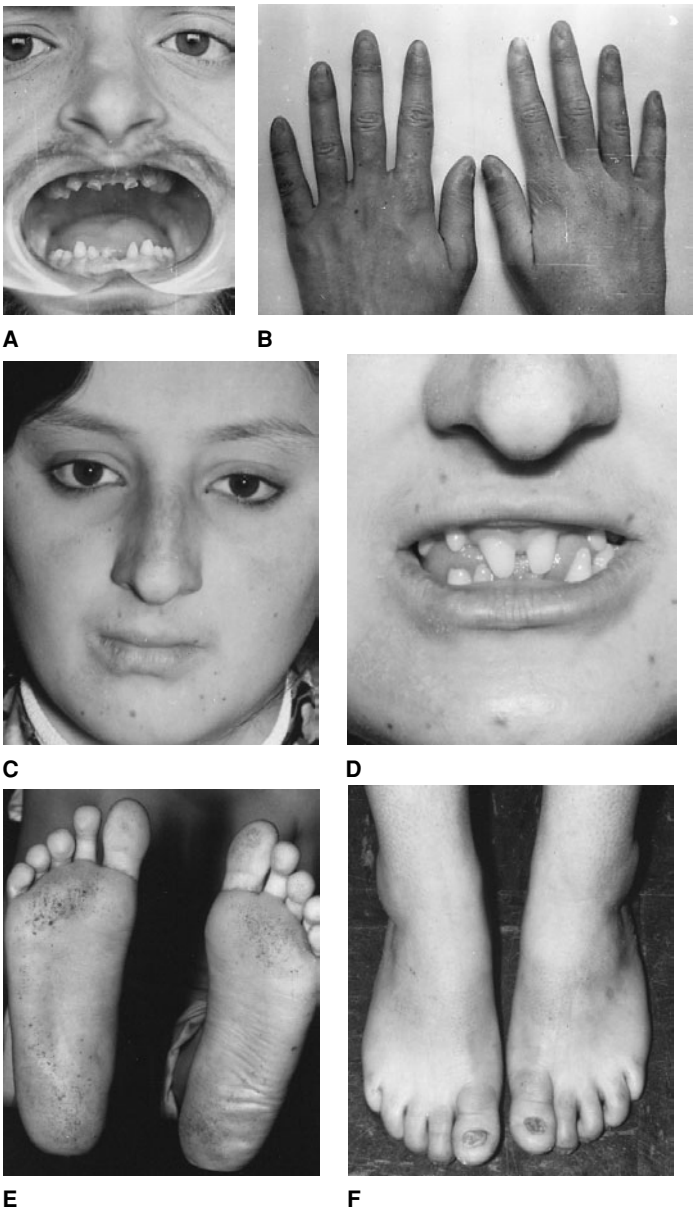


Fig. 13–72. *Dermo-odonto-dysplasia*. (A) Oligodontia and/or microdontia with persistence of deciduous teeth. (B) Hypoplastic thin, fragile fingernails. Odonto-onycho-dermal dysplasia. (C) Patient showing mild telangiectasia of nose and malar areas. (D) Peg-shaped anterior teeth. (E,F) Dystrophic nails and hyperkeratosis of soles. (A,B from M Pinheiro and N Freire-Maia, Clin Genet 24:58, 1983; C-F from M Fahdil et al, Am J Med Genet 14:335, 1983.)

stage is characterized by hyperkeratotic, warty lesions on the dorsal surface of the digits, knuckles, joints, and limbs. Although usually manifest at about 1 month of age, they may be present at birth. Resolution is usually spontaneous, with clearing being complete by 6 months in 80%, but rarely recurrent throughout childhood (41).

The third stage usually has onset between the third and sixth months of life, although it, too, may be present at birth. It is characterized by brownish-gray macules arranged in a reticulated pattern or in streaks, whorls, or patches more often on the trunk (especially the axillae and groin), although these lesions may occur in sites previously involved by vesicular or verrucous lesions, areas not significantly involved in either of the first two stages. The pigmentation tends to follow Blaschko lines (22). Lenz et al (36) reported unilateral involvement. Pigmentation, beginning to fade at about 2 years, usually disappears by the end of the second decade. It may resolve so completely as to be unnoticeable, although

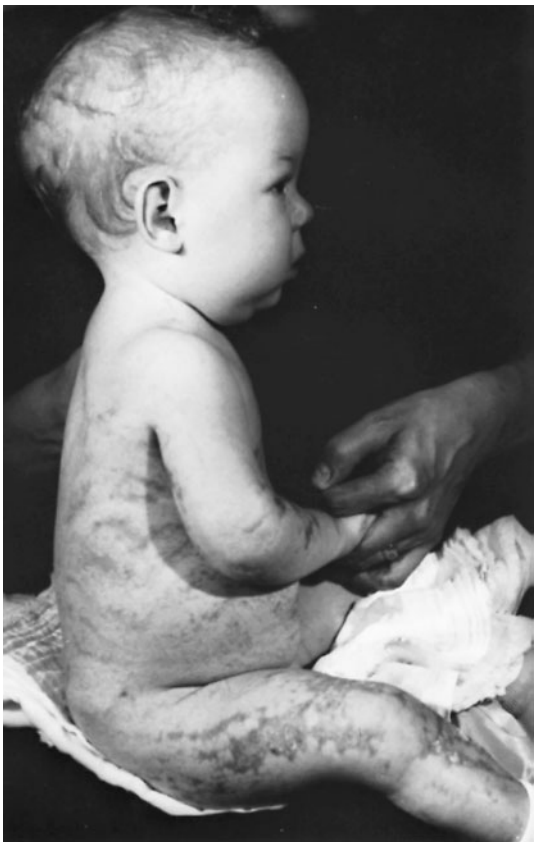
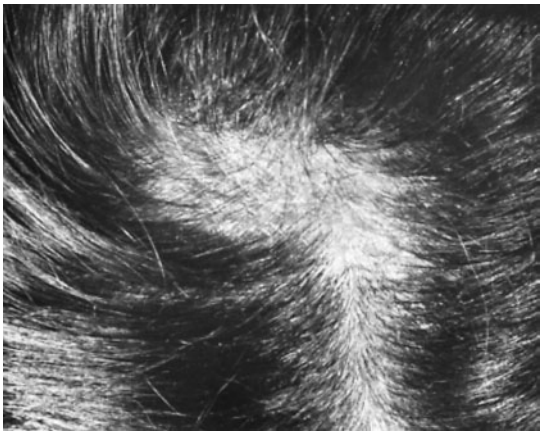


Fig. 13–73. *Incontinentia pigmenti*. Ten-month-old female manifesting bullae, verrucae, and whorled and linear distribution of pigment. Also note area of crusting and scarring on thigh.

some residuum is often present for life (74) (Fig. 13–73). The fourth stage is "burnt out" incontinentia pigmenti characterized by pale, hairless depigmented lesions of the posterior calves (73,76).

Alopecia of the atrophic, scarring (pseudopelade) type is seen near the apex of the crown in about 40% (Fig. 13–74). Occasionally, wiry and coarse patches of hair are noted. In about 35%, the fingernails are mildly dystrophic (ridging or splitting) and breasts are asymmetric. Painful subungual tumors have been reported (36,56,57). There may be underlying bony resorption (56). Rott (50) reported partial or complete lack of sweat pores on the palms and fingers of 5 female probands, consistent with lyonization of the X chromosome.

Fig. 13–74. *Incontinentia pigmenti*. Alopecia of pseudopelade type located at crown of head.



On light microscopic examination, the vesicular stage is characterized by intraepithelial vesicles containing eosinophils; spongiosis and individual dyskeratotic epithelial cells are also noted. Eosinophils are found in the connective tissue. The second stage is manifested by hyperkeratosis, acanthosis, papillomatosis and epithelial dyskeratosis. Basal cells are vacuolated and their pigment granules are decreased in number. A mild chronic inflammatory cell infiltrate is seen in the connective tissue as well as in the epithelium. In the third stage, extensive melanin deposits are found with melanophages in the upper dermis, usually associated with a decrease in basal cell pigmentation. Ultrastructural changes in the skin have been described (8,21,52,76).

Eyes. Ophthalmologic abnormalities are noted in 25%–35% (15,39,45,49). The most common alterations include strabismus (35%), congenital cataract (5%), optic atrophy, retrolental mass (2%) (described as persistent hyperplastic primary vitreous, pseudoglioma, or retrolental fibroplasia), retinal detachment, microphthalmos (3%), retinal telangiectasia, and irregular hyperpigmentation of the conjunctiva, iris, and retina (10%) (15).

Central nervous system. Central nervous system involvement occurs in 35%–40%. Mental retardation (15%), microcephaly (5%), cerebral infarction, hydrocephalus, paresis of eye muscles, and convulsive episodes (15%) have been reported (30). CT scans have demonstrated brain atrophy (1). Those with neonatal seizures appear to have a higher rate of mental retardation (41).

Oral manifestations. Oral changes limited to the teeth have been noted in 90% (9). Pegged or conically crowned teeth (30%), congenitally missing teeth (40%), and delayed eruption are characteristic (19,36) (Fig. 13–75). Both primary and permanent dentitions are affected. Congenitally missing and malformed teeth create diastemas. Cleft lip/palate has been reported (6,51,75), but may be due to chance.

Other abnormalities. Breast hypoplasia, displaced breast, and supernumerary nipples are increased in frequency.

Various tumors have been described: retinoblastoma, Wilms tumor, acute myelocytic leukemia, paratesticular rhabdomyosarcoma (47). Several reports have described IP patients who develop many unusual and recurrent infections, suggesting that immunodeficiency may be characteristic. See p. 551, *NEMO* gene discussion. Abnormalities of one or more serum immunoglobulins have been found in some patients (11), as have defects in neutrophil chemotaxis (11,28) and lymphocyte transformation (28). An increased number of chromosomal breaks has been described by some investigators (31) but not by others (24).

Differential diagnosis. Skin changes present in early infancy must be distinguished from those of congenital syphilis, *epidermolysis bullosa*, bullous impetigo, contact dermatitis, *dermatitis herpetiformis*, and verrucous nevus. Incontinentia pigmenti should be differentiated from hypomelanosis of Ito (incontinentia pigmenti achromians) and *Naegeli syndrome*, a dominant disorder (27,61).

Hypomelanosis of Ito (48,62,65) is a neurocutaneous syndrome characterized by development of linear areas of cutaneous hypopigmentation within the first year of life, as well as neurologic, ophthalmologic, and musculoskeletal anomalies. No preceding bullous, verrucous, or hyperpigmented lesions are noted. Consistent dental abnormalities have not been reported to be associated with this disorder. There is mounting evidence that hypomelanosis of Ito represents a nonspecific sign of somatic mosaicism (66).

Dental anomalies in IP resemble those of other ectodermal dysplasias, such as *Ellis–van Creveld syndrome, Witkop tooth-nail syndrome*, and *hypohidrotic ectodermal dysplasia.* In congenital syphilis, the primary dentition is rarely involved (except possibly a deciduous molar) because of the inability of the spirochetes to pass the placental barrier until at least the eighteenth week of pregnancy. The incisors in congenital syphilis are never conical; rather, the incisal edge is narrower than the cervical portion of the crown. In hypohidrotic ectodermal dysplasia, many more teeth are congenitally missing and those present are more severely malformed than in IP. In Ellis–van Creveld syndrome other oral anomalies not present in IP are found: fusion of the lip with the adjacent alveolar ridges and notching of the mandibular alveolar process. Witkop tooth-nail syndrome is autosomal dominant.

Laboratory aids. Blood eosinophilia during the vesicular stage or even later may be marked, in some cases reaching 65% (11,67).

Prenatal diagnosis can be accomplished for those with IP2 (12).

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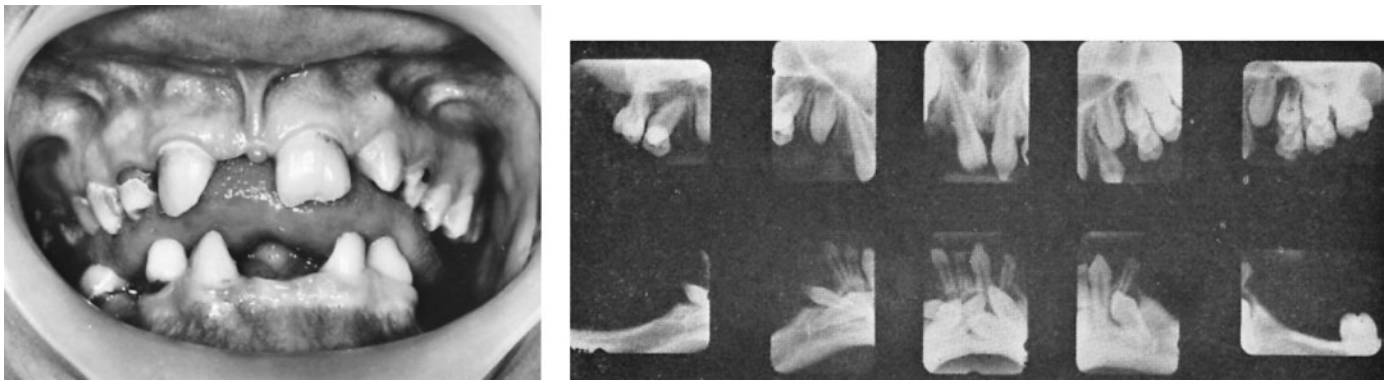
Fig. 13–75. *Incontinentia pigmenti*. (A) Missing teeth and teeth with conical crown form. (B) Dental radiographs of patient demonstrating missing teeth, impacted teeth, and conical crown form of several teeth. (From RJ Gorlin and JA Anderson, J Pediatr, 57:78, 1960.)



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Naegeli syndrome

Naegeli syndrome (2,5), a rare disorder, is characterized by reticular pigmentation of the skin that develops at about 2 years of life and is not preceded by an inflammatory stage. Heat intolerance and moderate hyperkeratosis of the palms and soles are also noted. Inheritance is autosomal dominant, and the gene has been mapped to 17q11.2–q21 (7). Sparrow et al (6) reported a family with what might also be Naegeli syndrome. Affected individuals had diffuse or patchy, mottled hyperpigmentation of the skin that developed in childhood. There was also thickening of the fingernails, onycholysis and subungual keratosis, decreased sweating, punctate keratoses on the palms and soles, and hypoplastic or absent dermatoglyphic patterns (1,3,4). A few patients had blistering of the heels during the first week of life. Male-to-male transmission was described.

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LEOPARD syndrome (multiple lentigines syndrome, progressive cardiomyopathic lentiginosis)

LEOPARD is an acronym coined by Gorlin et al (23), in 1969, to serve as a mnemonic. The syndrome as originally described consisted of multiple *L*entigines, *E*lectrocardiographic conduction abnormalities, *O*cular hypertelorism, *P*ulmonic stenosis, *A*bnormal genitalia, *R*etardation of growth, and sensorineural *D*eafness (23). It is also known as progressive cardiomyopathic lentiginosis, Moynahan syndrome, cardio-cutaneous syndrome, and lentiginosis profusa. Several reviews have been published (12,16,18,23–25,50,59,61,74). Several incompletely documented cases have been reported (20,29,31,35,36,38,39,49,57,73,77). A neural crest defect has been suggested to explain the clinical abnormalities (51,59). Over 100 cases have been tabulated by us.

Autosomal dominant inheritance with high penetrance and marked variation in expression has been demonstrated (6,15,23,25,40,48,59,67). The condition does not map to the neurofibromatosis 1 locus (19) in spite of a suggestion that it does (84).

Facies. The face is usually triangular with biparietal bossing, hypertelorism, ptosis, epicanthal folds, and low-set ears (Figs. 13–76 to 13–78). Strabismus is seen in 20% and mild mandibular prognathism in 10%. In our experience, mild pterygium colli is frequent. Cataracts were reported by Peter and Kemp (54) and Howard (32).

Skin. Many pinpoint black-brown macules may be found anywhere on the skin, including the scalp, face, neck, upper trunk, axillae, palms, soles, and genitalia, sparing only the oral mucosa (51,83). They may number in the thousands (40,59) and are usually a few millimeters in diameter (23,24,40,51,65) (Figs. 13–76 to 13–78). Although striking when present, pigmented macules are not found in all patients (23). They may be congenital (17,81) or appear soon after birth (42,51) and increase in number until puberty (43,48,51,59,65,70). On microscopic examination, the pigmented skin lesions are lentigines (14a,23,37,43,59,66,68,80,83). Intracellular giant pigment granules similar to those in neurofibromatosis have

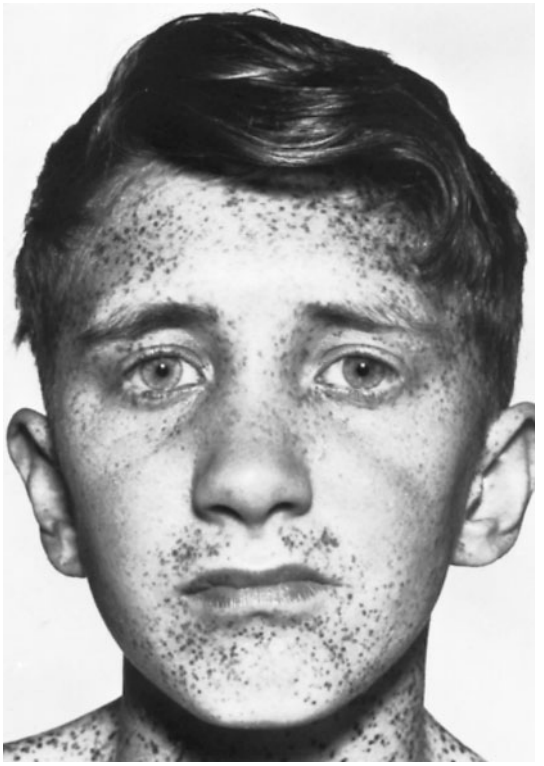
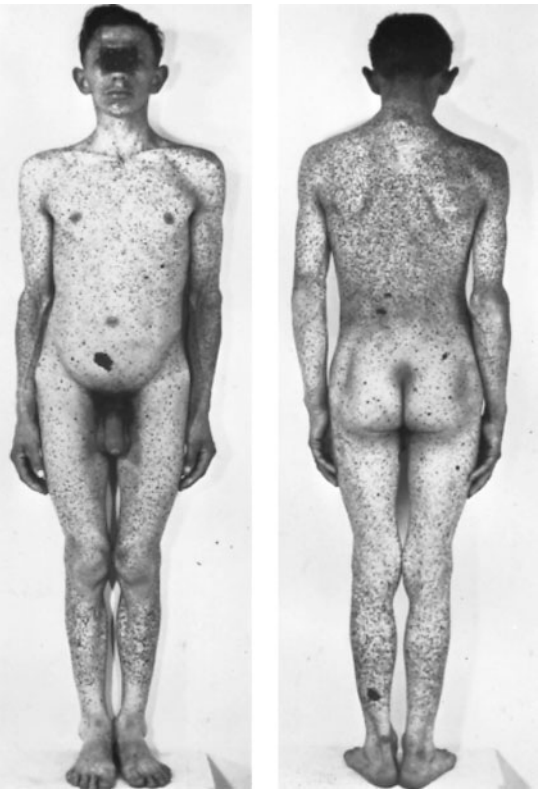


Fig. 13–76. *LEOPARD syndrome*. Ocular hypertelorism, numerous lentigines. (From PE Polani and EF Moynahan, Q J Med 41:205, 1972.)

Fig. 13–77. *LEOPARD syndrome*. (A,B) Twenty-seven-year-old with thousands of lentigines widely scattered over body. Lentigines first appeared at 4 years of age. Also note larger "café-noir" spots. (From JJ Herzberg, Z Kinderchir 2:187, 1965.)



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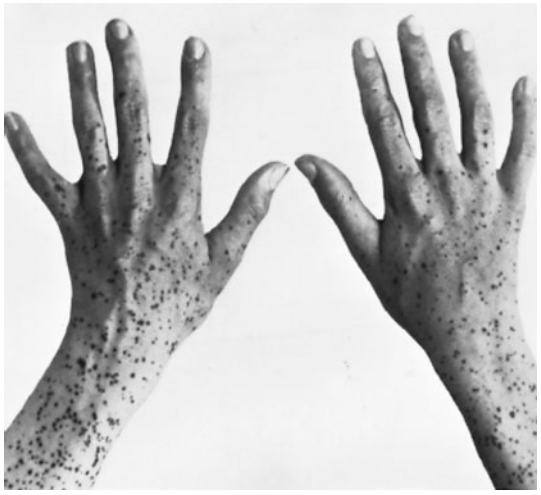

Fig. 13–78. *LEOPARD syndrome*. Numerous lentigines of hands. (From PE Polani and EF Moynahan, Q J Med 41:205, 1972.)

been noted (10,55,64,83). Large numbers of melanosomes accumulate in Langerhans cells (22). Features of compound nevi have also been found (63). Granular cell schwannomas of the skin of the limbs and thorax have been described (5,7,8,34,38,46,52,65,72,78). Café-au-lait spots are noted in about 20% (80). One commonly finds a few large (1–5 cm) dark *café-noir* spots scattered over the trunk (Fig. 13–77).

Cardiovascular system. Cardiac defects have been extensively reviewed (23,24,59,62,69,70,80). Valvular pulmonary stenosis, usually mild, appears to be the most common cardiac abnormality, occurring in 40% (35,80). In others, there is an unusual alteration in the pulmonary valve that has been termed "pulmonary valvular dysplasia" (35). The pulmonary valve reveals three distinct cusps but no commissural fusion. The obstruction is based on thickening of the pulmonary valvular leaflets by disorganized myxomatous tissue that renders the valve leaflets immobile. Clinically, patients with this type of valvular anomaly have a pulmonary systolic ejection murmur but no ejection click. Similar changes have been seen much less commonly in the aortic valves. About 20% have hypertrophic cardiomyopathy, involving primarily the interventricular septum, which results in both subaortic and subpulmonic stenosis (59,70). In other reports, associated atrial septal defect, infundibular or supravalvular pulmonary stenosis, or muscular subaortic stenosis has been described (35,41).

There is a unique and frequently present electrocardiographic anomaly that tends to characterize this syndrome regardless of the type of cardiac malformation. This feature is a superiorly oriented mean QRS axis in the frontal plane, generally located between −60 degrees and −120 degrees (S1,S2,S3 pattern) (48,67,69). This may not be demonstrable in every patient, but it may be present in others with the syndrome in whom no structural abnormality of the heart has been demonstrated. Electrocardiograms in some patients have revealed left axis deviation, first-degree AV block, posterior rotation, complete heart block, hemiblock, or complete bundle branch block (67,69).

Genitourinary system. Hypospadias is present in 50% of males (23,24,49,59,81,82). Unilateral or bilateral cryptorchidism is frequent (49,55,59), and the penis may be small (49). More cases have been transmitted through affected females. Absence or hypoplasia of an ovary has been reported (23,59). Late menarche is a common finding.

Skeletal system. Growth retardation is frequent; 85% are below the 25th centile for height and weight (24), and 20% are below the third centile in height (37,42,55,80). Hypopituitarism has been reported but is probably aleatory (44). Pectus carinatum (37) or excavatum (39,48,51,68,83) has been noted in about 10% (80), as has winging of the scapulas (17,37,70). Scoliosis is present in about 10% (42). In old age, there is a tendency to develop thoracic kyphosis. Spina bifida occulta, absent ribs, cubitus valgus, limitation of motion at elbows, and deficiency in the outer table of the temporal bone have been described (24,59,70). Bone age may be retarded (15). Hyperflexibility of metacarpophalangeal joints of fingers and thumbs has been noted.

Central nervous system. Hearing loss has been documented as early as birth (37), 1 year (13,51), and early childhood (42,70). Although hearing loss has been described in about 25% (80) as sensorineural (13,42, 51,83), the age of onset, degree, and type have not been well documented. Some young individuals have been reported with normal hearing (66,67,80), but loss may develop with advancing age. Vestibular changes have not been present (13). Chiari I malformation has been reported in a child (1).

Mild mental retardation (24,49,51,55,59,68,71) and electroencephalographic abnormalities (10,51,59) including diffuse encephalopathy (51) have been reported in about 30% (80). In others, intelligence was normal (17,37,42,80).

Oral manifestations. Oral mucous membranes have not been involved (14,23,24,43,51,59,65,67,69,79,80). One child has been reported with nasopharyngeal rhabdomyosarcoma (29).

Differential diagnosis. Lentigines differ from freckles in having darker color, no relationship to sun exposure, arising at an earlier age, and on biopsy having an increased number of melanocytes per unit skin area and prominent rete ridges. Segmental lentiginous nevus, which exhibits numerous pigmented macules on a café-au-lait background, probably represents a mosaic form of this or another gene, such as NF1 (3,4,30, 33,47,56,58,76,85). Granular cell schwannomas may be seen with this nevus (26,60).Blue nevi have been rarely found in association (30). Happle et al (27,28) and Tadini et al (75) view association of speckled lentiginous nevus with telangiectasia or with an organoid epidermal nevus as examples of twin spotting. Twin spots are paired patches of mutant tissue that differ from each other and from the background tissue. This comes about by somatic crossing over of two different recessive mutations localized to the same chromosome. This gives rise to two homozygous daughter cells that are the stem cells for two different mutant patches. Loss of heterozygosity can also result from chromosome deletion. Various conditions associated with increased nevi have been reviewed (45).

One can see generalized lentigenosis without systemic involvement (9).

The LEOPARD syndrome shares many features with *Noonan syndrome* and *Noonan-like syndrome, cherubism, and polyarticular pigmented villonodular synovitis*. Noonan syndrome patients do not have lentigines or hearing loss. Characteristics in common include hypertelorism, ptosis, short stature, QRS axis, pulmonary stenosis without an ejection click, cryptorchidism, delayed development of secondary sexual characteristics, and pectus. We suspect that LEOPARD syndrome and Noonan syndrome are allelic (11). One of us (RJG) has noted multiple granular cell schwannomas in both conditions. This has been recently confirmed (38a,61a). Pulmonic stenosis, abnormal QRS axis, short stature, delayed puberty, and hearing loss may be observed in *rubella embryopathy*. Swanson et al (74) reported an 18-year-old male with unilateral sensorineural hearing loss, nevi and freckles on his back, chest, and face, mild hypertelorism, normal electrocardiogram, lack of sexual hair, small penis, and renal abnormalities; he likely had a form of Kallmann syndrome.

Forney et al (21) described a dominantly inherited syndrome of short stature, bilateral conductive hearing loss with onset during the first decade of life, multiple freckles on the face and shoulders, and mitral insufficiency. In addition, there were skeletal anomalies, including fusions of the cervical vertebrae and carpal and tarsal bones.

Paver and Coleman (53) reported a male with generalized multiple lentigines, facial asymmetry and other craniofacial abnormalities, patchy sparse scalp hair, cicatricial alopecia, epicanthus, ophthalmologic abnormalities, and undescended testes.

Multiple lentigines have also been seen in *Carney syndrome. Neurofibromatosis* should also be excluded. Watson (82) reported a syndrome of short stature, mild mental retardation, pulmonary valvular stenosis, and café-au-lait spots. The gene for Watson syndrome has been mapped to the NF1 gene, representing intralocus heterogeneity (2).

Laboratory aids. Electrocardiogram and cardiac catheterization may be helpful. Biopsy may be used to confirm the diagnosis of lentigo.

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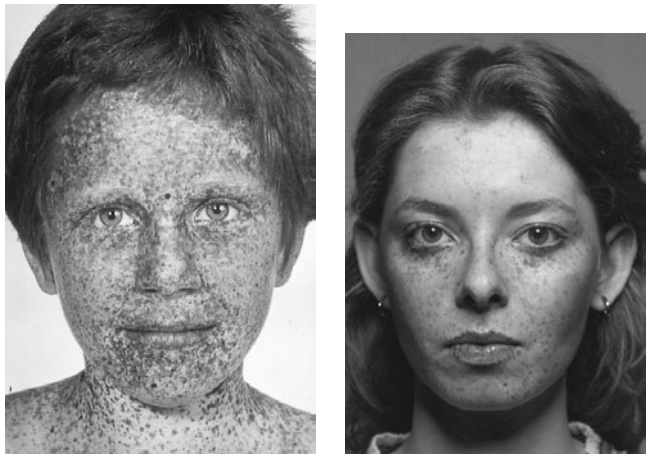
Macular cutaneous and mucosal pigmentation, myxomas, and endocrine neoplasia syndrome (Carney syndrome, NAME syndrome, LAMB syndrome)

The complex of myxomas (heart, skin, breast), spotty pigmentation of the face, lips, and conjunctiva (lentiginosis, blue nevi), endocrine tumors (adrenal, testis, pituitary), and schwannomas (upper gastrointestinal tract, sympathetic chain) is called Carney syndrome. Although some components may be congenital or apparent in early childhood, diagnosis is usually made in the second and third decades of life.

The condition, described in part by several earlier investigators (2–4, 24,39,43,45,46,49), was fully fleshed out by the superb studies of Carney and coworkers (6–14,62). Subsequently, at least 200 examples have been published (8,51).

Many have been sporadic cases (2,21,33,38,39,45). However, autosomal dominant inheritance with variable expression is evident (4,12,14,17, 19,31,41,43,49,50a,57,59,60). Approximately 50% represent new mutations. There appears to be genetic heterogeneity, the syndrome mapping to 2p16 (51) and to 17q22 (15,25). The gene, related to genomic stability of dividing cells (51), is the protein kinase A type 1-α regulatory subunit (30a). The mutation results in a gain of function (52). There may be further genetic heterogeneity (5,51,54).



A B

Fig. 13–79. *Macular cutaneous and mucosal pigmentation, myxoma, and endocrine neoplasia syndrome*. (A) Macular pigmentation of face and lips. (B) Note similar facial and mucosal pigmentation. There is a small myxoma of the right lower eyelid. [A from DL Atherton et al, Br J Dermatol 103:421, 1980. B from JA Carney et al, Medicine (Baltimore) 64:270, 1985.]

Skin. Multiple dark-brown macules (lentigines) are found in about 70% in decreasing order on the face (especially periocular and perioral), lips, conjunctiva or sclera (especially lacrimal caruncle and semilunar fold), eyelids, trunk, neck, vulva (especially labia minora), arms, thighs, and backs of hands (2,12,14,16,30,39,43,47) (Fig. 13–79). Sometimes present at birth (2), with additional lesions developing thereafter (2,22,45), they range from few to myriad in number. In general, lentigines and cutaneous myxomas (vide infra) are the first lesions to appear. The lentigines measure from 0.2 mm to 2 mm in diameter (2). Microscopic changes include somewhat acanthotic epithelium with increased numbers of clear melanocytes and increased pigment in the basal cell layer (12,39,43). Ephelides (freckles) are noted in increased numbers. Junctional and compound nevi are present in 65% (51).

Blue nevi, blue to black domed lesions, probably congenital, and measuring up to 8 mm, occur on the face, trunk, and limbs, but not on the hands or feet (2,21,45). Some patients have a few blue nevi, others up to a dozen lesions. Blue nevi situated high in the dermis are characterized by spindle-shaped melanocytes with elongated dendritic processes. Approximately 10% of the affected have both lentigines and blue nevi.

Approximately 40% develop multiple sessile papules or subcutaneous myxoid nodules during the first three decades of life (2,13,29,45). Myxomas have predilection for the eyelids (25%), external ear canals (15%), and nipples (20%) (23,29). Most lesions are 1 cm or less in diameter (Fig. 13–80). The myxoma, while sharply circumscribed, is usually not encapsulated. It is composed of scattered, polygonal, spindle and stellate mesenchymal cells set in a mucinous (often basophilic) matrix composed of proteoglycan (44). Approximately 25% of dermal myxomas exhibit an epithelial component that may be cystic or consist of thin epithelial strands (13).

Cardiac myxomas. The heart is the second most frequently affected organ. The myxomas may be single or multiple and occur in any or all chambers (36). Multiple myxomas [biatrial (40%), ventricular (15%), and recurrent (20%)], found in 65%–75%, are the most serious component (2,8,36,42,43,45,49,50) (Fig. 13–81). Embolization from the cardiac myxomas (33) occurs in 20%, with refractory congestive heart failure (39,45) in another 20%. In 40%, the cardiac myxomas are familial (59). Mean age of detection is about 25 years. With decreasing frequency, distribution is as follows: left atrium, right atrium, right ventricle, and left ventricle. Among all cardiac myxomas, those in Carney syndrome constitute about 7% (36).

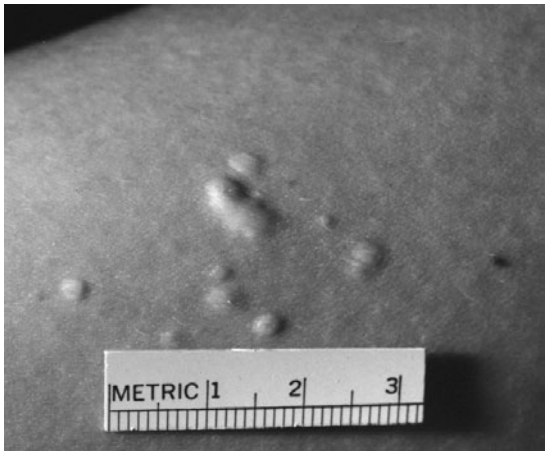


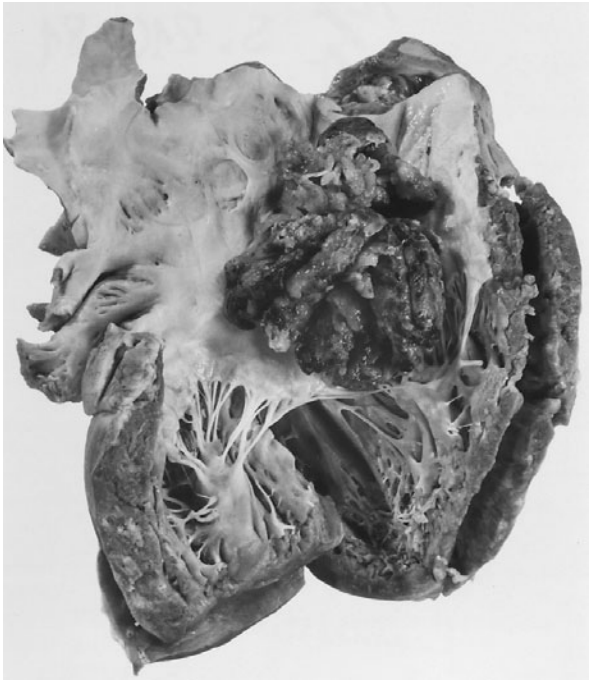
Fig. 13–80. *Macular cutaneous and mucosal pigmentation, myxoma, and endocrine neoplasia syndrome*. Myxomas on the skin of the arm. [From JA Carney et al, Medicine (Baltimore) 64:270, 1985.]

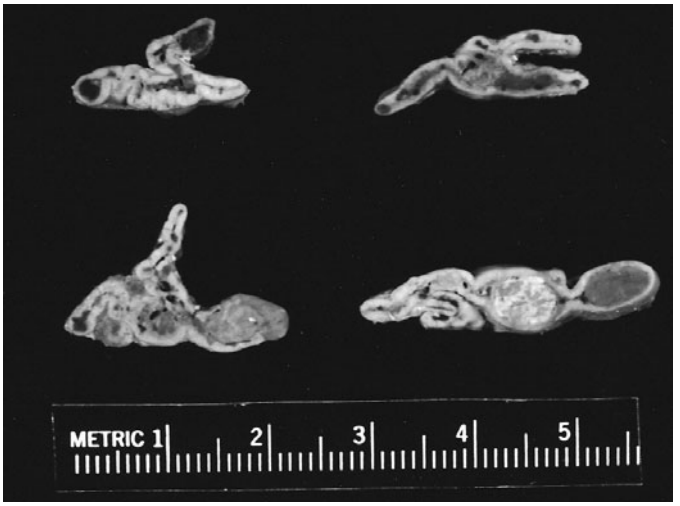
Eyes. Macular pigmentation (lentigo) is seen on the conjunctiva, particularly the lacrimal caruncle and conjunctival semilunar area (2,12, 16,29) or sclerae (45) in 65%. Myxomas frequently occur on the eyelids and commonly recur following excision (1,12,13,20,26,29,30,49).

Genitourinary tract. Multiple black macules (lentigines) may be found on the labia minora (12,39) and labia majora (12). Cutaneous myxomas have been reported on the vulva (45) and on the perineum (12). Myxoma of the uterus (4) and atypical mesenchymal tumor of uterus (37) have been reported.

Endocrine abnormalities. Cushing syndrome due to primary pigmented nodular adrenocortical disease has been found in about 30% (2,4,12,21,28,48–50,56) (Fig. 13–82). Some of these patients have had severe osteoporosis. Discovery is usually made during late adolescence or in the 20s (11). Primary pigmented nodular adrenocortical disease appears grossly as small (usually less than 5 mm) black brown, dark green, or red nodules in the adrenals. Microscopically, it is characterized by enlarged globular cortical cells with granular, eosinophilic cytoplasm which often contains lipofuscin (56).

Fig. 13–81. *Macular cutaneous and mucosal pigmentation, myxoma, and endocrine neoplasia syndrome*. Myxoma of heart. [From M Schweizer-Cagianut et al, Virchows Arch (A) Pathol Anat Histopathol 397:183, 1982.]





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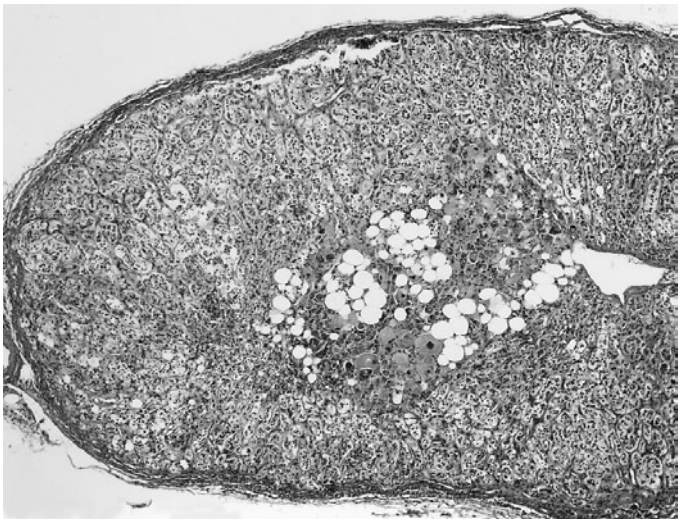

B

Fig. 13–82. *Macular cutaneous and mucosal pigmentation, myxoma, and endocrine neoplasia syndrome*. (A) Primary pigmented nodular adrenocortical disease. Note small pigmented nodules. (B) Primary pigmented nodular adrenocortical disease. Typical pigmented nodule composed of epithelial cells, fat cells, and a few lymphocytes, situated deep in cortex. The extra nodular cortex is disorganized and lacks normal zonation. (H&E, ×64). [A from JA Carney et al, Medicine (Baltimore) 64:270, 1985. B courtesy of JA Carney, Rochester, Minnesota, unpublished, 1987.]

Approximately 10% have thyroid tumors, approximately one-half of which are malignant. Benign papillary and follicular hyperplasia of the thyroid (45) and thyroid follicular adenoma (3,12,49,53) have been reported.

Acromegaly or gigantism due to growth hormone-secreting pituitary factor has been found in 10%, onset of symptoms ranging from adolescence to the late 20s (27,32,61).

Large-cell calcifying Sertoli cell tumor of the testis causing sexual precocity has been documented in 30% of male patients (12,34,36a,41;see 49). They are bilateral in 75% cases and multicentric in each affected testis. Most patients are in their early adolescence at time of discovery. The tumors are usually hard to palpation and nontender. Microscopically, the tumors are characterized by multifocal sheets and cords of cells with abundant acidophilic cytoplasm and large areas of laminated calcification.

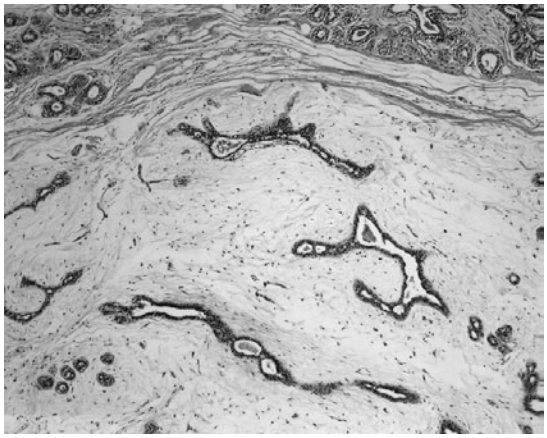

Fig. 13–83. *Macular cutaneous and mucosal pigmentation, myxoma, and endocrine neoplasia syndrome*. Unencapsulated myxoid fibroadenoma of breast. Note elongated proliferated ducts surrounded by hypocellular stroma. [From JA Carney et al, Medicine (Baltimore) 64:270, 1985.]

Leydig cell or adrenal cortical rest tumors may also be found (40,51). Pheochromocytoma has also been noted (4,32,59).

Schwannomas. Psammomatous melanotic schwannomas involve the upper gastrointestinal tract (esophagus, stomach) and paravertebral sympathetic chain in 20% (51). A few, however, have arisen in the skin (55,58). Although usually benign, metastasis with fatal consequences has been found in 10% (7,55).

Grossly, the tumors are dark and encapsulated. They are composed of large and small polygonal epitheliumlike cells and spindle cells in organoid pattern. Melanin is noted in the cytoplasm. Laminated calcification (psammoma bodies) are scattered throughout. S-100 protein immunostaining is positive (35).

Myxoid mammary fibroadenoma and ductal adenoma. Myxoid fibroadenomas of the breast have been noted in 25% of female patients (9). These may be multiple and often bilateral (10). The lesions may be painful or tender to the touch (8,12,17,18,46). They range in size from a few millimeters to 2 centimeters in diameter. Microscopically, they are composed of abundant hypocellular very myxoid stroma and hyperplastic mammary ducts (Fig. 13–83).

Ductal adenoma of the breast with tubular features may be unilateral or bilateral. The tumor, usually located close to the areola, has been found in females 27–61 years of age (10).

Oral manifestations. Pigmented macules (lentigines) may be found on the perioral skin or vermilion border of lip mucosa in over 90%. The buccal mucosa has lentiginous spots in 5% (2,12,17,49). Approximately 3% have myxoid tumors of the hard or soft palate (2,17,43,57) (Fig. 13–84). Myxomas have also been described on the tongue (45) (Fig. 13–85).

Differential diagnosis. The syndrome should be considered in any patient under 40 years old who has cardiac myxoma in other than the left atrium or who has more than one cardiac myxoma (6). The skin and mucosal pigmentation should not be confused with that found in *Peutz-Jeghers syndrome*. The condition should also be differentiated from the *LEOPARD syndrome*. Isolated familial cardiac myxomas have been reported (49).

Laboratory aids. Cushing syndrome can be diagnosed by measurement of 24-hour urinary cortisol following a low-dose dexamethasone suppression test on initial investigation.

Plasma somatomedin C is elevated if acromegaly or gigantism is present.

The testicular tumors can be detected by ultrasonography.

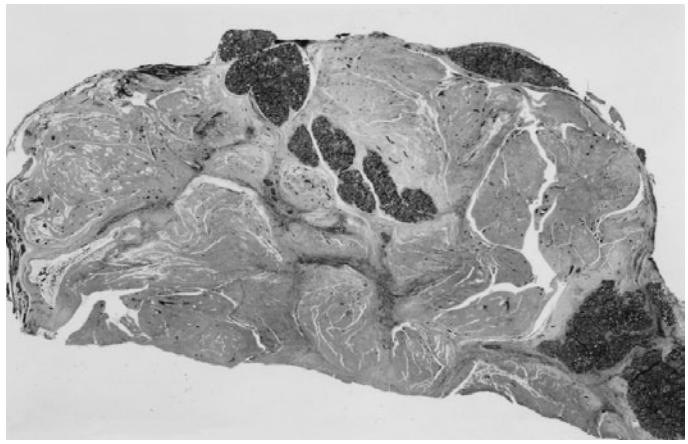

Fig. 13–84. *Macular cutaneous and mucosal pigmentation, myxoma, and endocrine neoplasia syndrome*. Palatal myxoma. Circumscribed by nonencapsulated myxoma of minor salivary glands of palate (Movat pentachrome stain, ×2). (From CA Cook et al, Oral Surg 63:175, 1987.)

References [Macular cutaneous and mucosal pigmentation, myxomas, and endocrine neoplasia syndrome (Carney syndrome, NAME syndrome, LAMB syndrome)]

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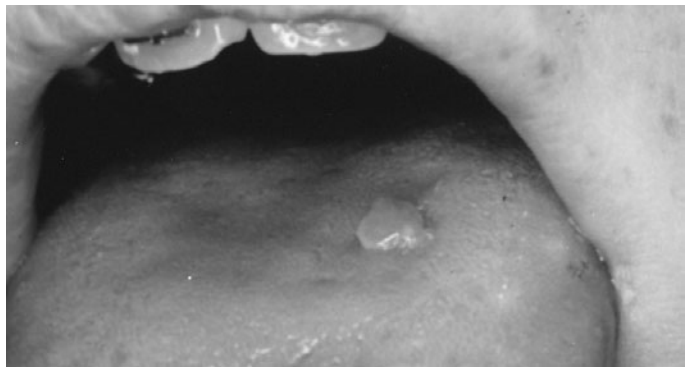
Fig. 13–85. *Macular cutaneous and mucosal pigmentation, myxoma, and endocrine neoplasia syndrome*. Myxoma on the tongue. (From AR Rhodes et al, J Am Acad Dermatol 10:72, 1984.)



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Waardenburg syndrome

The syndrome described so precisely by Waardenburg in 1951 (97) was reported earlier by Mende (58), van der Hoeve (96), Klein (45), and others (70). The main features include lateral displacement of the medial canthi and lacrimal puncta with a broad nasal root, poliosis, heterochromia irides, hyperplasia of the medial portions of the eyebrows, and congenital sensorineural hearing loss. The reader is referred to several excellent comprehensive reviews (24,39,70,79,90).

During the last 15 years, a number of studies (3,34) have separated Waardenburg syndrome (WS) into several forms, based on whether dystopia canthorum is present (type I) or absent (type II), and whether upper limb defects (type III, Klein-Waardenburg syndrome) (46) or Hirschsprung disease (type IV, Waardenburg-Shah) are present (83).

It has been estimated that type II is 20 times as common as type I (5). Several series have shown that hearing loss is much more common in type II (about 77%) (51) than in type I (about 25%), and heterochromia irides is more common in WS type II (47%) than in type I. Perhaps type II is more common among blacks, but more documentation is needed to substantiate this point. Pigmentary disorders are more frequent in type II. However, it has also been shown that patients with type I and hearing loss more commonly have pigmentary disorders of the eyes, hair, and skin than those with type I who have normal hearing. Arias (4) suggested a type II that he designated "pseudo-Waardenburg syndrome" characterized by absence of dystopia canthorum but with one-sided ptosis

of the upper lid. "Waardenburg syndrome type III" is also known as the Klein-Waardenburg syndrome on the basis of a patient described by Klein (45) in 1947 with "partial albinism" blue eyes, deaf-mutism, and musculoskeletal anomalies. However, it was found that this condition is due to an allelic mutation in the PAX3 gene (whose mutations are responsible for WSI), or is a contiguous gene syndrome due to deletion of the PAX3 gene and adjacent genes. Bard (10) also suggested further heterogeneity, but we are not convinced that his patient is not an extreme example of type II.

Waardenburg syndrome types I, II, and III exhibit autosomal dominant inheritance with essentially complete penetrance and variable expressivity (50,92). Estimates of prevalence suggest that this syndrome is found in 2%–5% of all congenitally deaf persons (11,17). Between 2 and 3/100,000 in the general population are affected in the Netherlands (97). However, since most probands have been recognized because of impaired hearing, there is ascertainment bias (13,70,72). New mutations for type I have been shown to be associated with advanced paternal age. However, most Waardenburg syndrome type IV variants follow the autosomal recessive pattern of inheritance (vide infra). Germ–line mosaicism has been reported for WS1 (44). Jones et al (43) noted a paternal age effect for new mutations.

In 1989, Ishikiriyama et al (41) suggested that the locus for WS1 is located at 2q35 or 2q37.3. Farrer et al (21), in 1994, found that all families with WS1 showed linkage to the *PAX3* region of chromosome 2. Baldwin et al (9), in 1995, described 10 mutations in the *PAX3* gene in families with WS1 and, in 1996, Wildhardt et al (100) described *PAX 3* mutations in 2 additional families.

De Stefano et al (15), in 1998, tried to establish genotype–phenotype correlations in 271 individuals with WS1 from 48 families collected by the Waardenburg consortium. They grouped the 42 unique mutations in the *PAX3* gene in 5 mutation categories: (a) amino acid substitution in the paired domain, (b) amino acid substitution in the homeodomain, (c) deletion of the ser-thr-pro-rich region, (d) deletion of the homeodomain and the ser-thr-pro-rich region, and (e) deletion of the entire gene. They found that individuals with deletion of the homeodomain and the pro-ser-thr-rich region had 2.8 and 5 times greater frequency of eye pigment abnormality, white forelock, and skin hypopigmentation, respectively, than those with an amino acid substitution in the homeodomain.

Hughes et al (40), in 1994, found that WS2 is heterogeneous. They suggested that WS2 mapping to 3p12–p14.1 be named WS2A, and the unlinked form(s) be called WS2B. The reader should also see Dow et al (18).

In patients with WS2, Tassabehji et al (89), in 1994, demonstrated mutation in the gene for microphthalmia-associated transcription factor (*MITF*; Gene Map Locus 3p13). Lawani et al (50), also in 1994, mapped a WS2 gene to 1p21–p13.3. Reviewing the WS2 patients, Read and Newton (79) reported that about 15% are heterozygous for mutations in the *MITF* gene. *MITF* transactivates the gene for tyrosinase and is critically involved in melanocyte differentiation. Absence of melanocytes affects pigmentation in the skin, hair and eyes, and hearing function. Therefore, hypopigmentation and hearing loss in WS2 are likely to be the results of an anomaly of melanocyte differentiation caused by *MITF* mutation (88).

Moreover, Watanabe et al (98), in 1998, presented evidence for epistatic relationship between *MITF* and *PAX3*. They showed that *PAX3*, a transcription factor with a paired domain and a homeodomain, transactivates the *MITF* promoter and thus directly regulates *MITF* function.

PAX3 mutations were also found in WS3 (9,90). Thus, it was concluded that the mutations of WS1 and WS3 are allelic. In 1998, myelomeningocele and WS3 were reported by Nye et al (67) in patients with interstitial deletions of 2q35 and the *PAX3* gene. These patients raise the possibility of a digenic etiology of their NTDs via a genetic interaction of the deleted *PAX3* gene with a second unidentified locus. Zlotogora et al (105) presented evidence that homozygosity for a *PAX3* mutation can cause WS3, with very severe upper-limb defects (Fig. 13–86). Aymé and Philip (7) reported a probable homozygous fetus with contractures and exencephaly.

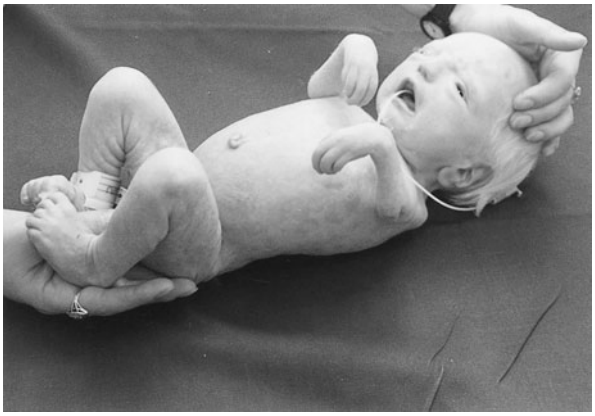
The Waardenburg-Shah (WS4) phenotype may be the result of a mutation in the endothelin-B receptor gene (*EDNRB*), in the gene for its ligand, endothelin-3 (*EDN3*), or in the *SOX10* gene (94). In 1995, van Camp (95) reported chromosome 13q deletion in patients with WS2 and Hirschsprung disease.

In 1995, Attie et al (6) described features of both Waardenburg syndrome and Hirschsprung disease in 2 girls born to consanguineous Tunisian parents. They found a homozygous missense mutation in exon 2 of the *EDNRB* gene. In 1996, Edery et al (19) demonstrated a homozygous substitution/deletion mutation of the *EDN3* gene in a patient with the Shah-Waardenburg syndrome. Independently, and also in 1996, Hofstra et al (38) identified a missense mutation in the *EDN3* gene. In 1998, Pingault et al (75) found 4 different types of *SOX10* mutations in patients with Waardenburg-Shah syndrome. These were nonsense mutations, insertions or deletions. They point to an essential role of *SOX10* in the development of two neural crest–derived human cell lineages. They further define the locus heterogeneity of the Waardenburg-Shah syndrome (37,47,87).

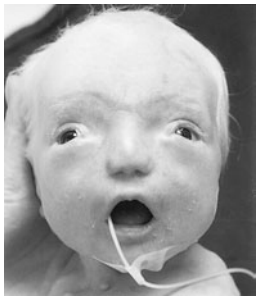
It seems, thus, that the Waardenburg-Shah phenotype resulting from mutations in *EDNRB* or *EDN3* is inherited as an autosomal recessive, whereas, when it is due to mutations of *SOX10*, the inheritance is autosomal dominant, probably as a result of haploinsufficiency of the *SOX10* product.

Facies. Poliosis, synophrys, heterochromia irides, broad nasal root, hypoplastic alar cartilages, and mild mandibular prognathism produce a remarkably striking appearance in those with type I syndrome (Fig. 13–87A,B).

Eyes. Although the interpupillary and outer canthal distances are normal in most affected individuals, an increased distance between the inner canthi (dystopia canthorum) is evident, resulting in blepharophimosis. This is a sine qua non in type I patients. The sclerae may be covered medially, giving a false impression of esotropia. Type II patients have a normal facies (Fig. 13–87C).

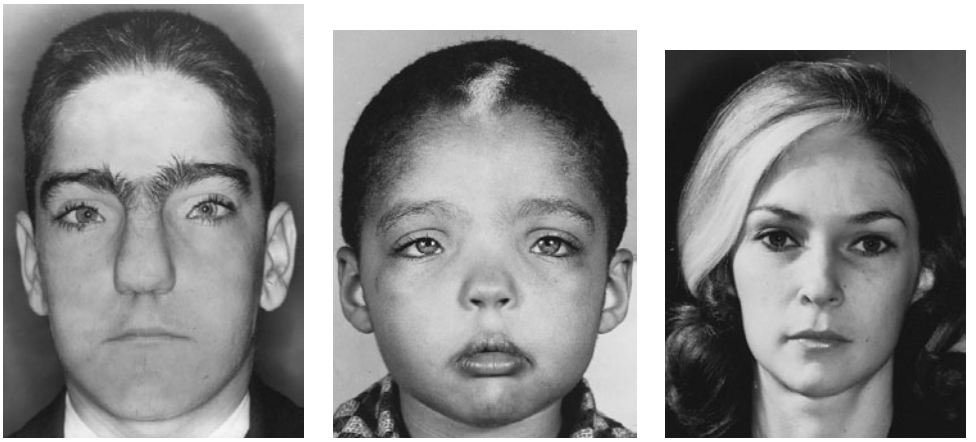


A



B

Fig. 13–86. *Waardenburg-Klein syndrome, homozygosity for PAX3 gene*. (A) Severe contractures and muscle hypotrophy noted in upper limbs; abnormal skin pigmentation. (B) Marked hypertelorism and dystopia canthorum. Hair is white.



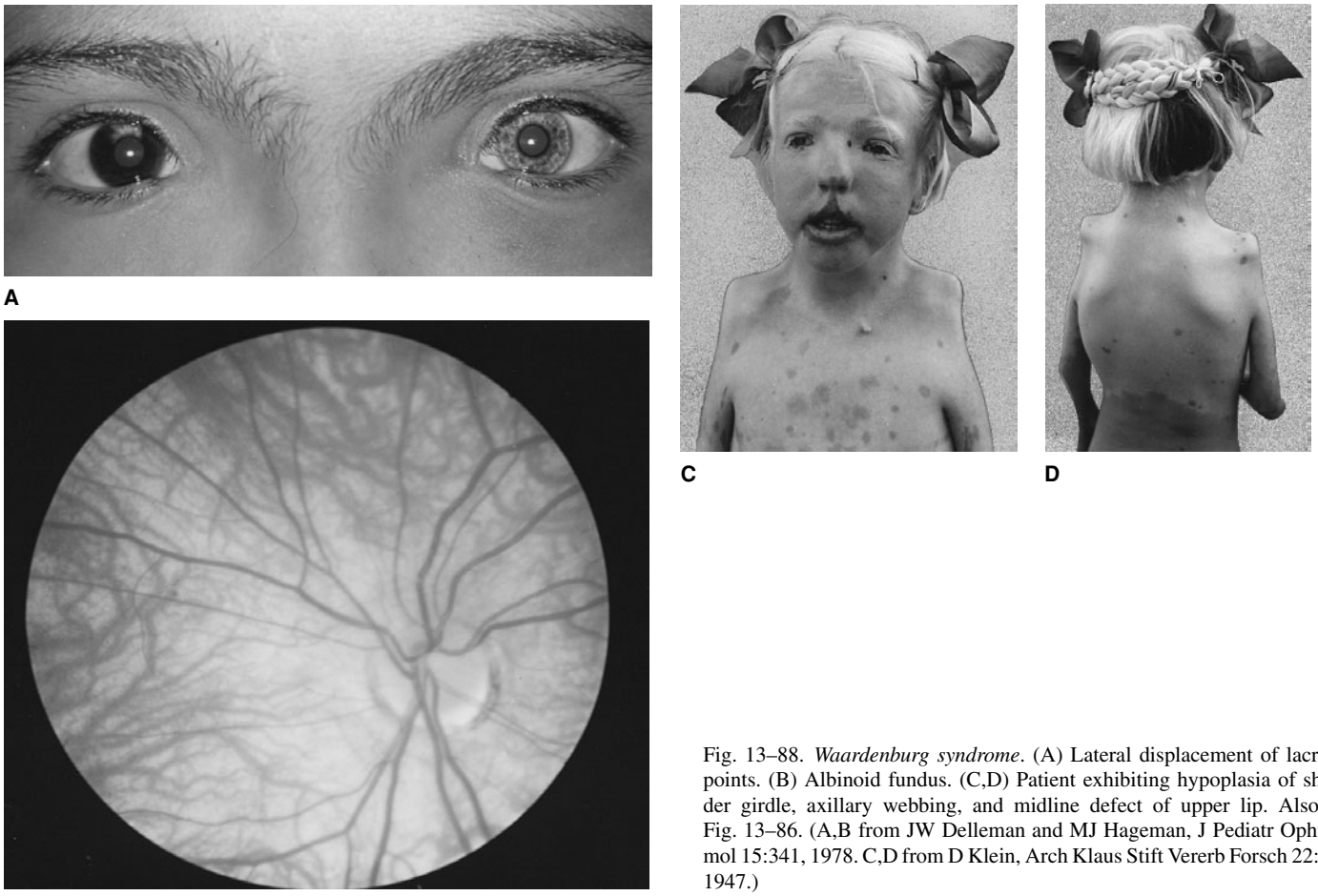
A B C

Fig. 13–87. *Waardenburg syndrome, type I.* (A) Heterochromia irides, dystopia canthorum, hypoplastic nasal alae. (B) White forelock, synophrys, dystopia canthorum, hypoplastic nasal alae. *Type II.* (C) Note absence of dystopia canthorum, presence of white forelock. (A from MW Partington, Can Med Assoc J 90:1008, 1964. B courtesy of M Goldberg, Chicago, Illinois.)

Arias and Mota (5) pointed out that clinical judgment regarding the presence of dystopia canthorum is not always accurate and that a W-index value should be calculated to separate type I from type II. Preus et al (76) suggested modification of the formula, and De Saxe et al (14) used a palpebral fissure index. For variability, the reader is encouraged to read Reynolds et al (80).

True ocular hypertelorism is present in about 10% (70). Normal inner canthal, outer canthal, and interpupillary values have been discussed by Pryor (77) and others (25,48,59).

The inferior lacrimal points are displaced laterally, sometimes as far as the cornea (Fig. 13–88A). There is an increased susceptibility to dacryocystitis (70). Hyperplasia of the medial portions of the eyebrows, or even confluence (synophrys), is present in 85% of type I and 25% of type II patients (34). This characteristic may be less evident in women, who often pluck these hairs (17,70). Heterochromia irides is seen in about one-third of the cases in both types. It may be partial or total, both irides ranging from a mottled to blue appearance. Hypoplastic sapphire blue irides are seen in 10%–15% of both types (34,102), although De Saxe et al (14) suggested that blacks with type II more often have clear blue eyes. Di George et al (17) and others (28) noted pigmentary mottling at the periphery of the fundi. The fundi are albinoid (16) (Fig. 13–88B). Morell et al (70) reported apparent digenic inheritance of Waardenburg



A B C D

Fig. 13–88. *Waardenburg syndrome*. (A) Lateral displacement of lacrimal points. (B) Albinoid fundus. (C,D) Patient exhibiting hypoplasia of shoulder girdle, axillary webbing, and midline defect of upper lip. Also see Fig. 13–86. (A,B from JW Delleman and MJ Hageman, J Pediatr Ophthalmol 15:341, 1978. C,D from D Klein, Arch Klaus Stift Vererb Forsch 22:336, 1947.)

syndrome type II (WS2) and autosomal recessive ocular albinism (AROA). In the family they studied, all individuals with AROA phenotype were either homozygous or heterozygous for TYR (R402A), and heterozygous for the 1 bp deletion in *MITF*. Other eye anomalies such as cataracts, microphthalmia, and ptosis have been reported in association with type I and type II patients (3,28,57,71,97,100). Convergent strabismus has been found in 20% (16).

Hair and skin. White forelock (poliosis) is present in 30%–40% of patients with either type I or type II (34). In some cases, only a few white hairs are evident. This feature may be present at birth but tends to disappear with age (14,22). In females, poliosis may not be evident because of the tendency to mask it by dyeing the hair (17). Premature (beginning in the 20s) graying of eyebrows, lashes, and hair occurs in 20%–35% of type I cases and in 5% of type II cases (34). Pigmentary anomalies, such as vitiligo, may be found in 15%–20% of affected persons of either type (70). Black forelock has also been reported in both type I syndrome (3) and in type II syndrome (14).

Ears and nose. Waardenburg syndrome accounts for over 2% of congenital deafness (61,62). Bilateral congenital sensorineural hearing loss has been observed in 20% of type I patients (34,97) and in 55% of type II patients (34). Little residual hearing is present for the lower frequencies. Approximately 15% of type I and 5% of type II have unilateral hearing loss, rarely of severe degree, in which moderate uniform loss for the lower and middle ranges occurs with improvement in the higher range—often with normal hearing for 6000–8000 cycles per second (23,34).

Hageman (33) demonstrated that where there is unilateral hearing loss, there is no correlation between the laterality of the hearing loss and the side having the blue eye in case of heterochromia irides.

The hearing loss has been shown to be due to absence of the organ of Corti and stria vascularis and a sparsity of ganglion cells (23,78).

Vestibular function was shown to be normal in 25 patients with type I syndrome (35). However, Marcus (55) noted abnormal vestibular function in type II syndrome in blacks. Tomographic findings of the inner ears of 24 type I patients were found to be normal by Nemansky and Hageman (64), but they pointed out that other investigators have discovered malformations of the semicircular canals.

The nasal root is broad, often with loss of the frontonasal angle. The alar cartilages are usually hypoplastic, resulting in narrow nostrils. The tip of the nose tends to be rounded and slightly upturned, revealing the columella (45).

Gastrointestinal system. There have been numerous reports (1,12, 20,56,68,78,83) of the association between type I Waardenburg syndrome and Hirschsprung disease, a disorder of intestinal motility characterized by absence of parasympathetic ganglion cells from the submucosal and myenteric plexuses of the gut (1,83). The association has also been documented in type II syndrome (26,54,57) and type IV syndrome (vide infra).

Waardenburg syndrome, type I, has also been reported in association with anal atresia (56,65) and with esophageal atresia (23,66), but these may well be chance findings.

The syndrome that combines features of Waardenburg syndrome and Hirschsprung disease has been referred to as the Waardenburg-Shah syndrome [Waardenburg syndrome (type IV or WS4)] (8,83). In 1981, Shah et al (83) reported studies on 7 male and 5 female babies with white forelock and white eyebrows and eyelashes, presenting with intestinal obstruction. One had isochromia irides, and in four, information was not recorded. No dystopia canthorum, broad nasal root, or white skin patches were found in 6 patients in whom the observations were recorded. None had deafness. Bonnet et al (11) reported two sisters, the offspring of consanguineous parents. Both had Hirschsprung disease, sensorineural hearing loss, hair, iris, and skin hypopigmentation, but no dystopia canthorum.

Skeletal system. Few cases have been reported in which full radiographic surveys were carried out. Among the cases reported, a variety of skeletal anomalies such as Sprengel deformity, skull anomalies, bony defects of the thorax, abnormal upper limb length, abnormal carpal bones, syndactyly, sacralization of the fifth lumbar vertebra, sacral dimple, and spina bifida have been noted (14,70,97).

Klein (45) reported a woman with Waardenburg syndrome and myo-osteoarticular defects of the upper limb and pectoral region with absence of muscles, rigidity of joints, axillary webs, and camptodactyly of all fingers (Fig. 13–88C,D). Waardenburg, on seeing this patient, investigated several Dutch institutions for the deaf and subsequently defined Waardenburg syndrome, type I. Waardenburg considered Klein's patient to have another disorder. Klein's view that his patient had Waardenburg syndrome has been subsequently vindicated by his finding of a father with essentially the same type of anomalies who has a child with full expression of Waardenburg syndrome, type I. There is a similarity to the homozygous form. Senrui (82) reported flexion contractures and limited supination of forearms. We believe that the family reported by Sommer et al (86) with flexion contractures of the hands actually had Waardenburg syndrome and does not represent a new entity. Other cases have been analyzed by Goodman et al (29). Although Goodman et al (29), Klein (46), and Sheffer and Zlotogora (84) have suggested that this represents still another type of Waardenburg syndrome (type III), we believe that the muscular and skeletal defects in the upper limb are part of the clinical manifestations of an allelic mutation at the same locus of WSI.

A patient described by Wilbrandt and Ammann (100) who also had arthromyodysplasia was noted in a family having otherwise typical Waardenburg syndrome.

Genitourinary system. A 16-day-old girl with Waardenburg syndrome type I presented with a right multicystic dysplastic kidney and hydronephrosis in the left kidney (42). Goodman et al (30) described absence of the vagina and adnexa.

Oral manifestations. The lower lip is especially full and protrudes. The mandible seems to be prognathic in most patients, although this feature has been studied cephalometrically in few instances (16,70, 94,97,100). Radiographic examination of the skull in a small series of patients has demonstrated greater lateral winging of the angle of the mandible, increasing the bigonial distance.

Facial clefting as an associated finding was pointed out by Giacoia and Klein (38) and by Gorlin et al (31). Cleft lip and/or cleft palate is about eight times as frequent in Waardenburg syndrome as in the normal population, being seen in about 1% of Waardenburg, type I populations (2,27,28,31,97). We suspect that the family reported by Pierpont et al (74) had WS type IV.

Differential diagnosis. Dystopia canthorum and hypertelorism may be seen in a variety of disorders (73). Synophrys is a feature of *de Lange syndrome* and may also occur with pilonidal cyst (81). Hypoplastic alar cartilages may be seen in *OFD I syndrome*. Poliosis, with or without piebaldism, may be inherited as an autosomal dominant trait and may be seen with *branchio-oculo-facial syndrome*. Poliosis, vitiligo, and dysacousia may be seen in combination with alopecia and uveitis in Vogt-Koyanagi syndrome (36). Heterochromia irides may be acquired, inherited as an autosomal dominant trait (23), or in association with *Romberg syndrome*. Partial albinism with deafness may occur as an X-linked dominant trait (103). Zlotogora (104) suggested that this kindred represents an X-linked dominant form of WSII. Vitiligo and congenital sensorineural hearing loss have been reported as an autosomal recessive combination (93). An autosomal dominant syndrome of white forelock, leukoderma, cerebellar ataxia, poor motor coordination, and mild mental retardation was described by Telfer et al (91).

An autosomal recessive lethal syndrome of almost total white hair (fringe of black hair at the nape), total aganglionosis, and congenital profound sensorineural hearing loss was reported in an inbred Kurdish syndrome by Gross et al (32). This cannot be mistaken for Waardenburg syndrome.

Hirschsprung disease has been reported by several authors to be associated with congenital sensorineural hearing loss (52,85,99) and with facial clefting. It should be emphasized that there is no evidence to indicate that any of these patients had Waardenburg syndrome. Various other pigmentation disorders have been reviews by Ortonne (69).

Laboratory aids. In dystopia canthorum, the inner canthal distance divided by the interpupillary is greater than 0.6 (71).

References (Waardenburg syndrome)

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Albinism, Black locks, neural crest Cellular malmigration, and sensorineural Deafness (ABCD) syndrome

Through the courtesy of Dr. Ursula Froster, Lübeck, Germany, one of the editors (RJG) was made aware of a child with trisomy 21 with cleft lip, white scalp hair except for that in the occipital area, aganglionic megacolon, and congenital profound sensorineural hearing loss (Fig. 13–89A,B). Gross et al, in 1995, described an autosomal recessive neural crest syndrome consisting of *A*lbinism, *B*lack locks, *C*ell migration disorder of the ganglion cells of the gut, and *D*eafness, which they termed the ABCD syndrome. The syndrome occurred in a highly inbred Kurdish family in which 5 of 14 siblings were affected. All 6 patients died soon after birth. Total aganglionosis was found (Fig. 13–89C–F).

Inheritance is autosomal recessive.

Reference [Albinism, Black locks, neural crest Cellular malmigration, and sensorineural Deafness (ABCD) syndrome]

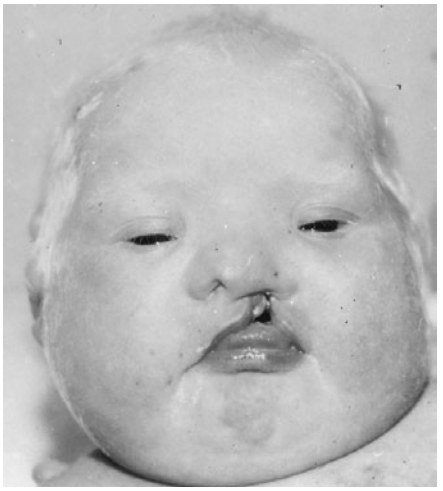
1. Gross A et al: Autosomal recessive neural crest syndrome with Albinism, Black locks, Cell migration disorder of the neurocytes of the gut, and Deafness: ABCD syndrome. Am J Med Genet 56:322–326, 1995.

Ataxia-telangiectasia (Louis-Bar syndrome)

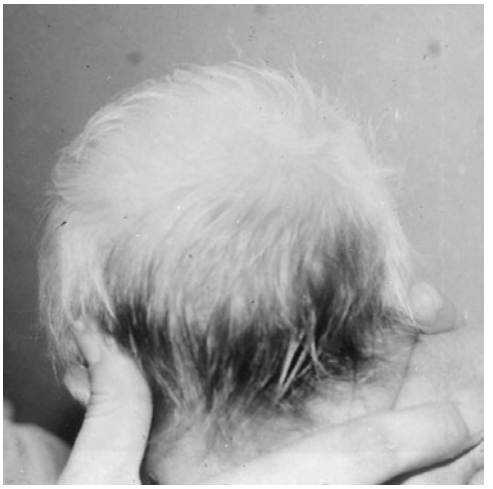
The syndrome of ionizing radiation sensitivity is characterized by progressive cerebellar ataxia, oculocutaneous telangiectasia, recurrent sinopulmonary infections, high incidence of neoplasia, variable immunodeficiency, and chromosomal instability. Mme. Louis-Bar (49) is credited for its delineation in 1941, although earlier examples were reported by Syllaba and Henner (79). Boder and Sedgwick (11) coined the term "ataxia-telangiectasia" and clearly defined the syndrome in 1958.[1] Boder (9,10) published exhaustive reviews in 1975 and 1985. Helpful summaries are those of McKinnon (52) in 1987, Cohen and Levy (17) in 1989, Gatti et al (32) in 1991, Shiloh (72) in 1995, Gilad et al (35) in 1998, and Meyn (52a) in 1999. There have also been useful texts on the subject (12,28).

The frequency of the syndrome in white populations has been estimated to be 1 per 40,000 live births (91). Its true frequency is undoubtedly greater because heterozygote frequency may be as high as 3% (78). Even if it is 1 in 60, then the disease must be 1 in 15,000. The most common ancestral countries of origin are England and Wales, Ireland, Eastern Europe, and Germany, but Turks, Italians, and Moroccan Jews have a high frequency (72). Five different complementation groups have been

[1] We see no reason not to hyphenate the name of the syndrome.



A



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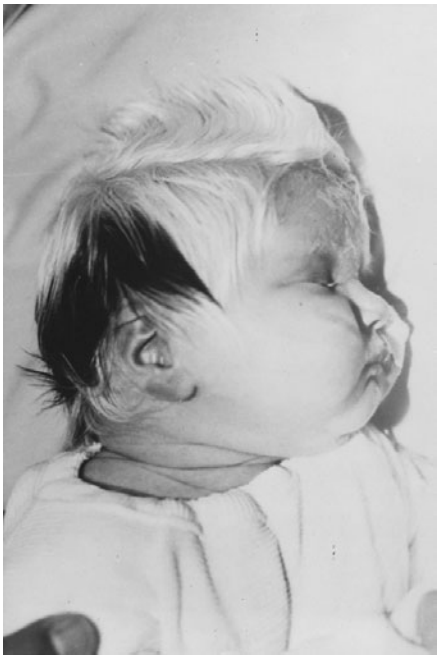
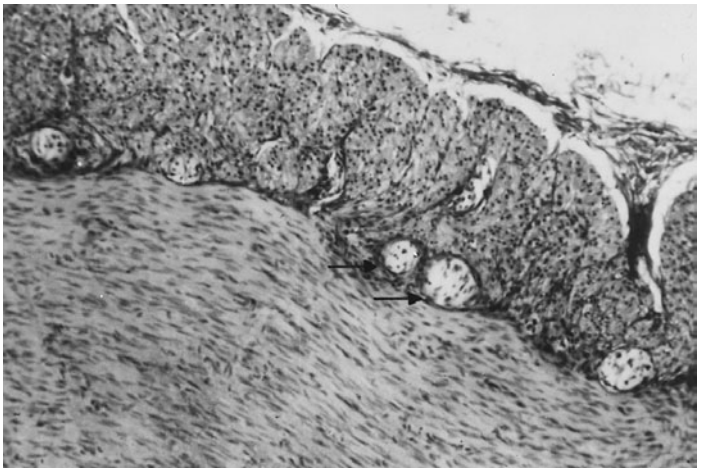


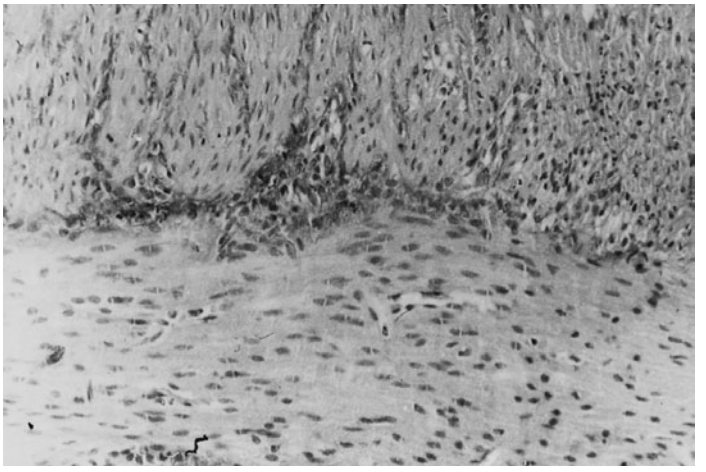
C

D

Fig. 13–89. *Albinism, Black locks, neural crest Cellular malmigration, and sensorineural Deafness (ABCD) syndrome*. (A,B) Child with Down syndrome, cleft lip, white hair with black backlocks, total aganglionosis, and profound sensorineural hearing loss. (C,D) One of five affected siblings with white hair, black backlocks, total aganglionosis, and profound sensorineural hearing loss. (E) Section of intestine showing normal ganglion cells. (F) Absence of ganglion cells in patient shown in C and D. (A,B courtesy of Ursula Froster, Lübeck, Germany. C–F from A Grosse et al, Am J Med Genet 56:322, 1995.)



E



F

demonstrated (43,55,78), and clinical heterogeneity has been claimed by some (81) but denied by other investigators (39).

Death usually occurs during the second decade from either overwhelming pulmonary infection or cancer, the disorder possibly being more lethal in blacks (54). There is heightened sensitivity to radiation and to radiomimetic drugs (80).

Genetics. Inheritance is autosomal recessive, but the parental consanguinity rate is very low (91,92). Oxford et al (57), in 1975, described chromosomal anomalies in ataxia-telangiectasia (AT) involving mostly chromosome 14.

In 1986, Aurias et al (4) described telomere-centromere translocation followed by double duplication between chromosomes 7 and 14 in cases of AT. Gatti et al (30), in 1985, and Aurias and Dutrillaux (2,3), in 1986, reported that the sites of breaks in rearrangements (7p14, 7p35, 14q12, 14qter, 2p11, 2p12, and 22q11–q12) are those where members of the immunoglobulin superfamily are located: IGK, IGH, IGL, TCRA, TCRB, TCRG.

Gatti et al (31), in 1988, localized the AT gene to 11q22–q23 and later, in 1993 (33), pointed out that all 5 complementation groups are linked to a single region at 11q22.3. This was confirmed by McConville et al (50a). However, Hernandez et al (40), in 1993, reported a large family with no linkage to this site. Genotype-phenotype associations have been discussed by Li and Swift (48a).

In 1995, Savitsky et al (66) identified a gene that they named *ATM* (for AT mutated) which was found to be mutated in AT patients from all complementation groups. *ATM* encodes a protein that is similar to phosphatidylinositol 3′ kinases which are involved in mitogenic signal transduction, meiotic recombination, and cell cycle control (13,52a). It was speculated that the discovery of *ATM* may have broad implications in clinical medicine and basic research (46,66). More than 100 *ATM* mutations broadly distributed throughout the *ATM* gene have been documented (18,65a,95). Most AT patients are compound heterozygotes (18). More than 70% of the mutations are predicted to lead to protein truncation. The haplotypes of patients with identical mutations indicated that almost all represent common ancestry, with very few spontaneously occurring *ATM* mutations (24,83).

Rare AT patients with milder manifestations have been designated AT variants. Gilad et al (35) reported in 1998 that cell lines from these patients exhibited considerable variability in radiosensitivity, along with the typical radioresistant DNA synthesis found in AT cells. The typical AT phenotype is caused, in most cases, by null *ATM* alleles that truncate or severely destabilize the ATM protein, whereas the AT variants had 1%–17% of the normal level of ATM protein. Gilad et al (35) studied the cell line derived from a patient reported by Curry et al (21) in 1989 and found it to be devoid of the ATM protein and homozygous for a severe *ATM* mutation. They concluded that certain AT variant phenotypes, including some of those without telangiectasia, represent mutations of *ATM*. Moreover, in a patient with ataxia-telangiectasia without immunodeficiency, Toyoshima et al (85), in 1998, discovered novel point mutations within and adjacent to the phosphatidylinositol 3-kinase–like domain. It is thus realized that the clinical spectrum of AT caused by *ATM* mutations may be broader than previously thought (6).

The role of ataxia-telangiectasia heterozygotes in breast cancer has been controversial (1,8,14,23,26,93).

Clustering of missense mutations in *ATM* was found in a sporadic T-cell leukemia (88). Occasional missense mutations in *ATM* were also found in tumor DNA from patients with B-cell non-Hodgkin lymphomas (B-NHL) and a B-NHL cell line (88).

Facies and appearance. Somatic growth is retarded. The face is described as thin, and the expression is relaxed, dull, impassive, or sad (Fig. 13–90). The patient often stoops with the shoulders drooped and the head held to one side. Mild athetoid movements may be noted around the shoulders. Growth is markedly diminished in over 65% of patients (69).

Central nervous system. The ataxia is of the cerebellar type and usually becomes apparent between 3 and 6 years of age (92). The truncal ataxia is slowly progressive. The ability to walk is usually lost after

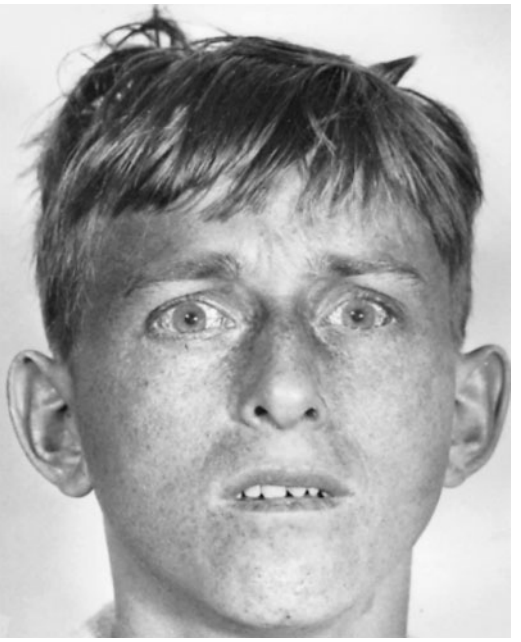


Fig. 13–90. *Ataxia-telangiectasia*. Note rigid facies marked by staring expression and prominent bulbar conjunctival vessels. (From SJ Miller and W Gooddy, Brain 87:581, 1964.)

10 years of age. Eventually there may be dyssynergia and intention tremor of the upper extremities. Hypotonia and diminished tendon reflexes are noted. Speech is slow, slurred, and often scanning (dysarthric). Dystonia and peripheral neuropathy are noted in 70%.

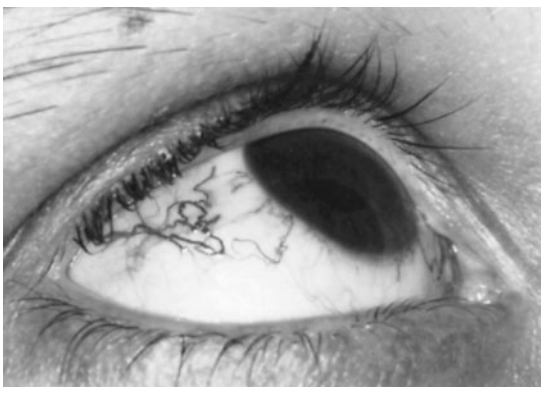
Mental deficiency is usually not apparent until the child reaches the age of 9 years, when mental development begins to taper off. This has been noted in about 30%.

Brain imaging studies show there is cerebellar atrophy, and, on necropsy, degeneration of Purkinje and granular cells without reactive gliosis (84). Degenerative changes have also been noted in spinal cord and ganglia, brainstem and peripheral nerves.

Eyes. Usually between 3 and 6 years, fine, symmetric, bright-red streaks are noted in the temporal and nasal areas of the conjunctiva. The telangiectasia has been shown to be venous and nonhemorrhagic (38) (Fig. 13–91).

Strabismus, poor convergence, photophobia, and nystagmus are commonly found. In all affected, movement of the eyes is slow and interrupted, halting midway on lateral and upward gaze (apraxia). This movement is often accompanied by rapid blinking. Fixation nystagmus is present in over 80% (69).

Fig. 13–91. *Ataxia-telangiectasia*. Telangiectasia of bulbar conjunctiva. (From G Karapati et al, Am J Dis Child 110:51, 1965.)



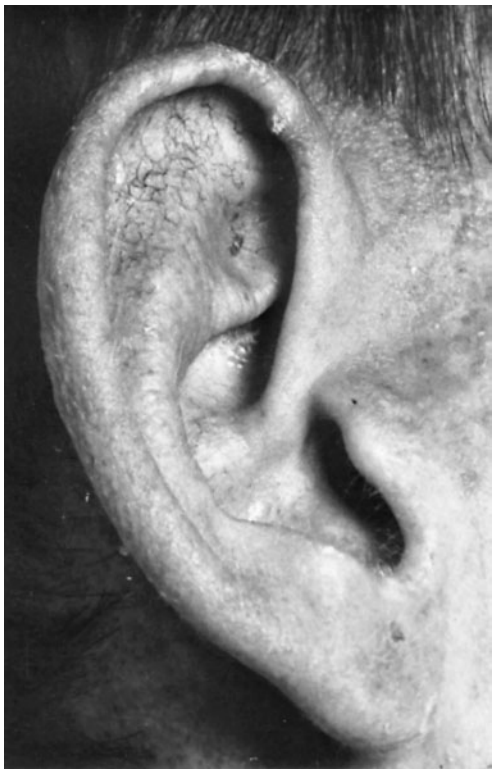


Fig. 13–92. *Ataxia-telangiectasia*. Telangiectasia of pinna. (From M Ruiter, Hautarzt 15:667, 1964.)

Skin. The cutaneous telangiectasia is first noted on the ears, butterfly area of face, bridge of nose, and periorbitally (Fig. 13–92). The distribution is not always correlated with sun-exposed areas (17). With time it extends to the neck, antecubital and popliteal areas, and the dorsum of hands and feet. Heterozygotes have increased numbers of telangiectases (17).

With continued sun exposure and/or aging, the skin tends to become sclerodermatous in appearance, with a mottled pattern of hyperpigmentation and hypopigmentation (poikiloderma). Café-au-lait spots have been noted in 35% (17). Diffuse graying of the scalp hair is noted in about 40%, even in young patients (17). Seborrheic dermatitis, follicular keratosis, and hirsutism of the arms and legs are constant features (9,11,69). A few patients have acanthosis nigricans (17), possibly related to insulin resistance (68). Approximately 15% are generally hirsute (17).

Even though telangiectasia is the classic cutaneous finding of ataxia-telangiectasia, cutaneous granulomas may be the presenting sign in this condition (22).

Respiratory system. Recurrent sinopulmonary infections have occurred in 75%–80% (11,64). These may vary in severity from acute rhinitis with otitis media to chronic bronchitis, recurrent pneumonia, bronchiectasis, and bronchiolitis obliterans (42).

Neoplasia. There is a high frequency (about 20%) of malignancy, usually lymphoreticular of T-cell type (17,27,38,51,61,67,76,77): non-Hodgkin lymphoma (45%), acute lymphocytic leukemia (25%), carcinoma (20%), Hodgkin disease (10%). Few B-cell lymphomas have been reported (45). Various types of cancer have included adenocarcinoma of the stomach, medulloblastoma, glioma, and carcinoma of skin, gallbladder, liver, larynx, ovary, breast, and parotid gland (17,34,37, 48,54,74,77,89). There is some evidence that young parents of affected children have a five-fold higher rate of cancer and autoimmune disease than do control parents (15,17,77).

Sexual maturation. Sexual maturation is retarded, with female hypogonadism being almost uniform (53).

Oral manifestations. Telangiectasia of the hard and soft palate has also been reported (10,11,64,87). Nasal mucosal involvement with telangiectasia may be inferred from recurrent episodes of epistaxis (64). Drooling has been noted in the vast majority of patients (11,69), but its cause has not been established (9). Speech, as noted, is often of the bulbar type. Oropharyngeal lymphosarcoma of the palate has been noted in several cases (36,73).

Differential diagnosis. Ordinarily considered in differential diagnosis are cerebral palsy, structural anomaly or neoplasm of the posterior fossa or foramen magnum, or any of several degenerative or metabolic disorders such as Friedreich ataxia, hepatolenticular degeneration, Pelizaeus-Merzbacher disease, and Hallevorden-Spatz disease. The *Nijmegen breakage syndrome*, an autosomal recessive condition with microcephaly, immunodeficiency, and chromosome instability, must be excluded. Conley et al (19) and Wegner et al (90) described still another disorder of immunodeficiency, chromosome instability, microcephaly, defects of skin pigmentation, and anal stenosis/atresia.

Laboratory aids. Synthesis of antibodies and certain immunoglobulin subclasses is disrupted due to disorders of B-cell and helper T-cell function. This has been characterized as a decreased production of α-globulin, particularly IgA and IgE in over 60% (9). IgG_2 is usually decreased (56). Probably all patients have IgA_2 deficiency (95).

In the blood, relative and absolute numbers of T cells are usually decreased. Whereas the number of B cells is usually elevated, T-helper cells are diminished and defective (29,86). Functionally, there is a defect in cellular immunity. The defect in T cells is manifested by poor stimulation to mitogens, antigens, and allogenic cells—that is, there is failure to respond to phytohemagglutinin (PHA), delayed homograft rejection, an inability to sensitize to dinitrochlorobenzene, and decrease in in vitro lymphocyte transformation (9,36,51,61).

Serum α-fetoprotein and carcinoembryonic antigen levels are elevated in 90% (29,75,89,91,92). There is an altered cell cycle (7) and an elevated frequency of in vivo somatic cell mutations.

Primary gonadal failure is indicated by hypoplastic uterus and absence of ovarian follicles (96). Bizarre nuclear change or cytomegaly has been noted in myocardium, endocrine organs, liver, and central nervous system.

The thymus usually appears vestigial, lacking corticomedullary differentiation and Hassall's corpuscles. Lymph nodes exhibit depletion of lymphocytes in the deep cortex (T-dependent areas), whereas follicles remain intact. The tonsils are hypoplastic, often exhibiting poor germinal follicles and secondary crypt formation.

Over 50% with ataxia-telangiectasia have abnormal glucose tolerance, but rarely with glycosuria and never with ketosis, implying insulin resistance (5,51,68).

Fibroblastoid and lymphoblastoid cells are hypersensitive to the cytotoxic and clastogenic action of ionizing, and radiomimetic chemical agents such as bleomycin, adriamycin, and hydrogen peroxide, reflecting a defect in response to DNA damage or a relative resistance of DNA synthesis (20,27,28,41,58,60). There is radiosensitivity to the chromosomes of heterozygotes (59).

Initially random chromosome breakage followed by a translocation involving the long arm of chromosome 14 and either the short or long arm of chromosome 7 has been found. In the final stage, a (14;14) translocation may be identified in some patients (39,50,51). Increased chromosome breakage has been used in prenatal diagnosis of this disorder (71). There is a different pattern in lymphocytes and fibroblasts (47).

An exfoliated epithelial cell micronucleus test obtained from the mouth or urine yields 4- to 14-fold values in homozygotes and elevated levels in 70% of heterozygotes (65).

CAT scans and magnetic resonance imaging (MRI) should be of help in diagnosing cerebellar atrophy.

The large size of the *ATM* gene, 66 exons spanning approximately 150 kb of genomic DNA, together with diversity and broad distribution of mutations in AT patients greatly limits the utility of direct mutation screening as a diagnostic tool (18).

Both AT homozygotes and heterozygotes showed significantly increased levels of radiation-induced chromatid damage. Thus, the G2-phase chromosomal radiosensitivity assay can be used for the detection of AT heterozygotes. Along with molecular genetic analyses, it may be used to determine the potential involvement of *ATM* mutations in tumor risk or tumor development (82).

A dominant form of chromosomal instability syndrome was reported by Ishikawa et al (41a).

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Focal dermal hypoplasia (Goltz-Gorlin syndrome)

Goltz et al (25) in 1962 and Gorlin et al (27) in 1963 defined a syndrome of focal dermal hypoplasia (FDH) consisting of asymmetry of face, trunk, and extremities; atrophy, telangiectasia, and linear hyperpigmentation of skin; localized cutaneous deposits of superficial fat; multiple papillomas of mucous membranes and periofacial skin; and abnormalities of skeleton, especially the extremities. Another example is that of Šalamon et al (67). The earliest case report appears to be that of Jessner (41) in 1921. Over 250 cases have been reported under a variety of names. An excellent survey of early cases was carried out by Braun-Falco and Hofmann (6). The reader is referred to several comprehensive reviews (6,23,25,26,30,54,79,88,91).

Approximately 95% of the cases have been sporadic examples and only about 10% have occurred in males (7,9,18–20,22,26,30,43,48,62, 66,72,74,82,83,89). There have been a few familial examples, mostly mother–daughter (25,50,63,66,75,91,92), but father–daughter transmission has been described (10,15,28,48,52). The transmitting parent is usually only mildly affected. The evidence suggests that the disorder is X-linked dominant, lethal in male hemizygotes, and with markedly reduced fertility in the female (16,91). Happle (33) suggested that affected males might be explained by mosaicism. The male cases cited earlier are always new mutations. An XXY state may explain some cases.

In 1988, Friedman et al (21) described a child with FDH who was found to have a terminal deletion of the short arm of the X chromosome with the breakpoint in Xp22.31. Schnur et al (70) and Naritomi et al (58) confirmed that FDH and MIDAS syndrome map to the same site and are probably allelic.

In a study of a father and daughter, both affected, Gorski (28), in 1991, suggested that FDH is associated with nonrandom X inactivation consistent with X-linked inheritance, with mosaicism for a mutant FDH allele, in the father. Irvine et al (38), in 1996, reported a child with a markedly skewed inactivation pattern in the proband, but random in her mother. Bellosta et al (4), in 1996, reported a family with affected females in 3 generations, consistent with X-linked dominant transmission with lethality in the male.

Facies. Mild microcephaly is common. The face and/or skull are asymmetric and the scalp hair sparse and brittle in about 30% (31). The nasal alae may be notched or underdeveloped (10). Due to midface hypoplasia, there is often mild relative mandibular prognathism. (Fig. 13–93). The pinnae are usually outstanding and poorly modeled. The auditory canals may be narrow (Fig. 13–94A).

Skin and skin appendages. Asymmetric skin lesions, present at birth in 50%–75%, include thin skin with linear or reticular hyperpigmentation or hypopigmentation, and telangiectasia (30,73). The lesions follow the lines of Blaschko (32). There is focal absence of skin at birth in 15% (30). The iliac crest area, groin, and posterior aspects of the thigh frequently show subcutaneous fatty collections, varying in color from tan to yellow or pinkish yellow (Fig. 13–95). Howell and Freeman (36) and Ishii et al (40) have suggested that it is heterotopic fat, not fat herniation. Supernumerary nipples are common (90). The breasts are often significantly asymmetric (42). In childhood, arborescent papillomas appear in the axillae, in the periumbilical area, or around the anus and vulva

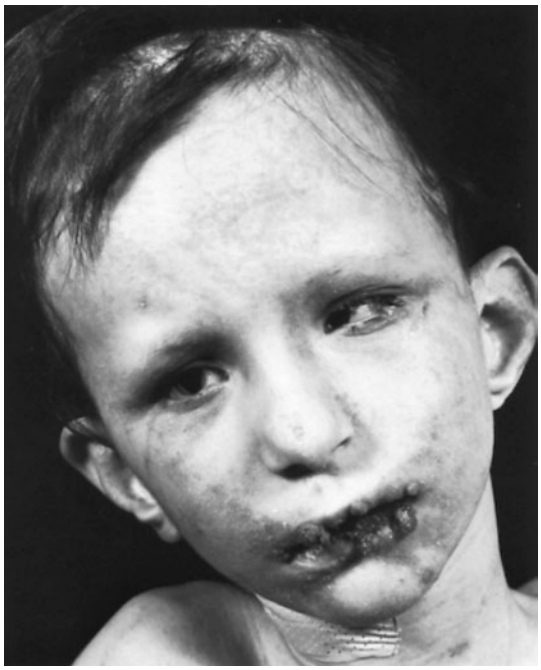


Fig. 13–93. *Focal dermal hypoplasia*. Note multiple frambesiform lesions on lips, coloboma of iris, strabismus, thin hair.

in 50%–60% (30,53,73). Those in the genital area may be mistaken for condyloma acuminatum (11). Stature is short in 15%.

Spotty hypotrichosis of the scalp or pubic hair has been found in 25% (30,80). The fingers and toenails may be absent, poorly developed, or spooned or grooved in 50% (Fig. 13–96). The epidermal ridges of the fingertips may be hypoplastic. Hidrocystomas (93) and apocrine nevi (86) have also been reported.

The population doubling time of fibroblasts in affected skin is double that of normal skin fibroblasts (84). These fibroblasts have a decreased amount of hyaluronic acid-derived disaccharide unit (delta Di-HA) (69).

Eyes. Approximately 40% have anomalies of the eyes. These have been extremely well reviewed in a number of articles (7,56,81,90). Among the more common findings are coloboma of the iris, choroid, retina, and optic nerve (40%), microphthalmia (15%), and strabismus (15%). Unilateral anophthalmia (39), obstructed tear ducts with associated photophobia (44,64), corneal opacifications (50), ectopia lentis (6%), lenticular opacities (47), optic atrophy, aniridia (3%), nystagmus, and conjunctival papillomas have also been reported.

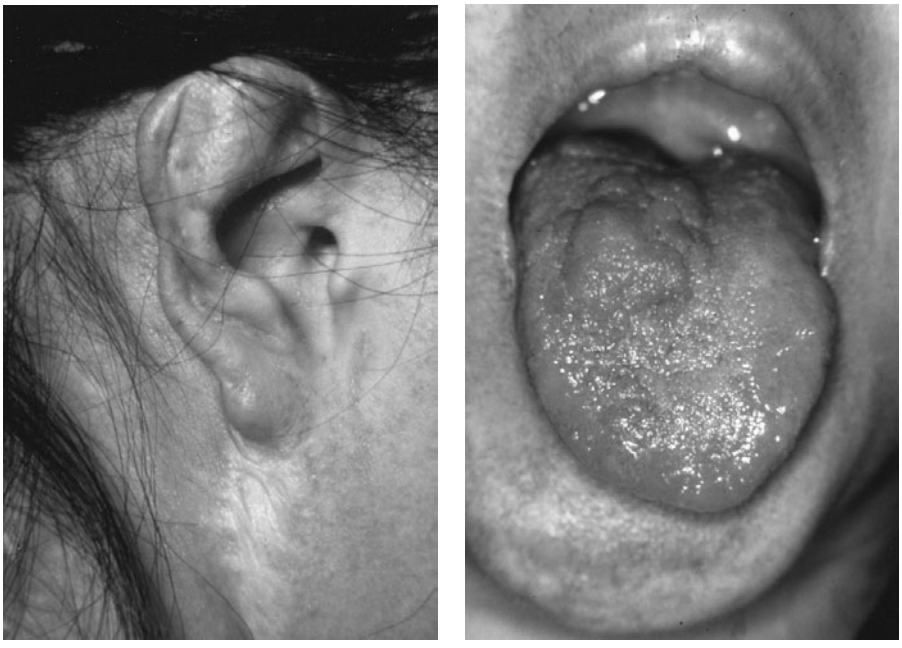
Central nervous system. Mental retardation, usually mild, has been documented in about 15% (11). Mixed hearing loss has been manifested in a number of cases (19,23,27,30,45,53,66,82). Myelomeningocele, hydrocephalus, agenesis of corpus callosum, and Arnold-Chiari malformation have been found (1,2,61).

Musculoskeletal system. Short and asymmetric stature is found in at least 25%. Syndactyly (75%), brachydactyly (60%), and oligodactyly (45%) are extremely common (Fig. 13–96). Postaxial polydactyly and clinodactyly have been found in a number of cases. The extremities, or parts thereof, are often asymmetric. Complete hemimelia of a limb has been reported (1,39). Brachydactyly can result from shortened phalanges, metacarpals, or metatarsals. The combination of split hand with syndactyly and absence of rays, the so-called lobster-claw hand, has come to be recognized as a striking feature of this condition (24). Rib anomalies have been reported (19). Midclavicular aplasia or hypoplasia (pseudarthrosis), apparently limited to the right side, is common (26).

Scoliosis (25%), spina bifida (7%), and congenital hip dislocation (17,26,29,34) are found. Osteopathia striata has been found in at least 20% (3,5,10,18,20,36,45,48,59,88) (Fig. 13–96C). Several authors have noted multiple giant cell tumors of long bones (12,42,51,71,78). An osteochondroma has also been reported (12a). A rudimentary tail (23) and a split sternum (14) have been documented.

Genitourinary system. Hydronephrosis (7,30), bifid ureter and renal pelvis (45), horseshoe kidney (48,77), hypoplasia of clitoris and labia (49,90), and cryptorchidism (19,72) have been sporadically described.

Miscellaneous findings. Umbilical hernia and/or omphalocele has been reported in 10%–15% (6,11,16,20,23,26,34,44,66,68,87). Diaphragmatic hernia (46,60), diastasis recti (6), and anterior displacement



A B

Fig. 13–94. *Focal dermal hypoplasia*. (A) Dysmorphic pinna with scarring of lateral neck. (B) Hamartomatous mass of dorsum of tongue. (From Gordjiani et al, Eur J Dermatol 9:618, 1999.)

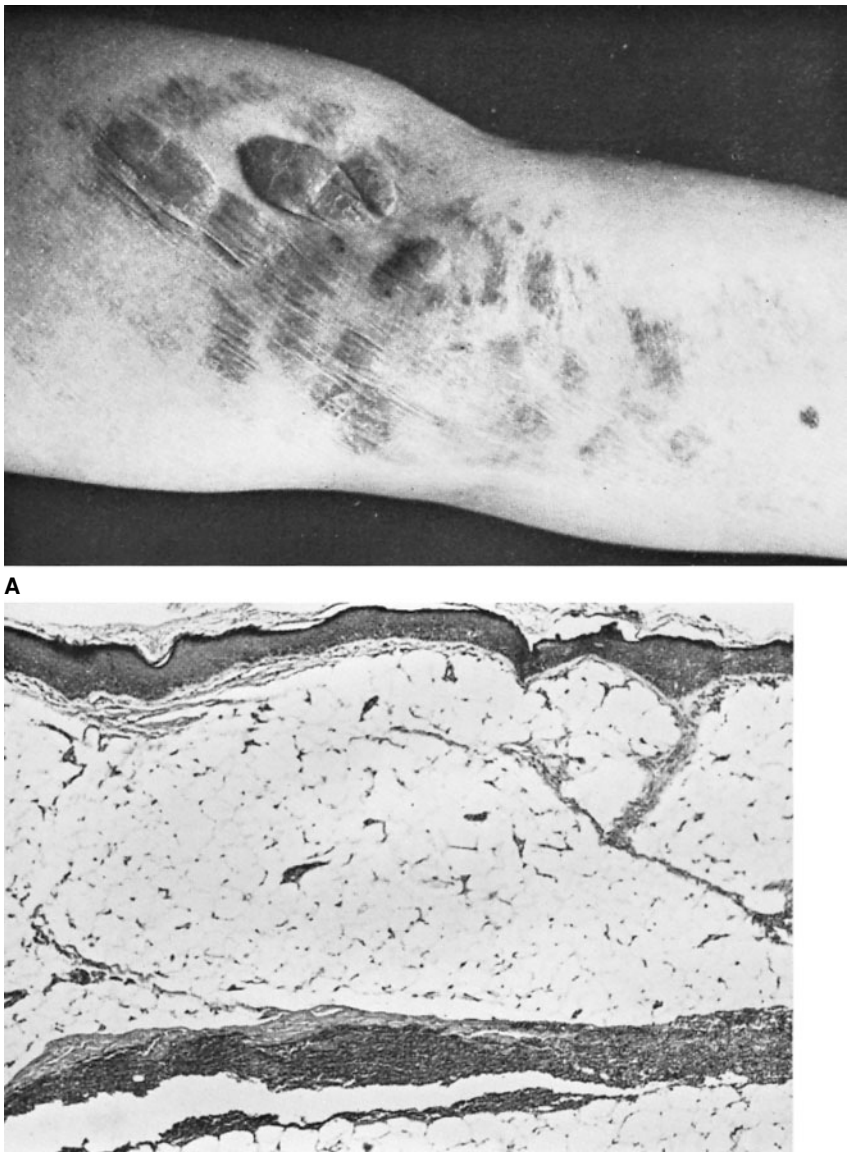


Fig. 13–95. *Focal dermal hypoplasia*. (A) Multiple sacular growths presenting in antecubital area. (B) Photomicrograph of focal dermal defect showing subcutaneous fat covered only by epithelium.

of anus (90) have been found. Intestinal malrotation and mediastinal dextroposition may also be present (38,60). Papillomatosis of the larynx has been described (29). Severe vascular anomalies have been described (31). Papillomatosis of the larynx has been described (29). The reader is referred to a detailed comprehensive article for other anomalies (30).

Oral manifestations. The most frequent dental findings is hypodontia or oligodontia, although supernumerary teeth have been reported (30). The teeth may be small with dysplastic enamel, irregularly spaced, malocclusion, and with delayed eruption (8,85) (Fig. 13–97).

Arborescent papillomas of the lips, gingiva, dorsum and base of tongue, and perioral skin have been noted in 40%–50% (22a,44,90). They have even been reported in the esophagus (93). Hamartoma of the tongue dorsum has been noted (29) (Fig. 13–94B).

Cleft lip and/or cleft palate have also been described (1,13,19,26, 64,73,87) as well as lateral oral cleft (1,57). The reader is referred to the detailed article of Hall and Terezhalmy (30) for other minor oral anomalies.

Differential diagnosis. Nevus lipomatosis superficialis (Hoffmann-Zurhelle) is characterized by neutral fat-bearing cells adjacent to blood vessels in the middle and upper layers of the skin (34). In differential diagnosis, *incontinentia pigmenti* and *Rothmund-Thomson syndrome* should be excluded (6). Some overlap with *EEC syndrome* has been cited, but we feel that both are generally distinctive (65). The patient documented by Sule et al (76) surely has *Delleman syndrome*.

Clavicular pseudarthrosis as an isolated finding is a right-sided anomaly in 90% of the cases and may be inherited as an autosomal dominant trait. Rarely it is bilateral (55). It is also found in the *Floating-Harbor syndrome*.

Laboratory aids. Skin biopsy of a fatty lesion demonstrates normal adipose cells in the corium. Less specific changes are found in the scarlike areas (23,34). Radiographic studies may show osteopathia striata and numerous skeletal changes previously described (Fig. 13–96).

References [Focal dermal hypoplasia (Goltz-Gorlin syndrome)]

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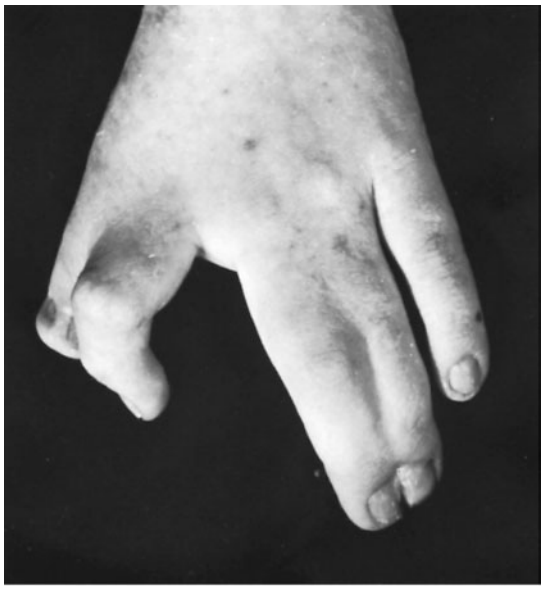

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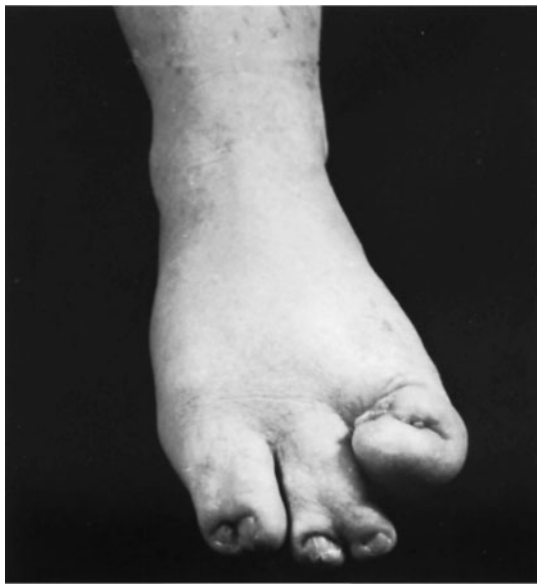

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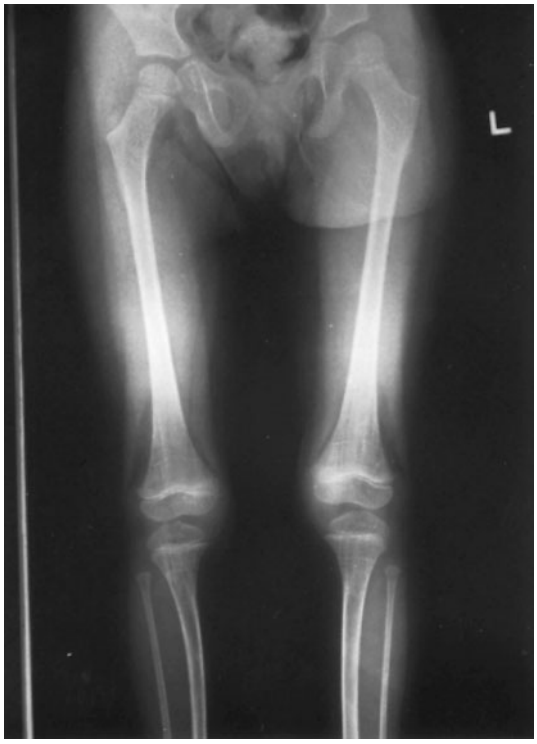

C

Fig. 13–96. *Focal dermal hypoplasia*. (A,B) Syndactyly of digits, bizarre nail formation. (C) Osteopathia striata is constant finding.

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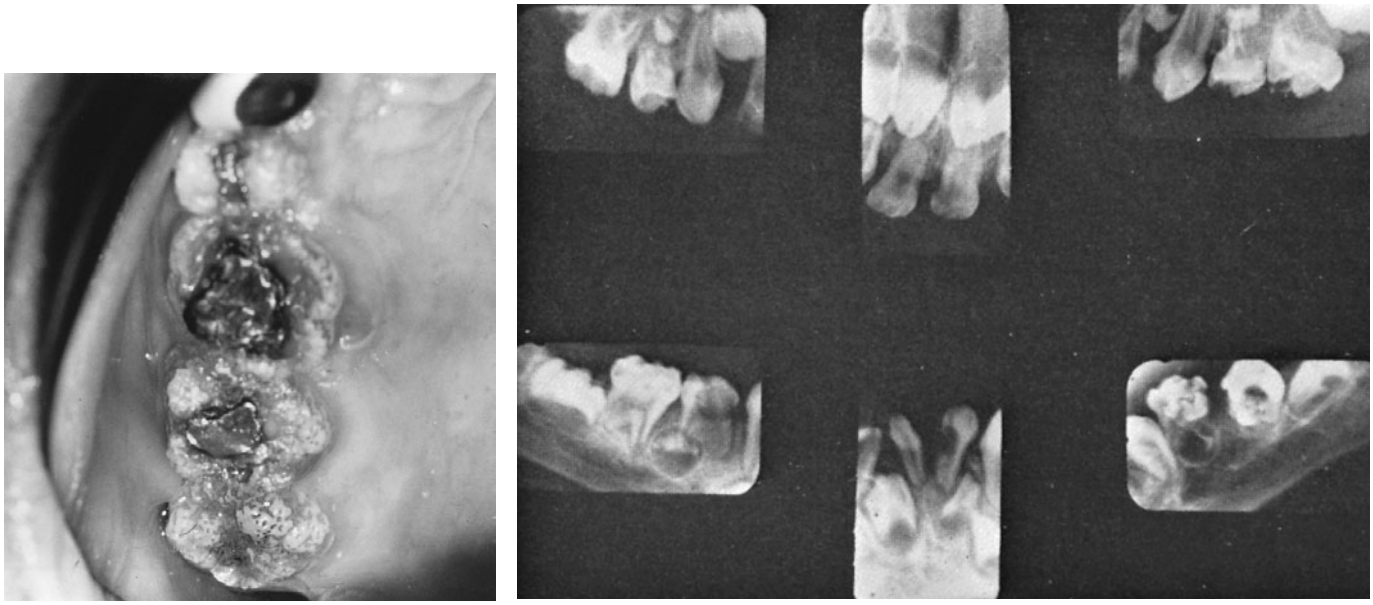

A B

Fig. 13–97. *Focal dermal hypoplasia*. (A) Severely hypoplastic enamel. (B) Radiograph exhibiting severe hypoplasia of teeth.

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Hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber syndrome)

The syndrome, characterized by familial occurrence of multiple capillary and venous dilations of skin and mucous membranes with repeated hemorrhage, was mentioned in 1864 by Sutton (81) and in 1865 by Babington (5). Rendu (71), in 1896, reported a patient with recurrent epistaxis and numerous dilated vessels on the face and oral mucosa. Osler (56), in 1901, gave a full account of the syndrome, and Parkes Weber (57), in 1907, pointed out that the condition becomes worse with age. The descriptive term "hereditary hemorrhagic telangiectasia" was suggested by Hanes (32), in 1909, and is now widely used, although various eponyms are still employed (31). There have been several excellent reviews (2,9,30,42,45) and discussion regarding diagnostic criteria (77a).

Estimates of frequency have ranged from 1 in 2500 to 1 in 40,000 (29). The syndrome is recognized more commonly among whites, but has been reported among all ethnic groups (66). It is rarely detected in infants (52).

Inheritance is autosomal dominant (24) with less than complete penetrance (63), making, at times, for difficult counseling. The lethal homozygotic state (78) is less than certain.

Linkage has been established to chromosome 9q34.1 (28,34,50,76) in some families, to 12q13 in others (39,65,88). The two major genes, termed *HHT1* and *HHT2*, each encode transmembrane proteins that participate in signaling through receptors of the TGFβ receptor family. The former gene (*HHT1*) encodes endoglin, which binds two ligands related to TGFβ (23,77). Endoglin is thought to alter the response to these ligands. *HHT2* encodes activin receptorlike kinase 1, which also binds a similar set of ligands in the presence of a TGFβ receptor (9,40). These glycoproteins, abundant on endothelial cell, and bound to TGFβ, modulate migration, proliferation, adhesion, composition, and organization of extracellular matrix (14). Both nonsense and missense mutations have been found. Both genes act through haploinsufficiency. It is possible that alteration of one or more of these factors causes the vascular dysplasia (48). A third gene has been described in one large family with hepatic involvement. Linkage has been excluded from both chromosomes 9 and 12 (60).

Hereditary hemorrhagic telangiectasia should be considered a generalized pleomorphic angiodysplasia of almost any organ. The telangiectases are direct arteriovenous connections without an intervening capillary bed. The telangiectasias are bright red, violaceous, or purple, and pinpoint, spiderlike, or nodular. When a glass slab is pressed on them, they blanch. Often the patients are pale, and they may have a history of fatigue and weakness caused by bleeding from the telangiectases, with resultant anemia. The hemorrhage, often nontraumatic, is the most severe complication and becomes more frequent with advancing age. It has been postulated that the hemorrhages are aggravated by anemia, thus producing a vicious cycle.

Skin. Telangiectases are observed on the facial skin (35%), especially on the cheeks, ears, and nasal orifices (Fig. 13–98). They may also occur on fingers, toes, and nail beds in about 40%. Usually appearing in the second to third decades of life and increasing in number and size with age, rare cases without external signs of the syndrome occur. The lesions may be purpuric. In elderly persons, spiderlike configurations may be seen.

Nasal mucosa. Telangiectases of the nasal mucosa are common. Approximately 95% experience recurrent epistaxis, which tends to become more severe with time in over 65% (63,70). Epistaxis usually precedes the appearance of telangiectasia on the skin, appearing in childhood or young adulthood (10–20 years) in 50% (1,63). Bleeding from the nose may be oozing, sometimes persisting continuously for several days. Profuse hemorrhage may be initiated by sneezing or coughing. Death due to hemorrhage has occurred in 2%–4% (49).

Other mucous membranes. The mucosa of the upper and lower gastrointestinal tract is often (20%–40%) involved, resulting in melena and hematemesis, which manifest most often in the 5th and 6th decades (70,86). The conjunctiva (35%) or retina (10%) (12,19) may be sites of telangiectasia. When located in the bladder, vagina, or uterus, telangiectases may lead to genitourinary bleeding.

Lungs. Multiple thin-walled aneurysms or arteriovenous malformations in which a pulmonary artery and pulmonary vein are connected may be found in both lungs. There is a special predilection for the lower posterior lobes (84). Approximately 5%–15% of those with hereditary hemorrhagic telangiectasia have pulmonary A-V malformations (61,70).

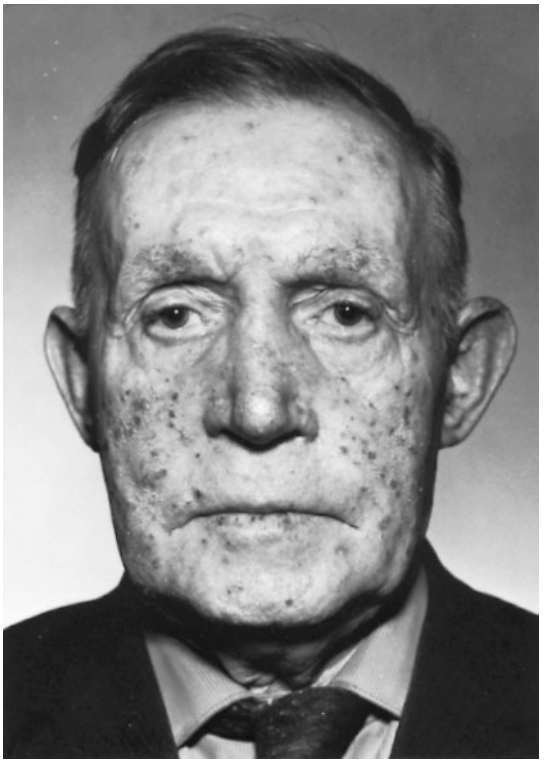

Fig. 13–98. *Hereditary hemorrhagic telangiectasia*. Note numerous telangiectases on face and lips.

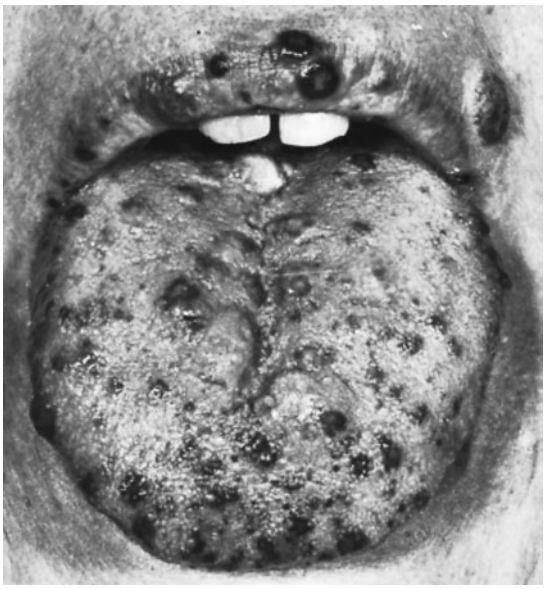

Fig. 13–99. *Hereditary hemorrhagic telangiectasia*. Close-up showing lesions of lips and tongue.

However, Piepgras and Sielecki (61) found that 50% have A-V malformations. Conversely, about 60% of those with pulmonary A-V malformations have hereditary hemorrhagic telangiectasia (18). However, recent genotype–phenotype studies have suggested that the frequency of A-V malformations depends on the specific gene mutation (34,47,64), more cases being associated with HHT1 (45,49a). The A-V shunts are right-to-left, producing, especially when multiple, cyanosis, profound dyspnea, fatigue, and polycythemia. Virtually all patients with cerebral abscesses have pulmonary A-V shunts.

Brain. Various neurologic symptoms, such as brain abscess, migraine headaches, stroke, seizures, transient ischemia attacks, and intracerebral hemorrhage are frequent in patients with the syndrome, particularly in those with pulmonary arteriovenous malformations (35,62,64,67,79,89). Brain abscess, transient ischemia, and ischemic stroke occur only in those with pulmonary A-V malformations and a right-to-left shunt, which permits the passage of emboli into the cerebral circulation (59). Román et al (73) found more than 200 reported cases with involvement of the nervous system. Approximately 60% of these were secondary to pulmonary arteriovenous fistulas. On CT scan about 5% of those with HHT have A-V malformations (49a,89). Adams et al (2) stated that about 5% of patients with arteriovenous fistulas develop cerebral abscesses. Conversely, virtually all patients reported with hereditary hemorrhagic telangiectasia and cerebral abscess had pulmonary arteriovenous fistula. Cerebral abscess must be considered a serious complication of hereditary hemorrhagic telangiectasia (20,63,73).

Other findings. Almost any other organ may be affected by angiodysplasias: bone, liver, spinal cord, and heart (10,33,46,51,70,73).

Intrahepatic arteriovenous fistulas, found in 17% of those with type 2 HHT, have also been reported to cause encephalopathy (32,49a). Duodenal ulcer has been found in about 5% but in almost 20% of those with gastrointestinal bleeding.

Oral manifestations. The lips and tongue (especially the dorsum and tip) are sites of telangiectasia in about 60% (Fig. 13–99). The palate, gingiva, buccal mucosa, and mucocutaneous junctions may be similarly affected in about 20%. Recognition of oral lesions has often led to the correct diagnosis. Bleeding from the mouth is second in frequency to epistaxis. It has been noted in about 20% (8). Hemorrhage from the gingiva and buccal mucosa occurs less frequently than from the lips and tongue. A dramatic report of bleeding from telangiectasia of the tongue was given by Bean et al (8). Philips (59) mentioned a fatal outcome after gingival bleeding. Gingival hemorrhages may become manifest at a rather late age. Labial lesions are more common (about 85%) in those with gastrointestinal bleeding. Dental prophylaxis has caused bleeding from lip telangiectases (59). Even toothbrushing should be carried out with great care in patients with gingival telangiectasia.

Pathology. Angiographic studies have demonstrated three different vascular abnormalities: aneurysms, arteriovenous communications, and angiomas (27). Histologically, the telangiectases are found just beneath the epidermis. Their walls are extremely thin, consisting of a single layer of endothelial cells on a continuous basement membrane. The telangiectases are not associated with new formation of vessels but consist solely in marked dilatation.

The small vascular lesions range from dilatation of postcapillary venules to dilated convoluted venules that connect directly to dilated arterioles. As the lesions become mature, the venules develop excess layers of smooth muscles without elastic fibers. Mononuclear cells, principally lymphocytes, collect in the perivascular spaces during the process (13). The arteriovenous malformations are merely much larger direct connections between arteries and veins.

Differential diagnosis. Scrotal angiokeratomas are present in 10%–20% of normal males over 50 years of age (7,66). Sublingual phlebectases (caviar spots) are present in about 15% of healthy males under 40 years (68) and in 50% of males and 20% of females between 50 and 60 years of age. Caviar spots increase with age, so that 60% of males and 75% of females between 70 and 79 have them (7). Spider nevi have been noted in over 45% of healthy school children (4) and in about 15% of normal adults (7). Cherry angiomas (de Morgan spots) are seen in 90% of patients over 40 years of age (75). Phlebectasia of the lips or oral mucosa was noted by Bean (7) in about 50% of normal individuals over 40 years of age. Autosomal dominant phlebectasia of the lips was described by Reed (69). There is a plethora of types of angiomatosis that may affect oral structures. The interested reader should carefully peruse the works of Bean (7,8) and Mulliken and Young (53). Labial involvement is common in *Fabry syndrome*, and oral angiomas occasionally occur in *Maffucci syndrome*. Multiple phlebectasia of the oral cavity (lower lip, oral floor, buccal mucosa, palate), jejunum, and scrotum is a

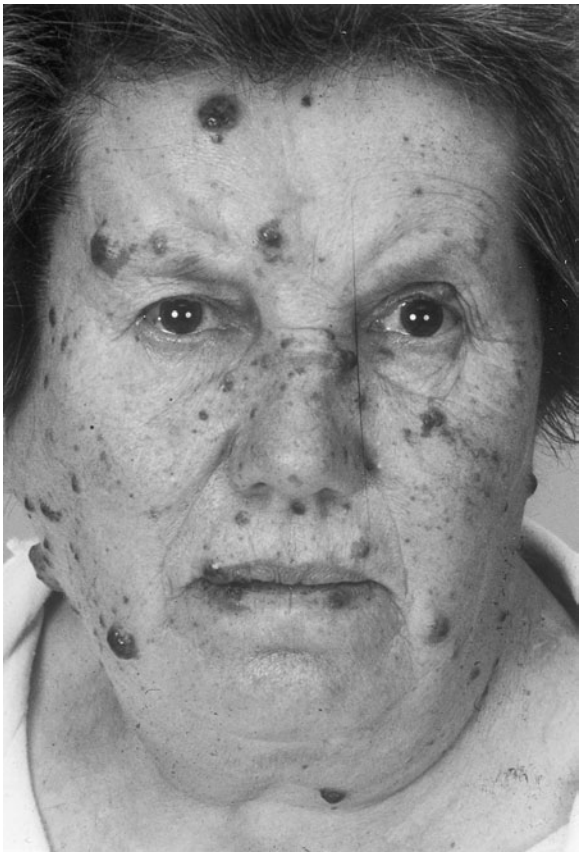

Fig. 13–100. *Blue rubber bleb nevus syndrome*. Note multiple bladderlike lesions of skin. (Courtesy of O Jumbou, Nantes, France.)

nongenetic, age-dependent association first described by Rappaport and Shiffman (68). Most patients have been males over 40 years of age. The scrotal lesions (Fordyce angiokeratomas) are round, raised, red to black, well-defined lesions less than 4 mm in diameter. Phlebectatic lesions are present in the wall of the jejunum, less often of the ileum or cecum. A number of patients have also had gastric or duodenal ulcer (68,75). Conversely, Gius et al (25) found that 25% of patients with peptic ulcers exhibit phlebectatic lesions of the lower lip.

Strawberry nevi with severe developmental delay, unusual facies, and flexed fingers has been noted (85). Massive lymphangiomatosis, lipomatosis, and hemangiomatosis has been described (55). *Facial angiomatosis, supraumbilical raphé, and non-union of the sternum* is a recognized syndrome.

Bean (7,8) defined the blue rubber bleb nevus syndrome as multiple, vascular, nipple, or bladder-like lesions of the skin and mucous membranes of the gastrointestinal tract that may be accompanied by gastrointestinal bleeding and hepatic and pulmonary angiomas. The lungs, liver, spleen, joints, and subcutaneous tissues are occasionally involved. The disorder has autosomal dominant inheritance. Oral and facial angiomas have been noted in several cases (6,37,38,80) (Fig. 13–100). The gene has been mapped to the short arm of chromosome 9 (22).

Autosomal dominant multiple glomus tumors exhibit only cutaneous involvement (74). Multilocular hemangiomatosis, separable from the above by the tendency of these lesions to disappear before the second year of life, may also involve the mouth (26,36). Katz and Askin (41) described oral lesions in a patient with multiple hemangiomas with thrombocytopenia, a variant of the Kasabach-Merritt syndrome. Also present were intraosseous angiomas and hepatosplenomegaly. Takato et al (82) reported a giant hemangioma of the parotid gland associated with Kasabach-Merritt syndrome. LaDow et al (43) noted a maxillary angioma in a patient with von Hippel syndrome, and Tasanen (83) described oral, retinal, and encephalic angiomatosis in a patient with thrombocytopenia. Arteriovenous aneurysms of the mandible and retina with hematemesis and epistaxis were described by Bower et al (11). The acral arteriovenous tumor is found on the face or less often on the extremities of middle-aged individuals (16). Vascular malformations (cavernous and capillary angiomas, A-V malformations), especially involving the oral mucous membranes and the skin and soft tissues of the extremities, were reported in an extremely large kindred (58).

Telangiectasia is also seen in CREST syndrome (*c*alcinosis, *R*aynaud's phenomenon, *e*sophageal dysfunction, *s*clerodactyly, and *t*elangiectasia), a form of scleroderma (21). This nonhereditary syndrome has marked female predilection. The various components of the syndrome characteristically appear at various times in a patient's life (72). Only rarely does the disorder present prior to puberty; in these cases, Raynaud's phenomenon first becomes evident (87). Calcinosis is usually limited to the areas of sclerodactyly. Telangiectasias of the face (especially of the cheeks, nose, and lips), oral mucosa, hands, and upper trunk are the most common. The nasal mucosa is characteristically spared. Primary biliary cirrhosis has been described in several individuals. CREST syndrome patients usually exhibit antinuclear and anticentromeric antibodies (24).

Laboratory aids. The hemoglobin and erythrocyte count may be lowered because of hemorrhage. When telangiectases are suspected in the gastrointestinal tract, gastroscopy and sigmoidoscopy may be done. To diagnose arteriovenous fistulas, angiography, computed tomography, and nuclear magnetic resonance (NMR) imaging are extremely helpful (28,54,84).

Hereditary hemorrhagic telangiectasia has been reported concomitantly with thrombocytomegaly, primary thrombocytopenia (17), hemophilia A (44), but most often with Von Willebrand's disease (3,15).

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Table 13–4. Comparison of clinical findings of autosomal dominant and recessive forms of pseudoxanthoma elasticum

Characteristics	Dominant I (%)	Dominant II (%)	Recessive I (%)	Recessive II (%)
Cutaneous changes				
Classical peau d'orange and flexural rash	100	25	75	
Macular rash		70	15	
General increase of extensibility	10	65	10	
General cutaneous PXE				100
Vascular disease				
Angina	55			
Claudication	55			
Hypertension	75	10	20	
Hematemesis	10	5	15	
Ophthalmic abnormalities				
Severe choroiditis	75	10	35	
Angioid streaks	35	50	50	
Washed-out pattern		15	2	
Prominent choroidal vessels		20		
Myopia	25	50	5	
Blue sclerae	10	40	10	
Other findings				
High-arched palate		55	15	
Joint hypermobility		35	5	

(Based on data presented by FM Pope, Arch Dermatol 110:209, 1974.)

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Acrolabial telangiectasia

Millns and Dickens (1) described blue lips, blue nails, and blue nipples in a mother and two daughters. There was also discrete telangiectasia of the chest, elbows, and dorsa of hands, varicosities of the lower legs, and migraine headaches. The syndrome is probably different from the hereditary benign telangiectasia reported by Ryan and Wells (2).

References (Acrolabial telangiectasia)

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Pseudoxanthoma elasticum

Originally described by Rigal (51), in 1881, and Balzer (4), in 1884, and grouped with the xanthomatoses, the syndrome of alterations of the skin, recurrent severe gastrointestinal hemorrhages, weak peripheral pulses, and failing vision was identified as a separate nonxanthomatous entity and named by Darier (15) in 1896. Angioid streaks were added to the syndrome by Grönblad (23) and Strandberg (59) in 1929, although they had been described as early as 1889 by Doyne (17). Various types have been described. Thorough reviews are those of McKusick (36) and Neldner (41). An excellent historic review was written by Pope (45). Classification has been recently reported by Lebwohl et al (33).

The data presented represent the average of the various types. If ascertainment is made from skin changes, then 65% of patients are female, although this may be due to cosmetic concerns. However, it has also been suggested that there may be an estrogen effect, based on the aggravation of cardiac symptoms during pregnancy (54). The actual risks of serious complications during pregnancy, however, may be overstated (74). If angioid streaks are used for discernment, there is no sex predilection. The combined prevalence of all types has been estimated at 1/40,000 by Altman et al (1) and 1/70,000 to 1/100,000 by Struk et al (60).

The primary alteration in PXE is calcification of elastic fibers due to the accumulation of polyanions within the fibers that may play a role in increased calcium binding (35). Gordon et al (21) found evidence that increased, abnormal catabolism of proteoglycans occurred because of increased secretion of serine protease. Baccarani-Contri et al (2) also suggested defective matrix production.

Elevated lysine and hydroxylysine levels in collagen (6) and raised glutamine, asparagine, glutamic acid, and aspartic acids in the elastin (7) have been discovered. There is some evidence that a relationship may exist between hyperphosphatasemia and PXE (38). Also see Differential diagnosis.

Pseudoxanthoma elasticum is genetically heterogeneous, but most cases have autosomal recessive inheritance (36,62). Pope (45–47) suggested that there are two recessive and two dominant forms. The alleged clinical differences are delineated in Table 13–4. However, Stutz et al (61), because of marked variability in expression, could not support two autosomal recessive types. Neldner (41) could not separate distinct phenotypes among 100 patients. Parental consanguinity is seen in at least 20% of those with a recessive form.

Viljoen (67) surveyed 81 patients with PXE in South Africa and Zimbabwe. Three had autosomal dominant PXE, type I, 3 autosomal dominant, type II, 19 autosomal recessive, type I, and 6 autosomal recessive, type II disease. However, 50 individuals of Dutch-French Huguenot extraction had a distinct clinical subgroup characterized by autosomal recessive inheritance, mild to moderate cutaneous and cardiovascular changes, but severe visual impairment by age 50 due to macular neovascularization and hemorrhage (16).

In 1997, Struk et al (60) reported linkage of PXE to 16p13.1. They suggested that allelic heterogeneity with different variants of a single disease gene residing on 16p13.1 accounts for both recessive and dominant forms of PXE. They commented on a more common autosomal recessive form and a less common autosomal dominant pattern of inheritance. Van Soest et al (66), in 1997, mapped an autosomal recessive PXE from a genetically isolated population in the Netherlands also to 16p13.1.

Mutations in a gene encoding ABC transporter cause both the dominant and recessive disorders (5a,33a,52). The gene is in the ATP-binding cassette superfamily which is involved in multidrug resistance.

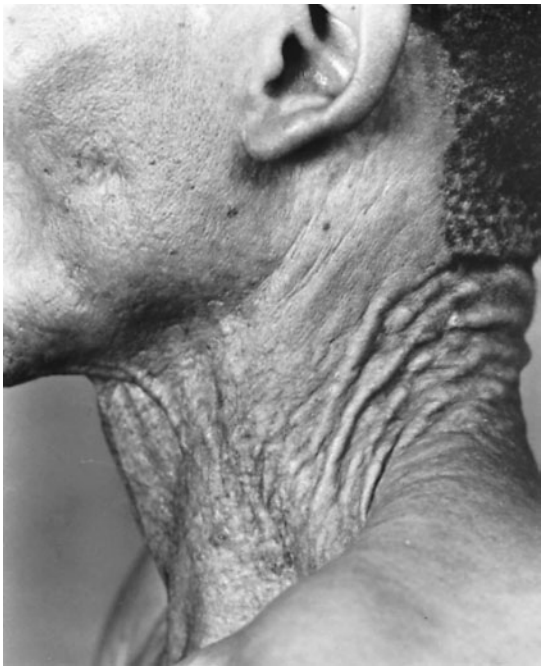

Fig. 13–101. *Pseudoxanthoma elasticum*. Skin becomes thickened and markings are accentuated by yellowish papules, especially around neck, axilla, elbows, and groin. (From T Heyl, Arch Dermatol 96:528, 1967.)

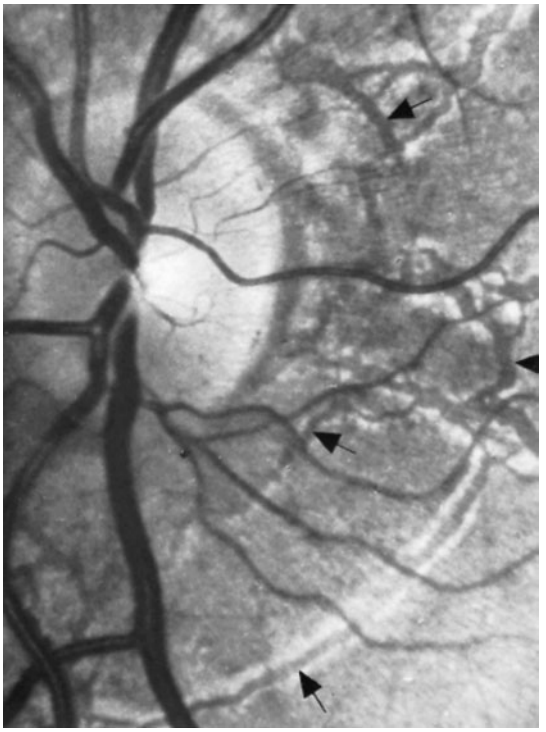

Fig. 13–102. *Pseudoxanthoma elasticum*. Arrows point to angioid streaks. Egg shell "fractures" in Bruch's membrane, usually grouped around optic disks, mimic appearance of blood vessels. (Courtesy of WF Hoyt, San Francisco, California.)

Skin. The skin becomes thickened and the markings are accentuated by raised, yellowish, flat papules, especially about the mouth, neck, axillas, elbows, groin, and periumbilical area (28). A few yellowish papules on the neck or axilla to virtually general cutaneous involvement have been described in association with calcification of the subcutis (27). These changes, usually recognized after the second decade, may appear as early as the third or fourth years of life. The yellowish skin becomes inelastic, redundant, thickened, and grooved, the normal skin marking becoming accentuated so that the skin resembles coarse-grained leather, especially on the neck and in the axilla (Fig. 13–101), Miescher elastoma has also been noted (36,55), and epidermal perforation was found in one woman with hypertension and chronic renal failure who was subsequently diagnosed as having PXE. Acne was present in 42% of patients in one study (68).

Ultrastructural changes consist of granular changes in elastin fibers (24). They exhibit an increased affinity for cationic stains (53). Thready material found in lesions consists of fibrinogen, collagenous protein, and glycoprotein (73).

Eyes. Visual disturbances have been noted in almost 30% of older patients (16). Funduscopic examination demonstrates atypical drusen and white, brown, or gray streaking (angioid streaks) in over 85% (10,11). The streaks probably appear in the second decade or later. They present as a ring around the optic disc extending outward beneath the retinal vessels. Although resembling vessels, they actually represent discontinuity in Bruch's membrane (Fig. 13–102). Retinal hemorrhage, followed by organization, eventuates in loss of visual acuity. Less often there is senile macular degeneration or central chorioretinitis (8,36,65). Other eye findings have included myopia in 26% and bilateral cataracts in 5% of 19 patients with PXE (68).

Cardiovascular system. By the third decade, there may be weakness or absence of pulses in the arms and legs, accompanied by variable degrees of intermittent claudication in about 20% (10,37). Radiographic examination has revealed calcification of peripheral arteries, especially those of the lower extremities, in about 15% (18). Renovascular hypertension has been noted in about 20% (18). Angina pectoris occurs in at least 50% of the patients (10), and abdominal angina due to stenosis of the celiac artery is common (36). Congestive cardiac failure is found in about 70% (50). Careful coronary artery evaluation is required in young patients with PXE, even though asymptomatic, because coronary artery disease seems to be frequent (29).

Lebwohl et al (31,32) reported that 71% had echocardiographic evidence of mitral valve prolapse. Others found mitral valve prolapse in only 18%; however, they suggested that mitral valve prolapse may be more common in the dominant forms of PXE.

Hemorrhage, especially gastrointestinal, occurs in 15% (13) because of involvement of small blood vessels. A number of patients have had peptic ulcer (1). Bleeding may occur in the retina, kidney, uterus, or bladder (8). Epistaxis (10) and hemarthrosis have been recorded. Aneurysms of the internal carotid artery have also been reported, and there is one report of ruptured aneurysm of the anterior spinal artery (30).

Oral manifestations. The skin about the mouth may become redundant, the nasolabial folds and skin creases becoming accentuated and producing a saggy appearance. The mucosal surface of the lips, especially the lower one, may exhibit yellowing intramucosal nodules (15,19,36) in about 10%. The buccal mucosa, soft or hard palate, and tonsillar areas may be similarly affected (10,39,46,47) (Fig. 13–103). The vaginal, gastric, and rectal mucosas have also been involved (10,20). Ultrastructural study of oral lesions showed large numbers of thickened and twisted collagen fibers (14). Highly arched palate has been occasionally noted, particularly in the autosomal dominant form (51).

Other findings. Neurologic deficits may result from complications of hypertension and cardiovascular disease: aneurysmal dilation of vessels, subarachnoid and intracerebral hemorrhage, bilateral carotid occlusion, psychiatric disorders, and seizures (10,18,25).

Mamtora and Cope (34) described two cases of pulmonary opacities, and cited two other cases. Jackson and Loh (26) reported a case of pulmonary involvement; lung biopsy showed deposition of calcium in arteries, arterioles, and venules, as well as in alveolar lumina and septa.

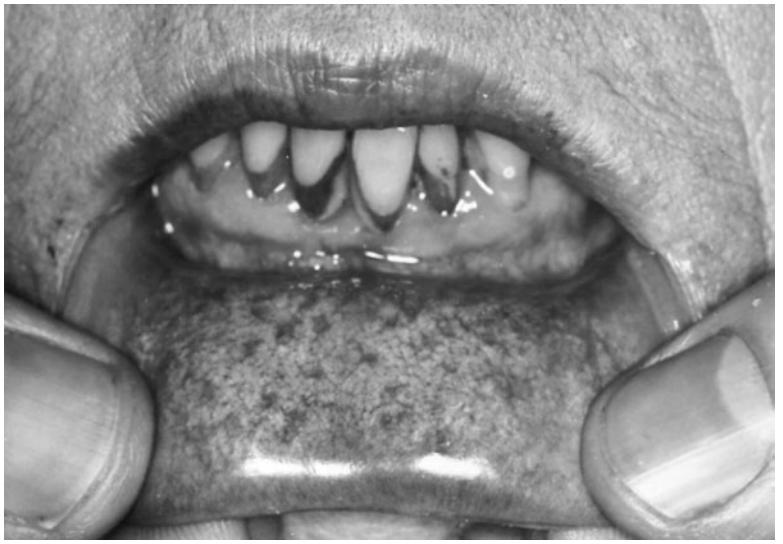

Fig. 13–103. *Pseudoxanthoma elasticum*. Mucosal surface of lower lip exhibits yellowish intramucosal nodules. (Courtesy of RM Goodman, Tel Aviv, Israel.)

Prick and Thijssen (49) described several skeletal anomalies, including dysplastic vertebrae and fibro-osseous dysplasia and transverse sclerotic bands of the metaphyseal regions of long bones. Joint hyperextensibility has also been noted in a few cases.

Hashimoto's thyroiditis, hypothyroidism, hyperthyroidism, and diabetes mellitus have also been occasionally reported (40).

Berde et al (5) summarized the pregnancy histories in seven women with PXE and noted that five suffered severe gastrointestinal hemorrhage during one or more pregnancies. In four, the bleeding that occurred during pregnancy was the first such episode in their lives. It is suggested that a diagnosis of PXE be considered for any patient with gastrointestinal hemorrhage, especially if routine clinical and endoscopic examination fails to reveal the cause, and if raised yellow plaque-like lesions are seen in the stomach by endoscopy (12,58). In one instance of intrauterine growth retardation, it was suggested that maternal vascular compromise led to chronic uteroplacental insufficiency (9). Miscarriage during the first trimester of women with PXE is increased (69).

Differential diagnosis. Angioid streaks may also be seen in Paget's disease of bone. A combination of Paget's disease and PXE has been described by Woodcock (72), Shaffer et al (56), and others (36). Angioid streaks have also been seen in sickle-cell disease, possibly because of iron deposits in Bruch's membrane (23), and in osteoectasia with macrocranium (hyperphosphatasia). Angioid streaks in combination with tumoral calcinosis and hyperphosphatemia have been noted in several families (3). The clinical skin changes in senile elastosis somewhat resembles those on PXE. They may be seen in the Ehlers-Danlos syndrome, following trauma, and in other disorders (24). Pseudoxanthoma elasticum-like changes have also been found in patients treated with high doses of D-penicillamine (64).

Laboratory aids. The involved skin or mucous membrane presents a characteristic microscopic picture. The changes are observed in the middle and lower part of the corium. The elastic tissue appears as fragmented masses, presenting a granular structure that is due at least in part to the presence of calcium salts demonstrated by von Kossa staining (Fig. 13–104). The amount of normal collagen fibers is reduced, whereas reticulum fibers are present in large amounts. The finding of calcium salts in ostensibly normal elastic fibers indicates that calcification is the primary event in PXE (14). Increased amounts of calcium have also been found in the skin on microincineration (33). Photographs of the fundus following injection of fluorescent dye clearly demonstrate the angioid streaks (57).

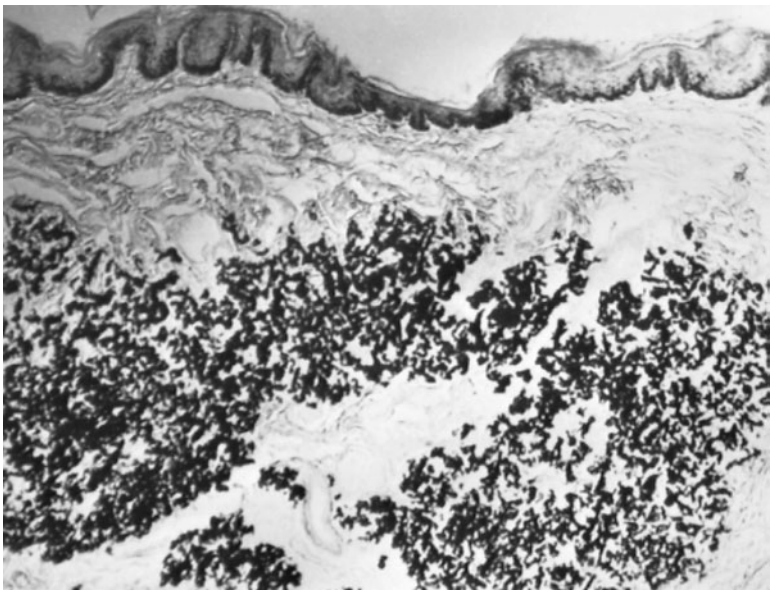

Fig. 13–104. *Pseudoxanthoma elasticum*. Elastic tissue appears fragmented and granular because of presence of calcium salts (von Kossa stain). (From T Heyl, Arch Dermatol 96:528, 1967.)

Using light and electron microscopy, Vogel et al (71) noted differences in appearance between elastic fibers in patients with dominant and recessive forms. In addition, patients with the dominant condition had only an unusual aggregation of small and large collagen fibrils. However, Pierard (44) did not find any significant differences between dominant type I and recessive type I skin biopsies, stating that variations among individuals were greater than variation between the two types. Hausser and Anton-Lamprecht (24) described specific ultrastructural changes.

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Progeria (Hutchinson-Gilford syndrome)

Progeria, consisting of dwarfism, early aging, and characteristic craniofacial appearance, was first described by Hutchinson (35) in 1886 and Gilford (26,27) in 1897 and 1904. Approximately 85 cases have been recorded to date (5,48). The frequency of progeria is about 1 per 4 to 8 million live births with a 2:1 male/female ratio (6). Autopsies have been performed in fewer than a dozen cases (3,27,57,63). Good reviews on the subject are those of Badame (4) and Beauregard and Gilchrest (6). An early review is that of Gabr (22).

The patient reported by Feingold and Kidd (19), followed only until 22 months of age, had prominent eyes and prognathism, although early scleroderma, anterior hair loss, and a horse-riding stature certainly suggest progeria, as do the three sibs reported by Monue et al (45). Rodriguez et al (55) described a lethal neonatal form.

Since the aging process is accelerated in progeria, cultured fibroblasts from affected individuals possibly might show an earlier appearance of altered gene products or a more severe disturbance of such products. Enzyme thermolability studies from cultured fibroblasts (32) were consistent with both possibilities, showing a significantly higher percentage of heat-labile glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, and hypoxanthine-guanine phosphoribosyltransferase. No significant association between HLA type and progeria has been detected (8). Sister chromatid exchange frequencies in progeria have not differed significantly from normal (13).

Aminoaciduria has been documented (60). Hypermetabolism has been suggested by some (60,62), but denied by others (55). Many patients have exhibited elevated cholesterol or phospholipid levels (54,65). Rosenthal et al (57) suggested that progeria was a disease of intermediate lipoprotein metabolism. Villee et al (65) reported unresponsiveness to growth hormone, relative insulin resistance, and highly cross-linked collagen. Hyperglycemia and insulin resistance were documented by Rosenthal et al (57).

In 1993, Clark and Weiss (11) observed a glycoprotein of M(r) 200 kDa that was consistently present in protein preparations from progeria fibroblasts and that was absent, or markedly reduced, in preparations from control fibroblasts. This glycoprotein, observed in progeria fibroblasts in vitro, could reflect a perturbation in glycosylation that may underlie the connective tissue defects seen in progeria.

Affected sibs were reported by Franklyn (21), Lejman (39), Maciel (41), and Mostafa and Gabr (46), and affected cousins by Khalifa (37). Consanguinity has been noted in a few instances (21,37,46). Monozygotic twins concordant for progeria were reported by Viégas et al (64). However, autosomal recessive inheritance is debatable, as most cases have been sporadic and the consanguinity rate is low. It may be dominant, the few familial cases representing gonadal mosaicism. Fathers of affected children tend to be older (36). Brown et al (10), in 1990, described identical twins with progeria who developed heart failure at the age of 8 and died within one month of each other. Cytogenetic analysis from a post-mortem skin biopsy revealed an inverted insertion of chromosome 1 described as XY, inv ins (1;1)(q32;q44q23) in 70% of cells. The seriousness of the condition with its early demise during teenage years may have an effect on many parents as far as having further offspring (9).

Growth. Average birth weight is 2.7 kg. Growth proceeds almost normally until the first year, when it essentially plateaus until about 10 years of age. By the end of the first decade, height is approximately that of a normal 3-year-old; only rarely do patients exceed 110 cm in height or 15 kg in weight (14). There is no sexual maturation.

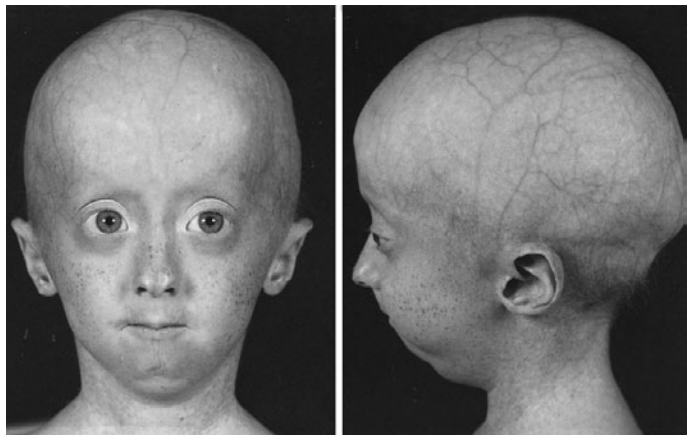
Abdenur et al (1), in 1997, reported that elevated GH levels are characteristic of this disease and that an elevated basal metabolic rate could be the cause of the failure to thrive seen in Hutchinson-Gilford progeria. Combined nutritional therapy and growth hormone treatment improved the growth velocity, increased the levels of growth factors, and resulted in decreased basal metabolic rate. However, the response to these therapies decreased over time and did not seem to prevent the progression of atherosclerotic disease.

Performance. Intelligence is normal. The voice is high-pitched and squeaky (25,56,58). Hearing may be deficient (47).

Craniofacial appearance. During the second year of life, scalp hair is lost and replaced by downy fuzz. Eyebrows and, occasionally, eyelashes are lost. The face is disproportionately small in relation to the cranium, although, in fact, head circumference is usually 2–4 cm smaller than average. Frontal and parietal bossing occur together with prominent scalp veins. The ears are small without lobules and the nose is thin and rather beaked (Fig. 13–105). Micrognathia and delayed dental eruption of the permanent teeth are common features, the deciduous dentition often being retained. The mandibular angle may be increased. The plane angle is steep and the anterior fontanel is open. There are no frontal sinuses and mastoid development is poor. Teeth may be crowded because of mandibular hypoplasia with normal teeth. However, teeth have been irregular in form, small, discolored, and deficient in number in most cases (34,67). Microscopic evidence of senile changes in the dental pulp has been reported (2,12,14,56).

Musculoskeletal system. The chest is narrow or pyriform and the abdomen protuberant. Mild flexion of the knees results in a horse-riding

Fig. 13–105. *Progeria.* (A,B) Face is small in comparison with cranial vault. Lashes are absent, brows are sparse. Note beaklike nose, mandibular hypoplasia, absent earlobes, prominent scalp veins. (From L Atkins, N Engl J Med 250:1065, 1954.)



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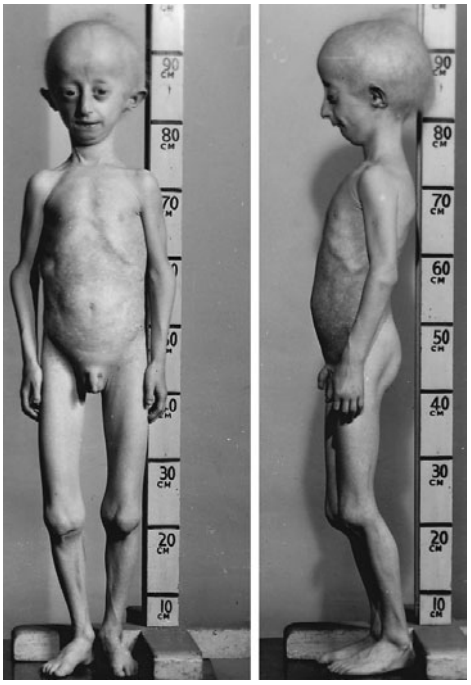

Fig. 13–106. *Progeria*. Clavicles are short, hands, elbows, and knees contracted, giving "horse-riding" stance. Note senile appearance. (From L Atkins, N Engl J Med 250:1065, 1954.)

stance (Fig. 13–106). The bones are delicate and osteoporotic, although bone maturation is normal. The joints of the extremities become prominent and limited in extension from periarticular fibrosis, which appears in some patients as early as the sixth year. Less frequently affected are the spine, elbows, and knees. Hip pain, subluxation, and eventual hip dislocation result from degenerative changes in the acetabulum (24,44).

Radiographically, terminal phalanges undergo progressive osteolysis and become abnormally short and taper abruptly to pointed ends (Fig. 13–107A). The clavicles also undergo progressive osteolysis. Coxa valga and acetabular degeneration are constant findings. There may be some predilection for fracture of the humeral shaft. There is also loss of muscular and subcutaneous fat. The calvaria is remarkably thin, the anterior fontanel is open, and frontal sinuses are often absent. The neurocranium is normal in size and configuration. Mastoid development is poor (2,3,21,23,38,43,44,49). Osteosarcoma has been reported by King et al (38).

Cardiovascular system. Cardiac murmurs appear after 5 years of age, followed by diastolic systemic hypertension and cardiomegaly. Atherosclerosis is early and severe, and anginal attacks and cerebrovascular accidents have been experienced as early as 7 years of age, but, in most instances, death occurs by approximately 14 years of age (5,17,42,62) from myocardial infarction or congestive heart failure. However, a 45-year-old man had been documented (48). Baker et al (5) reviewed the cardiovascular abnormalities.

Skin and skin appendages. The skin is thin, atrophic and often pigmented, with sparse subcutaneous fat (29). Scleroderma-like changes have been recorded in some patients. Veins are especially prominent over the scalp and thighs. Electron microscopic studies of scalp hairs reveal abnormal longitudinal depressions with minor cuticular defects. The nails are thin, yellow, atrophic (Fig. 13–107B), or absent (3,12,20, 56,61,63,69).

Differential diagnosis. Several patients with *Hallerman-Streiff syndrome* have been erroneously labeled as having progeria. It may mimic scleredema of infancy (18). Occasionally patients with *Bloom syndrome, mandibuloacral dysplasia*, or *Cockayne syndrome* have also mistakenly been thought to have progeria (52). *Werner syndrome* is also a condition of premature aging. Other progeroid syndromes have been discussed elsewhere including the *Ehlers-Danlos syndromes, Wiedemann-Rautenstrauch (neonatal progeroid) syndrome, De Barsy syndrome, Mulvihill-Smith syndrome*, acrogeria (15), metageria (28), acrometagyria (30), and a unique disorder described by Ruvalcaba et al (59). The patient of Green (31) surely had a form of Ehlers-Danlos syndrome. Delatycki et al (16) described a lethal neonatal progeroid syndrome that may have X-linked inheritance. Perhaps another example is that of Le Merrer et al (40). We suspect that the brothers reported by Parkash et al (50) and Ramesh and Jain (53) had mandibuloacral dysplasia. Other patients represent a distinct progeroid disorder (51,66). Still another unknown progeroid condition is that of Hagadorn et al (33). The patients of Grossman et al (32) had Seckel syndrome or Cockayne syndrome.

Laboratory aids. Marquart et al (43) reported increased secretion of fibronectin and collagen by fibroblasts of an affected patient. There is reported increase in urinary hyaluronic acid (68).

References [Progeria (Hutchinson-Gilford syndrome)]

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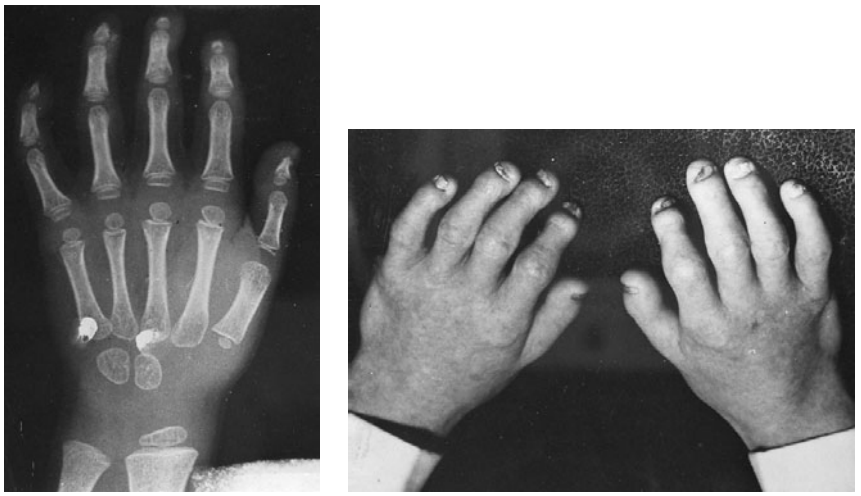

A B

Fig. 13–107. *Progeria*. (A) Terminal phalanges are short and taper abruptly. (B) Skin of hands is dry, taut, and mottled; fingers are short with enlarged joints. Nails are dry, brittle, and hypoplastic. (From MM Album and JW Hope, Oral Surg 11:985, 1958.)

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Werner syndrome

The syndrome, first delineated by Werner (59) in 1904, consists of shortness of stature, premature graying of hair (canities), baldness, scleropoikiloderma, trophic leg ulcers, juvenile cataracts, hypogonadism, diabetes mellitus, calcification of blood vessels, and osteoporosis. Confusion with Rothmund-Thomson syndrome occurred until Oppenheimer and Kugel (42), Thannhauser (56), and Greither (23) clearly separated the two syndromes.

The frequency of the disorder was estimated to be between 1 and 20 cases per million population in the United States (9). It appears to have a high frequency in Sardinia (5) and Japan (9). Over 150 cases have been reported (9,15,24,34,36,45).

Autosomal recessive inheritance has been established (9,19). In the United States, parental consanguinity has been found in 20%–35% (9), while in Japan it is 70% (19).

In a study of 21 Japanese families, Goto et al (20), in 1992, demonstrated close linkage of the gene (*WRN*) to a group of markers on chromosome 8. The region was narrowed down to 8p11.1–21.1 by Yu et al (61) in 1994. In 1996, Yu et al (62) identified the *WRN* gene by positional cloning. The predicted protein showed significant similarity to DNA helicases. Gray et al (22), in 1997, and Huang et al (26) confirmed that Werner syndrome (WS) protein is indeed a DNA helicase.

For DNA replication, recombination, repair and transcription, the unwinding of double-stranded DNA by helicases is essential (12). Werner syndrome (WS) patients represent defects in at least three different types of biological function. First, WS cells show prolongation of the S-phase of the cell cycle, diminished frequency of initiation of DNA features implicating *WRN* in DNA replication (46,60). Second, an increased frequency of chromosomal rearrangements and DNA deletions is present in cells with mutations in *WRN*. This suggests that *WRN* plays a role in DNA recombination (14). Third, the hypersensitivity of WS cells to the DNA damaging agent 4NQO suggests that *WRN* has also a function in the repair of damaged DNA (41). Homozygous mutations, all of which lead to truncation of the protein, lead to Werner syndrome (4).

Matsumoto et al (31,32), in 1997, defined the genomic structure of the gene, identified 35 exons, and found the common mutation among Japanese. Later, several different types of mutations of *WRN* were reported in WS patients (21,43,62,63). In 1998, Marciniak et al (30) determined nucleolar localization.

Most or all of the mutations have been null mutations and not a single missense mutation had been identified. This would suggest that the heterozygous carriers of *WNR* would have a Werner helicase activity approximately 50% of normal. With a high carrier prevalence of 1/150 to 1/200, a vulnerable carrier state could have potential implications in public health.

The disorder becomes apparent in the third and fourth decades of life. Graying of the hair occurs at about 20 years, skin changes and loss of hair by 25, cataracts by 30, diabetes mellitus by 35, and death at about 45 years.

Short stature, due to arrest of growth at puberty, is a constant feature. Mean height is 157 cm for males and 146 cm for females (9,65). Weight is low, relative even to the short stature. Thinness of arms and legs and diminution in size of hands and feet are striking. In contrast, the trunk is often stocky and the abdomen protuberant (Fig. 13–108). Patients characteristically develop abnormally high-pitched, sometimes squeaky, or less often, hoarse voices due to vocal cord atrophy.

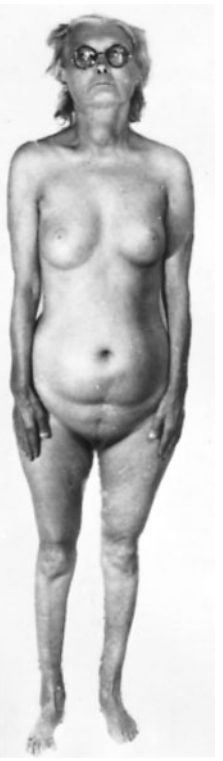
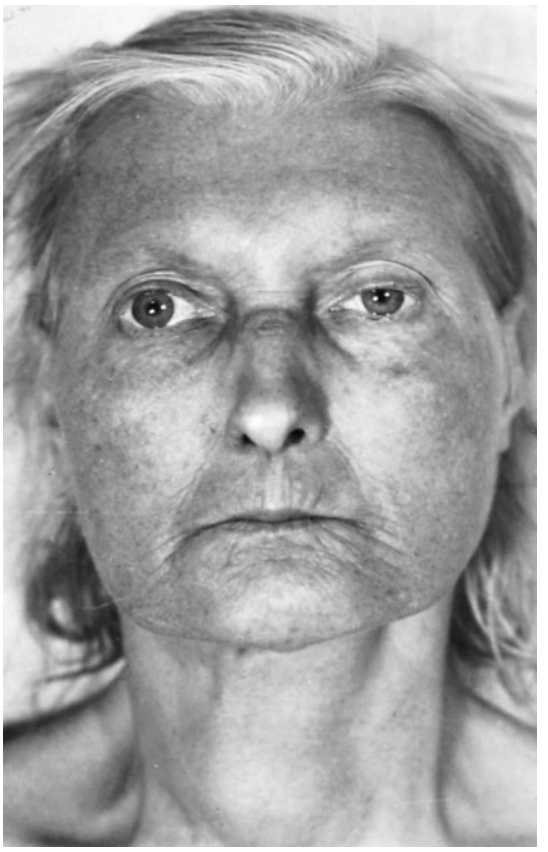


Fig. 13–108. *Werner syndrome*. Aged appearance together with marked thinness of arms and legs. (Courtesy of S Jablonska, Warsaw, Poland.)

Facies. The combination of atrophic skin changes, baldness, and graying hair (80%) gives these patients, even while young, an appearance of being 20–30 years older than their age. Although the cheeks are full, the nose assumes a pinched or beaked appearance due to hypoplasia of nasal cartilages (Fig. 13–109).

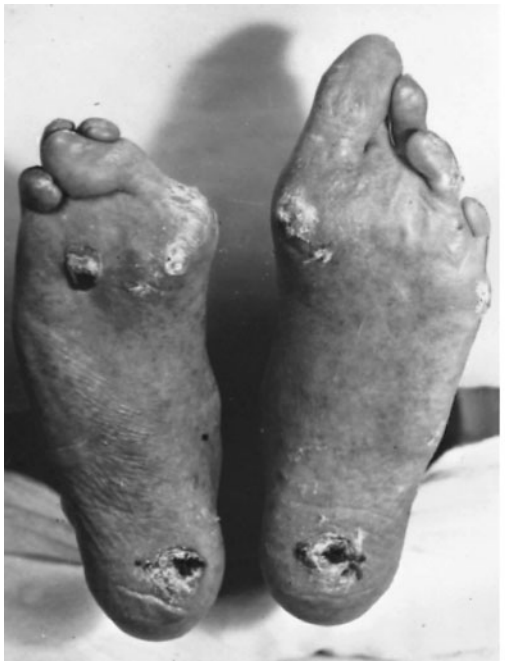
Fig. 13–109. *Werner syndrome*. Premature graying of hair, aging of skin. (Courtesy of S Jablonska, Warsaw, Poland.)



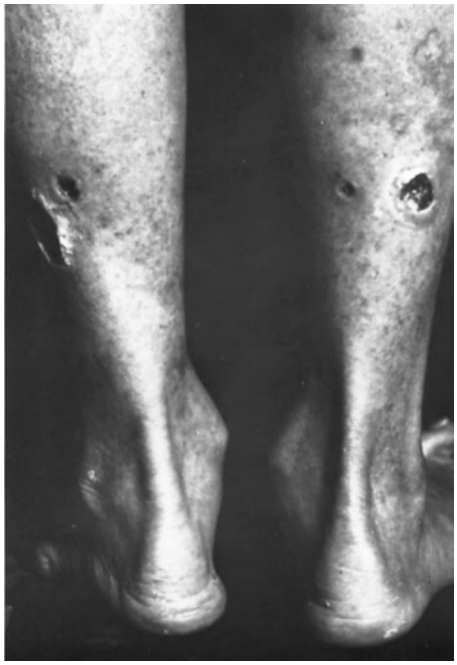
Skin. The principal areas of skin involvement are the face and distal extremities, especially the feet. There is atrophy of the skin over areas depleted of adipose tissue, connective tissue and musculature. This results in shiny smooth skin that adheres to the underlying tissues, giving a sclerodermoid appearance. In about 40% there is ischemic ulceration (Fig. 13–110). The eyes appear protuberant because of loss of circumorbital tissues. The ears may become stiff and inelastic. Circumscribed hyperkeratoses develop over bony prominences and on the soles, and may become ulcerated, with slow or no healing (49).

Localized or, less commonly, generalized hyperpigmentation, depigmentation, and telangiectasia occurring on the arms and legs are seen in nearly all patients with the term "poikilodermatous" then being applied. Some have generalized lentiginosis (28).

Eyes. Senile cataracts, another cardinal feature seen in 95%, are invariably bilateral, usually posterior, cortical, or subcapsular, and homogeneous or striate. They have abrupt onset during the third or fourth decade. Retinitis pigmentosa, senile macular degeneration, chorioretinitis, and corneal calcification have also been described (27,44,49).



A



B

Fig. 13–110. *Werner syndrome*. (A) Hyperkeratosis and ulceration of soles. (B) Ulceration and pigmentation of ankles. (A courtesy of S Jablonska, Warsaw, Poland. B from W Knoth et al, Hautarzt 14:145, 1963.)

Hair. Premature loss and graying of scalp hair with onset usually before 20 years is characteristic and seen in almost all patients (Fig. 13–109). Generalized hair loss involving the scalp, eyebrows, eyelashes, and body (axillary and pubic) hair may be secondary to hypogonadism.

Musculoskeletal system. Osteoporosis and profound wasting of the musculature of the legs, feet and hands are noted in at least 40% (Fig. 13–110). The feet are usually flat. Soft-tissue calcification has been observed in 35%, especially in the tendons, ligaments and synovia of the knees, elbows, and ankles (9). The tissues adjacent to these areas may also exhibit soft-tissue calcification similar to that observed in scleroderma (48).

Cardiovascular system. Patients develop severe, often generalized atherosclerosis. Calcification occurs in peripheral (Mönckeberg) vessels of the legs and in the mitral and aortic valves and coronary vessels in about 20% (9,48). Peripheral vascular disease further complicates or promotes atrophy and ulceration of the skin.

Endocrine system. Diabetes mellitus has been recognized in 45%–60% (9). However, the usual complications of diabetes (nephropathy, retinopathy, neuropathy) have not been observed. Neither the vascular disease nor the cataracts are well correlated with the diabetes mellitus.

Hypogonadism occurs in both sexes. Most males have small testes and penis, with diminished pubic hair. Women have poorly developed genitalia and breasts, and some never develop secondary sex characteristics. Menses are sparse and irregular. However, there are valid reports of men who have sired children and women who have borne children.

Central nervous system. Some patients may be mentally retarded (48), and about one-third may have mild neurologic deficits, such as loss of deep-tendon reflexes, paresthesias, and dizziness (9).

Oral manifestations. The skin around the mouth is often radially ridged (64) (Fig. 13–109). Frenkel (11) described atrophy of the oral mucosa.

Neoplasia. Over 10% have an unusual array of both benign and malignant neoplasms (meningiomas, paragangliomas, adenomas of the pituitary, thyroid, and adrenal glands); various malignant epithelial neoplasms (basal and squamous cell carcinomas of the skin, especially melanomas); adenocarcinoma of the thyroid, stomach, ovary, and liver; and malignant connective tissue tumors (fibrosarcomas, neurofibrosarcomas, leiomyosarcomas, osteosarcomas) (2,9,19,25,34,37,42,47–49,55,58,64). German (16) presented a critical analysis of reported tumors.

Differential diagnosis. In *Rothmund-Thomson syndrome*, the onset of skin changes and cataracts occurs during the first 10 years of life. Photosensitivity is present in about 35%. The skin also shows telangiectasia, scaling, and pigmentary changes. Skin cancer is a prominent feature.

Progeria, in contrast to Werner syndrome, has very early onset. There is severe dwarfing, nearly complete alopecia, absence of subcutaneous fat, and characteristic facies. Generalized atherosclerosis leads to early death.

Acrogeria refers to thin skin largely limited to the distal extremities (6). The subcutaneous vascular pattern is usually evident over the trunk. Several so-diagnosed patients really have *Ehlers-Danlos syndrome*. A definite inheritance pattern has not been established. Small stature and micrognathia have been present in several cases. Mulvihill and Smith (35) reported a syndrome of *premature aging, microcephaly, unusual facies, multiple nevi, and mental retardation*.

Mandibuloacral dysplasia is characterized by early onset, small mandible, and brachytelephalangy. Inheritance is autosomal recessive.

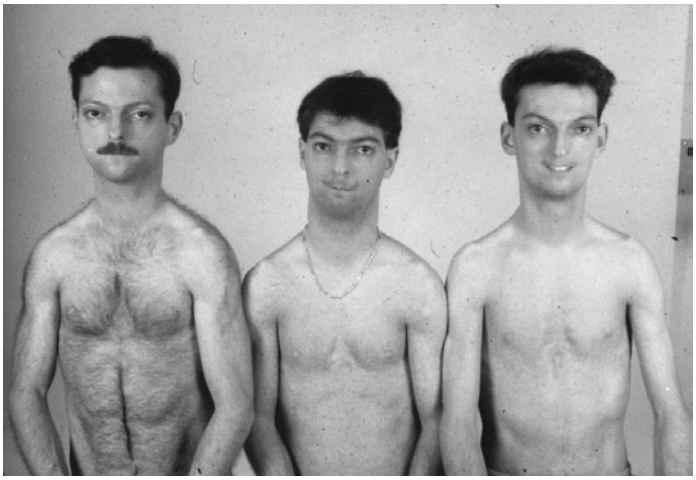
Metageria, an autosomal recessive disorder apparent at birth, is characterized by normal height and diabetes mellitus of early onset. There is no loss of hair and no cataracts. The skin is dry, atrophic, and mottled. The face is pinched with a beaked nose (17).

Myotonic dystrophy frequently has its onset in the second and third decades. Cataracts, diabetes mellitus, premature frontal baldness, and atrophy of the skin are features of the disorder. Testicular atrophy occurs, but the external genitalia are otherwise normal. Inheritance is autosomal dominant.

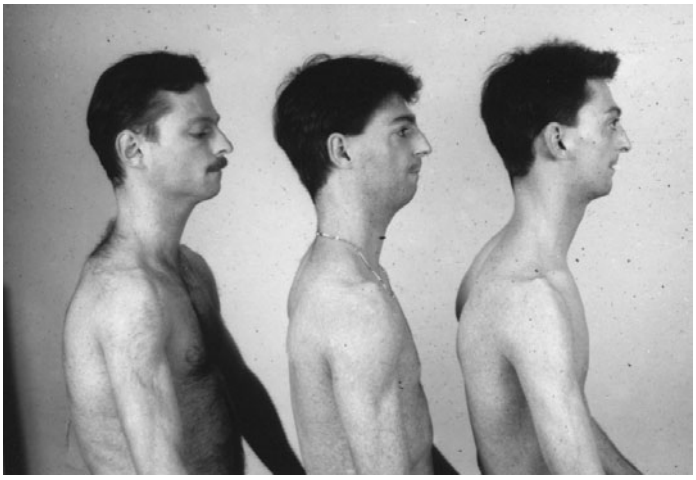
A Werner-like syndrome has been reported in three brothers (33), but in our opinion (RJG), they have *mandibulo-acral dysplasia* (Fig. 13–111).

Laboratory aids. Karyotypes of long-term cultured skin fibroblasts show multiple, variable, predominantly stable, essentially random translocations that are clonal in nature (variegated translocation mosaicism) (8,50–52,54). In contrast, lymphocyte cultures are only rarely reported to be abnormal (53). However, an increased number of chromosome breaks has been found (40).

Cultured fibroblasts have a greatly reduced potential for in vitro growth and a reduced lifespan (51). Bauer et al (1) found enhanced collagen



A



B

Fig. 13–111. *Werner-like syndrome*. Werner-like syndrome in three brothers believed to have *mandibulo-acral dysplasia*. (From H Mensing, Hamburg, Germany.)

synthesis. There is a slower rate of DNA replication (13,39), but repair function appears to be normal. An altered immune mechanism has been noted (7,38), but further studies need to be carried out.

Increased urinary hyaluronic acid has been found by several investigators (3,10,18,29,57).

DNA testing of WRN mutations is possible for the diagnosis of both Werner syndrome patients and heterozygote carriers.

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Mulvihill-Smith syndrome (premature aging, microcephaly, unusual facies, multiple nevi, and mental retardation)

Mulvihill and Smith (7) described a male with low birth weight, somatic anomalies and mild to moderate mental retardation, multiple pigmented nevi of the face, neck, and trunk, micropenis, and hypospadias (Fig. 13–112). A similar example in a female was reported by Wong et al (12). However, intelligence was normal.

The craniofacies is characterized by microcephaly, broad forehead, fine scalp hair, sparse facial hair, disproportionately small face with reduced lower facial height, small pointed chin, and marked micrognathia. Facial subcutaneous fat is deficient. Some have cataracts (6). There is moderate progressive sensorineural hearing loss. The voice is high pitched and hoarse. The ears are lobeless. Oligodontia is a constant feature. Approximately 10 cases of this condition have been described (1,2,4,5,9–11).

Ohashi et al (8) described a 30-year-old deaf, microcephalic, and severely mentally retarded woman with pigmented nevi and freckles, but also with immunodeficiency. The patient had severe T-cell dysfunction, severe verruca vulgaris of the hands, and a chronic, active Epstein-Barr virus infection. They suggested that immunodeficiency is a late development. The parents are first cousins, which suggested autosomal recessive inheritance. Some of these findings have been noted in WHIM syndrome (5a).

Bartsch et al (2) restudied a patient previously reported by Tympner et al (11) as a condition with "progressive combined immunodeficiency and ectomesodermal dysplasia." This patient, on follow-up, exhibited keratoconus (9) and locomotor ataxia and died of gastric carcinoma at 23 years (3).

De Silva et al (4) reported a 5-year-old boy with physical features suggestive of this condition. He had lymphopenia, low IgG2 and IgG4 immunoglobulins, and an absent in vitro proliferative response to pokeweed mitogen. Skin fibroblast growth was slow in culture, and the cells had a large number of inclusions.

One must exclude *Leopard syndrome*.

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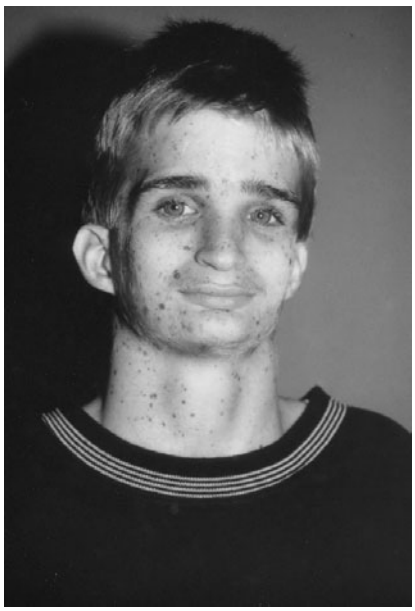
Wiedemann-Rautenstrauch syndrome

In 1977, Rautenstrauch and Snigula (12), believing that they were dealing with progeria in sibs, described a new progeroid syndrome that was recognized as such by Wiedemann (18), who two years later noted two unrelated male children. Approximately 20 examples have been described (1–5,6a,8–18). Inheritance is clearly autosomal recessive (2,3,11,12,18).

An aged facies is present from birth. Children are born small for dates and subsequent growth is slow. IUGR occurs late during the third trimester, with variable onset (7). Frontal and biparietal bossing, together with small facial bones (pseudohydrocephaly), gives the child a hydrocephalic aged appearance. The anterior fontanel is large and closes late. The sutures tend to persist. Scalp hair tends to be sparse but is of normal consistency. The scalp veins are prominent (16). The nose is small and beaked and the ears are low set and posteriorly angulated. The facial bones are hypoplastic, producing a triangular face. With time, the nose appears beaked. The mouth is small and the chin is somewhat prominent (13,14). Natal incisors are noted in 75% (5a,11,13) (Fig. 13–113). The syndrome is usually lethal by 7 months, but a few have survived into adolescence.

Subcutaneous fat is generally deficient, allowing the veins and muscles to become prominent, but lower-back fat accumulates during infancy (5). The abdomen is prominent. Height is short. The hands and feet are large with long fingers and toes. Radiologic studies done soon after birth show partial nonossification of the atlas and hypoplastic iliac bones but after 1 year, the changes have disappeared (8). There is delayed bone age and delayed closure of the anterior fontanel.

Mental and, especially, motor development are usually deficient (11). Horizontal nystagmus is noted with limited visual acuity (13). There is progressive neurologic degeneration by the age of 5 years. Lack of head control, hypotonia, severe truncal ataxia, dysmetria, and intension tremor are common. Martin et al (8) found extensive demyelinization of the central nervous system with an occasional tigroid pattern and large



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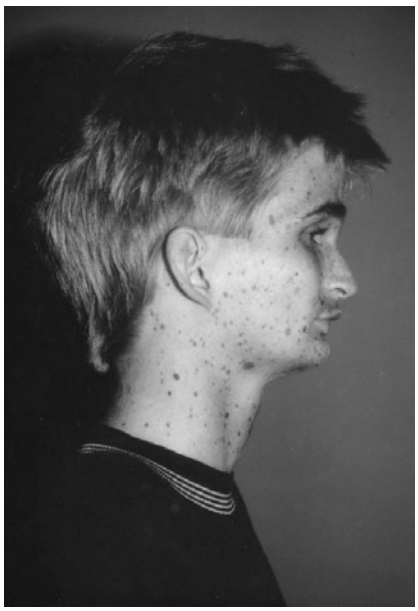

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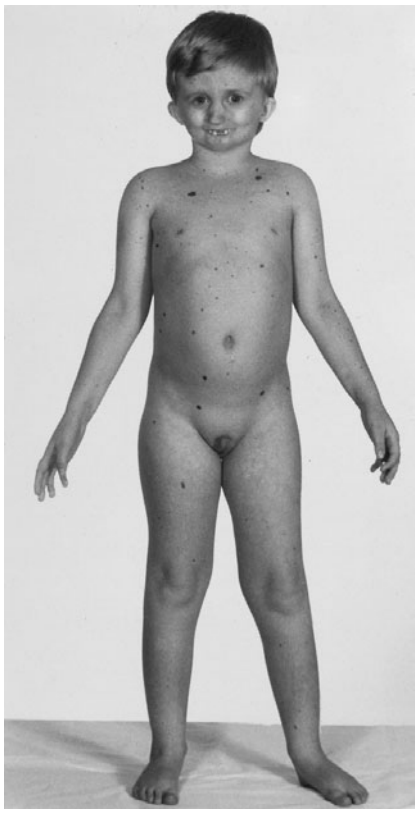

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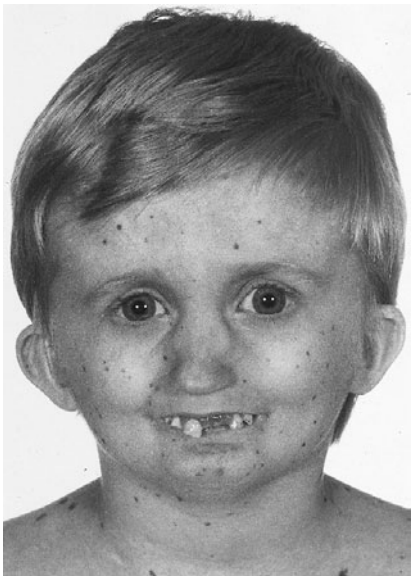

D

Fig. 13–112. *Mulvihill-Smith syndrome (premature aging, microcephaly, unusual facies, multiple nevi, and mental retardation).* (A,B) Microcephaly, broad forehead, sparse facial hair, disproportionately small face with reduced lower facial height, and numerous pigmented nevi of face and neck. (C,D) Note other patient similarly affected. (A,B courtesy of O Bartsch, Lübeck, Germany. C,D from M Baraitser et al, J Med Genet 25:53, 1988.)

amounts of neutral fat and myelin breakdown in macrophages, a picture characteristic of pure sudanophilic leukodystrophy (15).

Cryptorchidism has been noted (1,13), as well as enlarged penis (10,18). Recurrent respiratory tract infections are common. Most of the children die prior to the age of 5 years.

Arboleda et al (1), in 1997, reported increased levels of prolactin, testosterone, estradiol, and T4, with normal TSH levels and increased serum triglycerides and very-low-density lipoprotein in one case. They proposed that disturbance in the mechanism of bone maturation as well as hormone and lipid metabolism may be important in the etiology of the Wiedemann-Rautenstrauch syndrome. Study of collagen has not been fruitful (13).

A form of sudanophilic leukodystrophy has been suggested (8). Prenatal ultrasound diagnosis has been accomplished (3).

To be excluded are other sudanophilic leukodystrophies, *Cockayne syndrome, Hallermann-Streiff syndrome*, *progeria* and various progeroid syndromes, and *Berardinelli-Seip* and other lipodystrophic syndromes. We cannot accept the cases of Hou and Wang (7) and Hagadorn et al (6).

References (Wiedemann-Rautenstrauch syndrome)

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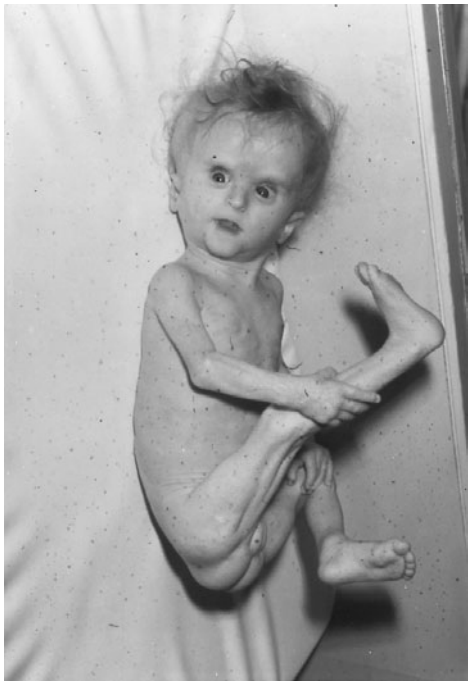

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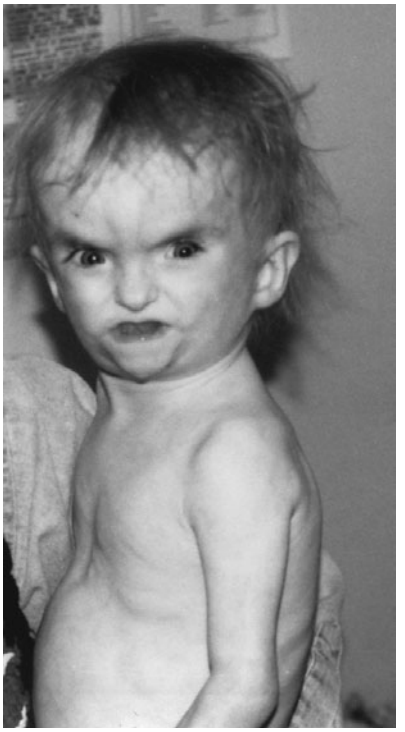

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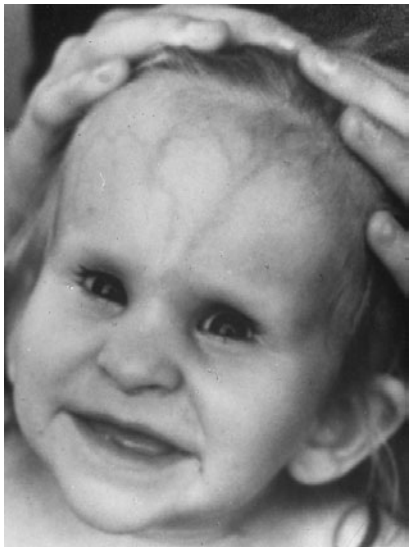

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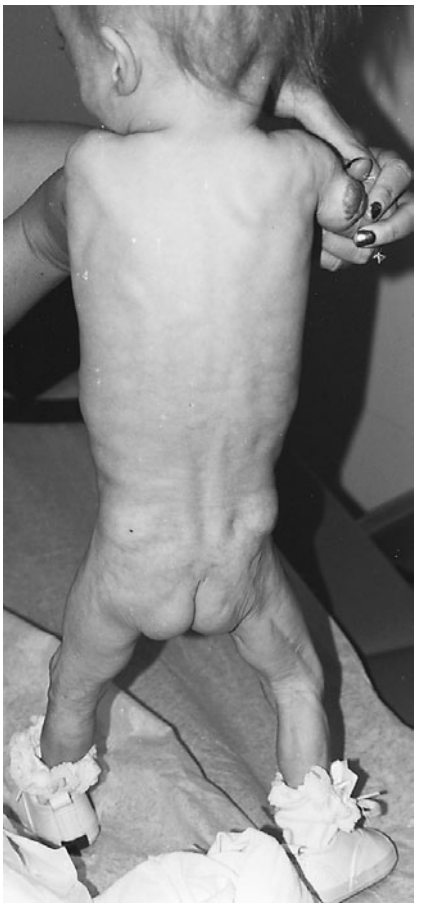

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Fig. 13–113. *Wiedemann-Rautenstrauch syndrome*. (A–C) Frontal and biparietal bossing and small face cause children to appear hydrocephalic. Note prominent scalp veins. Anterior fontanel is large. Nose is small and beaked, and mouth is small. (D) Caudal fat accumulates during infancy. (A–C courtesy of T Rautenstrauch, München, Germany. D courtesy of B Hall, Lexington, Kentucky.)

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Rothmund-Thomson syndrome

The syndrome of infantile poikiloderma, cataracts, and hypogonadism was described independently by Rothmund (49), in 1868, and Thomson (57), in 1923. Over 200 cases have been reported to date (64). Especially good reviews of the syndrome are those of Taylor (56), Greither and Dyckerhoff (17), Rodermund and Hausman (44), Vanscheidt et al (61), Vennos et al (64), Vennos and James (63), and Moss (38).

The syndrome has autosomal recessive inheritance. A significant female excess (35,55,56) has been reported but was not supported by our survey. Parental consanguinity has been present in about 16% (4,34,35,42,47,49,51,60). The syndrome has been found in identical twins (15). Report of the condition in mother and son (20) raises the question of genetic heterogeneity. However, this may represent pseudodominance, that is, a female homozygote marrying a carrier male and producing an affected child. There also appears to be a verrucous type with warty hyperkeratoses that has a tendency to malignant degeneration (13,16,45,47,66) (vide supra).

A number of chromosome anomalies have pointed to chromosome 8 (10,33,67). Kitao et al (28) and Lindor et al (33a) noted that mutations in *RECQL4*, a helicase, located at 8q24.3, result in Rothmund-Thomson syndrome. Compound heterozygotic brothers have been described (33a). However, there is surely genetic heterogeneity (64a).

Several authors (27,38,41) reported reduced DNA repair.

Craniofacial features. A large head with frontal bossing and broad low nasal bridge has been described (3,44,53,57,58). However, microcephaly has also been mentioned (12,22,46,57,58). The eyebrows and lashes are sparse in at least 50% (Figs. 13–114 and 13–116).

Table 13–5. Clinical features of Rothmund-Thomson syndrome

Feature	Percent
Poikiloderma	100
Short stature	100
Musculoskeletal abnormalities	95
Hypogonadism	94
Thin hair	65
Abnormal teeth	59
Cataracts	45
Dysplastic nails	42

Adapted from DG Starr et al, Clin Genet 27:102, 1985.

Skin and skin appendages. Dermatologic features have been extensively discussed by Rook et al (47). The skin of the cheeks and ears, uninvolved at birth, becomes red and swollen at about 3–6 months of age. The buttocks and the extensor surfaces of the hands, forearms, legs, and thighs then become involved but usually to a lesser degree, the exposed surfaces being more severely affected. The trunk is often spared. The inflammatory phase soon subsides and leaves areas that manifest varying combinations of pigmentation, depigmentation, atrophy, and telangiectasia. The dull-brown, irregular macular or reticular pigmentation usually follows the appearance of the atrophy and telangiectasia (Figs. 13–115 to 13–117).

Sensitivity to sunlight in the form of blister production is seen in at least 33% (13,15,34,47,53,56). It is usually more severe in early life. Scalp, pubic, and axillary hair is often somewhat sparse, and may be almost absent in some patients (4,46). Eyebrows and lashes are frequently missing or severely diminished (4,15,23,34,35,46,53,56–58) (Fig. 13–116) (Table 13–5).

Warty hyperkeratoses, especially over the joints (21,35,46,52,57, 58,66), appear in 25% between 6 and 10 years of age. Late-developing squamous cell carcinoma and palmoplantar keratoses have been found in about 35% (8,12,16,20,32,35,45–47,51,65). Malignant eccrine poroma has been found in one case (60a). Nail dystrophy has been noted in at least 25% (4,23,34,35,53,56).

Central nervous system. Mental retardation of variable degree has been found in about 10%.

Endocrine system. An endocrine disorder, most frequently hypogonadism, occurs in about 25% (4,23,35,46,50,53). Scanty menstruation is common, and few affected women have borne children. Micropenis has been noted (53). The combination of Rothmund-Thomson syndrome and Addison disease has also been reported (31).

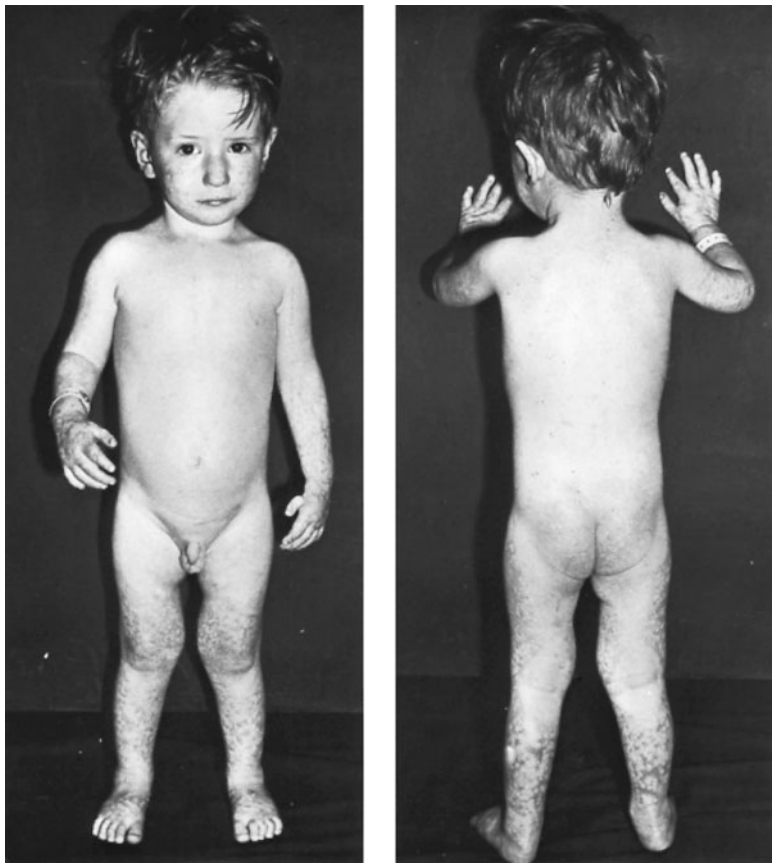
Musculoskeletal system. At least 65% have been markedly short (2). The growth retardation has been proportionate (4,7,12,19,20, 23,46,49,50,53). The limbs are often slender or delicate, the terminal phalanges abbreviated, and acrocyanosis may be severe. Soft tissue contractures may be an important cause of disability in the older patient (19).

Absence of thumbs and occasionally rudimentary ulnae and radii have been reported (3,29,39,42,47,52,57,58,61) (Fig. 13–115). Jäckli (23) described bipartite patella and bone sclerosis. Several authors (7,18,29,49,56,58) noted cystic areas similar to fibrous dysplasia; others have reported osteogenesis imperfecta (43,48). Phalangeal tufts may be resorbed (36).

Eyes. Anterior subcapsular, perinuclear, and posterior stellate cataracts have been described in 50%–75% (4,34,35,49,53,56). The cataracts are bilateral and usually appear between the fourth and seventh years (35), although they may appear earlier (53) (Fig. 13–117). They are complete and semisolid and produce loss of vision within weeks.

Various eye anomalies less frequently encountered include band keratopathy, microcornea, and strabismus (30).

Neoplasia. Osteosarcoma (1,7a,11,13,14,18,24,29,31a,34a,37,41a, 42,48,54,54a,55,59,62), fibrosarcoma (8), and late-developing squamous cell carcinoma (vide supra) have also been described. Oral squamous cell



A B

Fig. 13–114. *Rothmund-Thomson syndrome*. (A,B) Skin of cheeks and ears, uninvolved at birth, assumes a poikilodermatous appearance about the third to sixth month of life. There is similar involvement of legs, thighs, and buttocks.

carcinoma has also been noted (35). Cataracts do not seem to occur in those with cancer.

Other findings. Gastric carcinoma (11) and hypertension have been noted (9). Low vitamin A levels have been reported by Sexton (51) and Whittle (66). Taylor (56) found an abnormal peak in the α_1-globulin fraction of the blood.

Oral manifestations. Microdontia, multiple crown malformations, delayed and ectopic eruption, supernumerary and congenitally missing teeth, and short conical roots have been mentioned (5,23,35). Bifid uvula has also been noted (22,28).

Differential diagnosis. A somewhat similar syndrome in adults is *Werner syndrome* consisting of short stature, premature graying of hair, scleropoikiloderma, trophic ulcers of legs, arteriosclerosis, juvenile cataracts, hoarse and high-pitched voice, hypogonadism, osteoporosis, and diabetic tendency. It also has autosomal recessive inheritance. In contrast to Rothmund-Thomson syndrome (Table 13–5), patients with Werner syndrome are essentially normal until 20–30 years of age, when the hair becomes gray. Skin changes and cataracts develop after the hair changes color. Short stature and atrophy of muscle and subcutaneous fat of the distal extremities are more pronounced in Werner syndrome. Arteriosclerosis, diabetic tendency, and osteoporosis are not seen in Rothmund-Thomson syndrome. Skin involvement in Werner syndrome

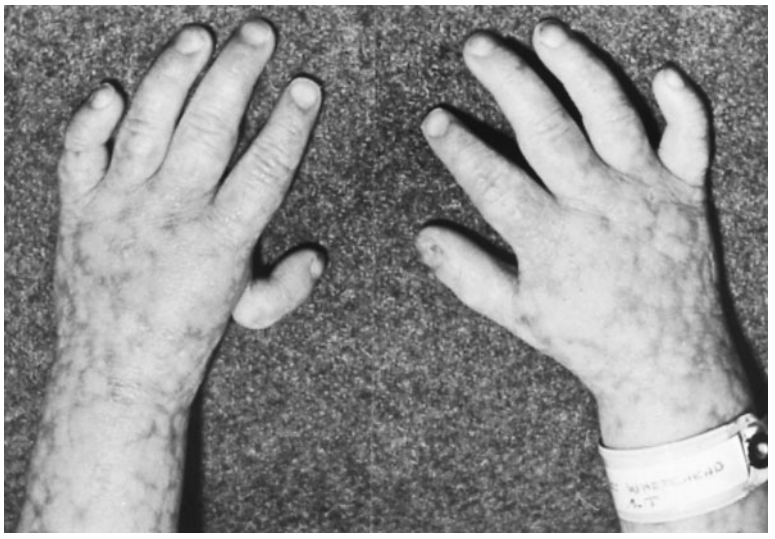


Fig. 13–115. *Rothmund-Thomson syndrome*. Similar involvement of hands with hypoplasia of thumbs. (From RK Oates et al, Australas Paediatr J 7:103, 1971.)

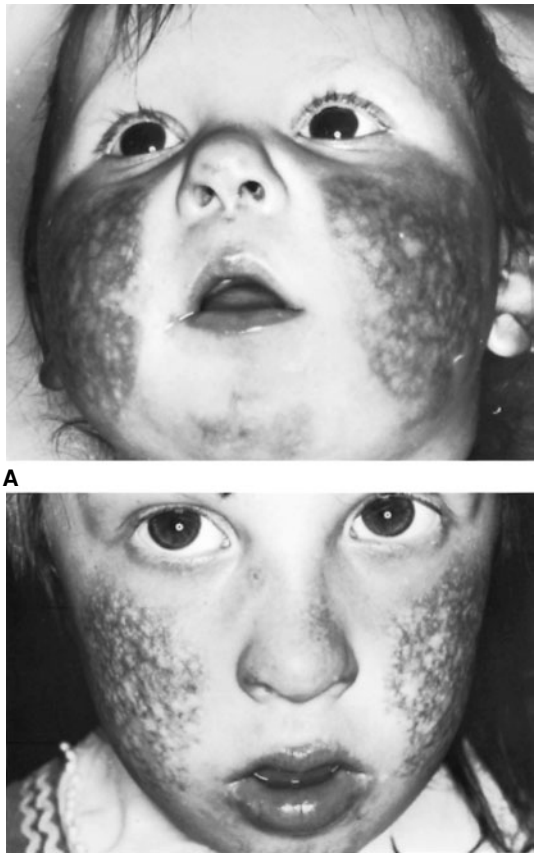
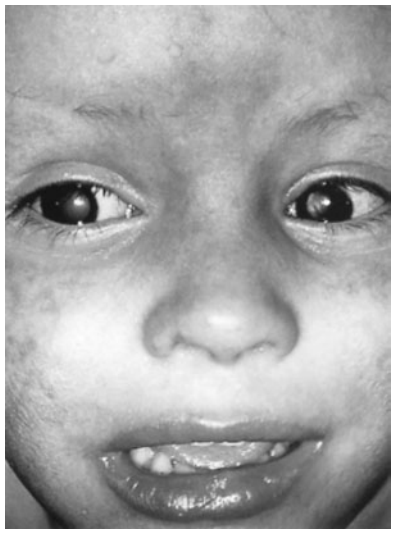


Fig. 13–116. *Rothmund-Thomson syndrome.* (A,B) Affected 2- and 4-year-old sibs showing characteristic facial poikiloderma. (Courtesy of S Alexander, Barking, Essex, England.

is different from that in Rothmund-Thomson syndrome. In the former, the forearms, hands, and face are chiefly involved. Hyperkeratotic areas are present on the soles, and ulcers are present over the heels, toes, and ankles.

In *gerodermia osteodysplastica*, there is premature senescence of the skin, nanism, and various anomalies of the eye (including microcornea and congenital corneal opacities), bony anomalies, and yellowish teeth,

Fig. 13–117. *Rothmund-Thomson syndrome*. Bilateral cataracts. (Courtesy of GB Sexton, London, Ontario, Canada.)



presumably due to an enamel defect. *Cockayne syndrome* consists of primordial short stature, flexion deformities, kyphosis, hyperostosis of skull bones, sensitivity to sunlight, and various eye anomalies such as optic atrophy, retinal degeneration, and cataract. The child appears prematurely senile, with sunken eyes, prognathic mandible, and carious teeth. *Bloom syndrome* is characterized by dwarfism, sunlight sensitivity, chromosomal breakage, a tendency to develop leukemia, and autosomal recessive inheritance. There is some superficial resemblance of Rothmund-Thomson syndrome to *focal dermal hyperplasia*, a disorder that also has poikilodermatous changes and for which it has been mistaken (25). One should also exclude Clericuzio syndrome (neutropenic poikiloderma), an autosomal recessive disorder seen in the Navaho. It is characterized by postinflammatory poikiloderma neutropenia, chronic sinopulmonary infections, thick toenails, and epidermal inclusion cysts of the elbows and ear rims. In contrast to Rothmund-Thomson syndrome, Clericuzio syndrome does not have photosensitivity, alopecia, cataracts, or congenital malformation (C Clericuzio, personal communication, 2000).

The reader is referred to the comprehensive analysis by Kaufmann et al (26) of disorders associated with growth hormone deficiency.

Laboratory aids. Growth hormone deficiency has been reported (23).

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Cockayne syndrome

Cockayne syndrome (CS) is characterized by cachectic dwarfism, premature aging, mental deficiency, microcephaly, intracranial calcifications, neurologic deficits, retinal pigmentary abnormalities, sensorineural hearing loss, and photosensitivity. It manifests defective repair of damage induced in DNA by ultraviolet light.

Cockayne (8), in 1936, described proportionate dwarfism with retinal atrophy and deafness in two sibs, and 10 years later published a brief review of their progress (9). The syndrome becomes apparent at around the second year of life, but pre- and perinatal onset has been observed (25,38,45,60,68,69). Based on this difference of onset, it has been proposed that classical examples of CS, with onset at age 2 years or later, be classified as CS type I and the prenatal or neonatal cases be CS type II (37). The latter has been called CAMFAK syndrome (69). Patton et al (52) dispute this belief. The disorder has been reported in a female patient with normal intelligence and onset at age 19 years, with worsening at age 23 during a second pregnancy (29).

Complementation studies indicate genetic heterogeneity (30) (vide infra). Four types have been identified.

The disorder has autosomal recessive inheritance (8,9,17,25,38,51–53). Familial cases as well as increased parental consanguinity have been observed.

Lehmann (32), in 1982, studied cultured cells from patients with Cockayne syndrome for complementation in cell-fusion studies. The gauge of complementation was sensitivity to UV irradiation as measured by RNA synthesis after exposure. Three complementation groups were found. Mayne and Lehmann (42), also in 1982, suggested that the defect in Cockayne syndrome (CS) resides in the repair of transcribed genes; this was confirmed by Venema et al (74), in 1990. They reported that CS fibroblasts have lost the preferential repair of active genes but are proficient in overall genome repair (47).

Henning et al (22), in 1995, demonstrated that the type I or *CSA* gene maps to chromosome 5. They cloned the gene and found that the

CSA cDNA uniquely and specifically corrects UV sensitivity in CS-A cells. Mutations of *CSA* were identified in all CS-A cell lines.

Fryns et al (16), in 1991, presented a patient with late-onset Cockayne syndrome who had interstitial 10q21.1 deletion in all his cells. In 1992, Troelstra et al (71) studied the *ERCC6* gene and showed that it corrects the repair defect in type B CS cells (CS type II). In keeping with nomenclature recommendations (34), the *ERCC6* gene was referred to as *CSB*. Neither the site nor the nature of the mutation correlated with the severity of the clinical features. Severe truncations were found in patients with either classic or early-onset forms of the disease (40,62).

Between the two complementation groups of CS-A and CS-B, 80% of the patients have been assigned to the CS-B complementation group.

Czeizel and Marchalko (15) used the designation "Cockayne syndrome III" for the disorder in a teenage girl with clinical manifestations of Cockayne syndrome but with high intelligence.

Greenhaw et al (18), in 1992, reported sibs with clinical manifestations consistent with De Sanctis–Cacchione syndrome, which is a subgroup of *xeroderma pigmentosum* (XP) with severe neurologic and developmental involvement. The patients did not have characteristic physical features of Cockayne syndrome. Fibroblasts derived from these patients showed a failure of recovery of RNA synthesis after UV irradiation and a normal level of unscheduled DNA synthesis. These findings were consistent with the laboratory findings of Cockayne syndrome but not those of xeroderma pigmentosum. Later, in 1996, Itoh et al (27) assigned these patients to Cockayne syndrome complementation group B by cell fusion studies.

Stefanini et al (65), in 1996, analyzed cell cultures from 22 Cockayne syndrome patients from different countries and racial groups. They detected no racial, clinical, or cellular distinctions between the two complementation groups of CS-A and CS-B.

Damage to actively transcribed DNA is preferentially repaired by the transcription-coupled repair (TCR) system. Van Gool et (72) and Cooper et al (12), in 1997, suggested that Cockayne syndrome may represent a defect in TCR.

Wood (79), in 1991, stated that 3 patients with XP complementation group B also exhibited clinical manifestations of CS. The locus of *XPB* is at 2q21. A patient with XP/CS was reported by Hwang et al (26) in 1996 to have a frameshift mutation in XPB, a subunit of transcription factor TFIIH and a $3' \rightarrow 5'$ helicase involved in DNA repair.

Cleaver (7), in 1994, pointed out that mutation in the XPD gene, the locus of which is at 19q13.2–q13.3, has also been associated with Cockayne syndrome. XPD is also a subunit of the transcription factor TFIIH with a $5' \rightarrow 3'$ helicase activity in DNA repair.

Vermeulen et al (75,76) reported genetic studies of 2 patients with clinical characteristics of Cockayne syndrome but with a biochemical defect typical of xeroderma pigmentosum. These were assigned to XP complementation group G.

In 1997, Nouspikel et al (49) studied the nature of the molecular defect in the first 3 documented cases of combined XP-G and Cockayne syndrome, reported by Jaeken et al (28), Vermeulen et al (75), and Hamel et al (21). They found a common mutational pattern in the 3 patients with XP-G/CS that was distinct from the one found in 2 sibs with XPG (48) with XP phenotype but no CS symptoms. *XPG* gene encodes a structure-specific endonuclease that nicks damaged DNA 3′ to the lesion during nuclear excision repair (NER). Nouspikel et al (49) found that the 3 XP-G/CS patients had mutations that were predicted to produce severely truncated XPG proteins. In contrast, the two XP-G patients without CS were able to make full-length XPG protein, but with a missense mutation that inactivated its function in NER. According to their results, XP-G/CS mutations abolish interactions required for a second XPG function and the loss of this second function leads to the CS clinical phenotype. (See also the sections on Xeroderma pigmentosum and Trichothiodystrophy.)

Habraken et al (20), in 1996, suggested that mutations in *XPB*, *XPD*, and *XPG* that cause Cockayne syndrome produce a defect in interaction of their encoded proteins with CSA protein, CSB protein, or both. At transcriptional pause sites, the human equivalent of nuclear excision repair factor 3 (NEF 3), along with CSA and CSB proteins, may facilitate the resumption of transcript elongation. A deficiency in the rate of elongation of certain transcripts, stemming from the mutational inactivation of *XPB*, *XPD*, *XPG*, *CSA* and *CSB*, is considered to be the etiologic origin of Cockayne syndrome.

Fig. 13–118. *Cockayne syndrome*. Note marked enophthalmos and horse-riding stance. (Courtesy of RL Summitt, Nashville, Tennessee.)

Facies. Lack of subcutaneous facial fat, particularly of the cheeks, gives prominence to the facial bones. This feature, combined with microcephaly, sunken eyes, thin often beaklike nose, and large ears, gives the patient a birdlike appearance (Figs. 13–118 and 13–119).

Eyes. Enophthalmos is a virtually constant feature. The retina is studded with fine, speckled pigment of salt-and-pepper type, with the greatest concentration in the macular area. Optic atrophy and arteriolar narrowing are common (6,9,25,39,41,78). Cataracts develop by adolescence (9,10,19,25,70). A poor response to mydriasis with homatropine or Neosynephrine has been noted (10). Corneal dystrophy with recurrent epithelial erosions, nystagmus, and photophobia are less frequently observed (5,41,70). Histopathologic examination of the eyes demonstrated optic atrophy, retinal pigmentation, loss of nerve fibers and myelin sheaths, and atrophy of retinal nerve fibers and ganglion cell layers, findings consistent with those observed in demyelinating disease (35).

Skin. Photosensitivity is a prominent feature (25). Dermatitis appears on the sun-exposed parts of the body by the second year of life, with a butterfly arrangement on the face (36,78). The forehead is spared, but the pinnae and chin are involved. The photodermatitis may result in scarring and pigmentary changes in older patients (56). Seborrheic dermatitis may also be present. The scalp hair and, sometimes, the eyebrows are diminished (17). Subcutaneous fat appears to be decreased throughout the body except for the suprapubic areas (17). Microdissection studies of the eccrine sweat glands have demonstrated these glands to be abnormally small for the patient's age (30). Remarkably, in striking contrast with xeroderma pigmentosum, another disorder with UV hypersensitivity, no significant increase in skin cancer is noted (46).

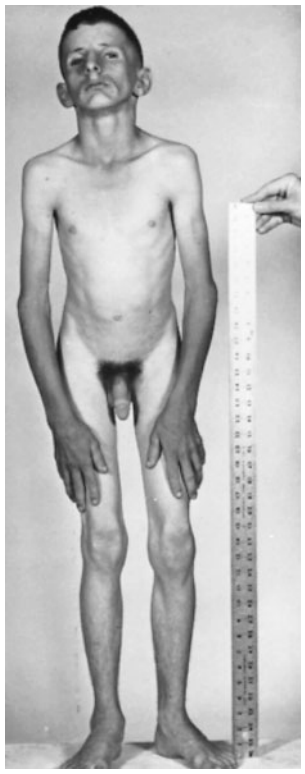

Fig. 13–119. *Cockayne syndrome*. Sixteen-year-old male who experienced marked mental and somatic retardation, eye difficulties, deafness. Note wizened appearance, photodermatitis of sun-exposed areas, horse-riding stance. (Courtesy of RM Paddison, New Orleans, Louisiana.)

Musculoskeletal alterations. Proportionate dwarfism is the most prominent feature of the disorder. Growth retardation becomes evident during the second year of life after a normal gestation, birth weight, and infancy. Kyphosis and osteoporosis are frequent (17,39,52,55,78). The limbs are disproportionately long, and the hands and feet disproportionately large (52,60). Flexion contractures may involve the ankles, knees, and elbows. The interphalangeal joints of the hands and feet may show periarticular thickening (Fig. 13–119).

Radiographic studies show abnormalities in the skull, extremities, and spine. There is increased thickening of the bones, particularly the skull base and calvaria, most noticeable in the frontal and parietooccipital regions (25,39,55,60). Often there is associated osteoporosis (55). Platyspondyly with tonguelike protrusion of the anterior aspects of the vertebral bodies, hypoplasia of the iliac wings and acetabular roofs, brachydactyly, and marble epiphyses in the terminal phalanges of the hands have been described as characteristic (1,64).

Nervous system. Progressive neurologic signs include cerebellar ataxia, choreoathetosis, moderate to severe mental deficiency, sensorineural deafness, and blindness (63). Neuropathologic studies of the brain have shown microcephaly, widespread mineralization in the cortex, basal ganglia, and cerebellum, and patchy demyelinization, often severe, in the subcortical white matter (14,25,43,57). Biopsy of the sacral nerve showed the main pathologic change to be segmental demyelination and remyelination with onion-bulb formation and moderate decrease in the number of myelinated fibers (50). Normal intelligence has been reported in one patient (31). CAT scans show strio-pallido-dentate calcinosis (Fig. 13–120).

Other findings. Hypertension and renal disease are frequent complications. Elevated peripheral vein renin and deposits of immunoglobulins and complement in the kidney vessels and glomeruli have been reported (23). Undescended testes (19), small breasts, and oligomenorrhea (29) have also been noted.

Oral manifestations. An increase in dental caries has been reported by most authors (9,19,36,41,57). In some patients, numerous permanent teeth were congenitally absent (17,57–60). Atrophy of alveolar processes (6,60), condylar hypoplasia (13), and short conical roots (59) have also been observed.

Differential diagnosis. CS is one of a group of disorders that has certain common characteristics. The photosensitivity may suggest *Bloom syndrome*, Hartnup disease, *xeroderma pigmentosum*, or erythropoietic porphyria. Bloom syndrome has many of the features of CS except for the neurologic and ophthalmologic findings. Both have reduced IgA levels (8). No patient with CS has been reported with leukemia or lymphoma, and chromosomal breakage is absent (52,78). Patton et al (52) have suggested that Cockayne syndrome overlaps strongly with *cerebro-oculo-facial-skeletal syndrome. Rothmund-Thomson syndrome* is not a neurologic disease; although cataracts are seen in about half the patients, there are no retinal changes. Xeroderma pigmentosum is characterized by multiple cutaneous malignancies in light-exposed areas. Skin cancers have not been reported thus far in the photosensitive areas in patients with CS. Cases of CS with xeroderma pigmentosum have been described (44,56) (vide supra). *Progeria* does not feature photosensitivity, neurologic

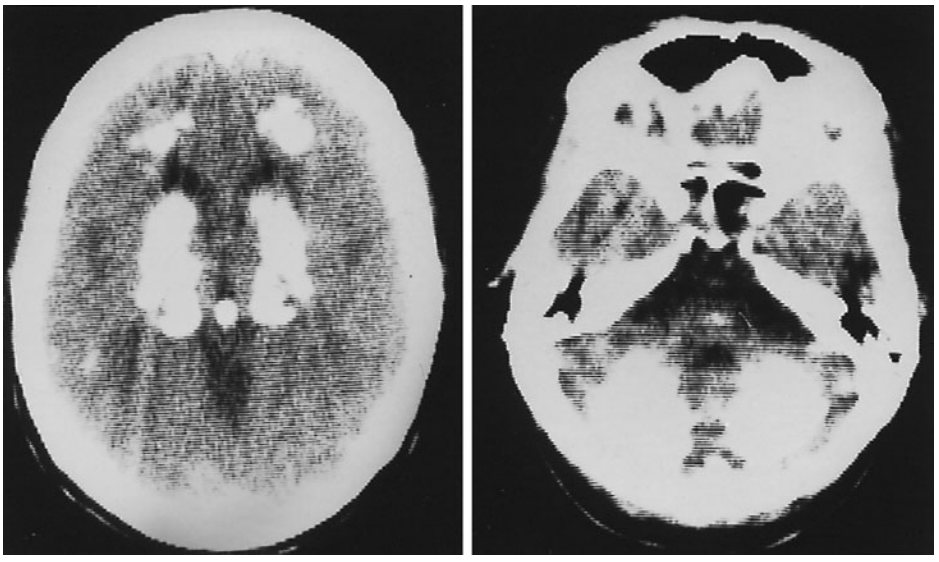

Fig. 13–120. *Cockayne syndrome*. CAT scan showing calcification of basal ganglia and dentate nuclei. (From MG Smits, Clin Neurol Neurosurg 85:145, 1983.)

disease, or retinal changes, and the phenotype is quite different from that of CS.

Laboratory aids. Cells from patients with CS demonstrate defective repair of damage due to ultraviolet (UV) radiation and mitomycin C, but they have normal unscheduled DNA synthesis and repair normally in the presence of caffeine (caffeine interferes with normal postreplication repair). This suggests a defect in either replication or excision repair and not in postreplication repair (24,53,54,58,61). The degree of hypersensitivity to UV radiation varies from patient to patient, possibly reflecting clinical and cellular heterogeneity for CS (52,68). Studies of complementation groups in patients with CS have shown patients to belong to group A, B, and C (32). UV treatment of fibroblasts obtained from obligate heterozygotes has yielded conflicting results (53,77). Thus, no reliable method to identify heterozygotes presently exists (51).

Thymic hormone serum level has been found to be undetectable or significantly reduced in patients with CS, whereas T lymphocytes and mixed lymphocyte functions are normal (2). These findings indicate premature immunological aging.

Prenatal diagnosis is possible using an assay of the colony-forming ability of UV irradiated cells, obtained from the amniotic fluid (67). CS cells are significantly more sensitive to UV radiation than normal control cells.

Hyperinsulinemia and hyperlipoproteinemia but normal growth hormone levels have been noted in several patients (11,13,17).

Autopsy findings have included pancreatic islet hyperplasia, atrophy and fibrosis of ovaries, and atrophic epidermis with small hair follicles and sweat glands (66).

Prenatal diagnosis has been effected by Lehmann et al (33). Cultured amniocytes exhibit significantly reduced RNA synthesis after irradiation with UV light.

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Xeroderma pigmentosum

Xeroderma pigmentosum (XP), originally described by Hebra and Kaposi (30) in 1874 and named by Kaposi (40) in 1882, is characterized by defective excision repair of DNA damaged by ultraviolet light (UV). When exposed to sunlight, the UV radiation induces thymine dimers and other damage in the DNA of human cells (69). Normal individuals have several mechanisms for repairing damaged DNA. These mechanisms are absent to various degrees in patients affected with XP. Not only UV radiation but certain chemicals, carcinogens, and ionizing radiation can induce severe damage to patients with XP (71). Based upon the cellular ability to repair DNA after UV irradiation of cultured fibroblasts (see Laboratory aids), XP had been divided into nine subgroups classified as complementation groups A through I and XP "variant." More recently, however, the complementation groups have been limited to seven, from A to G (4). All have autosomal recessive inheritance (vide infra). These groups are defective in excision repair of DNA following UV damage. The XP "variant" had normal excision repair but abnormal replication of UV damaged DNA (9,31,53). The XP "variant" in Japan has been subdivided into caffeine-resistant and caffeine-susceptible subgroups based on the capability of XP cells to achieve caffeine potentiation of UV lethality. Patients with caffeine-resistant cells do not develop neoplasms (28). Excellent surveys on the subject are by Cohen and Levy (11) and Bootsma et al (4).

Division into the various complementation groups is based on (a) the rate of UV-induced unscheduled DNA synthesis in fibroblast colonies, measured in percentage of the value obtained from normal fibroblasts, and (b) the UV dose required to reduce fibroblast colony-forming ability in vitro. The degree of sun sensitivity, neurological abnormalities, and other clinical manifestations associated with XP varies from group to group (20,23,35,93).

De Sanctis and Cacchione (14) described a form of XP associated with severe neurologic abnormalities. This phenotype and variants can be associated with any of the complementation groups, most often group A and, occasionally, group D. The complementation groups tend to segregate differently in various populations (2,33,42,47,55,57,71).

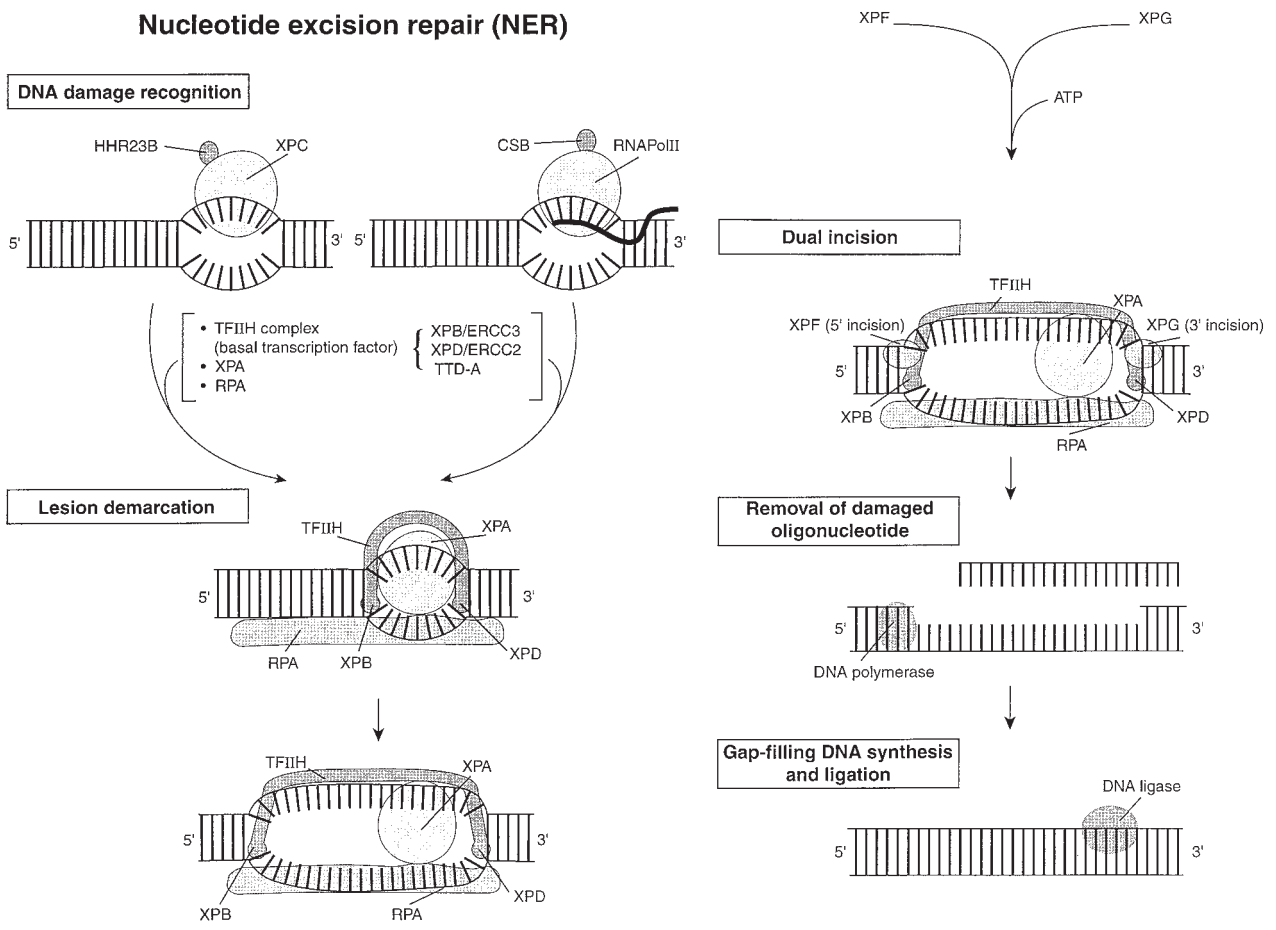
Jung (36) and Jung and Bantle (38), using the term "pigmented xerodermoid," describe a group of patients presenting solar cutaneous degeneration with eventual development of skin neoplasms after the age of 30. Cleaver et al (8) suggested that cells from patients with pigmented xerodermoid have the same post-UV synthesis and repair abilities as cells from patients with XP "variant." Pigmented xerodermoid may well represent XP "variant" with late onset (2). Follow-up studies of one patient, originally reported by Jung (36), showed that in that kindred the condition had autosomal recessive inheritance (32). Anderson and Berg (1) reported a family with a variety of XP possibly having autosomal dominant inheritance. Other authors have reported similar families (36,47). This autosomal dominant variety represents a mild form of XP, possibly within the range of complementation group E. Imray et al (34) suggested 100% penetrance. Affected individuals present marked xeroderma, dark pigmentation, and freckling with severe erythematous reaction when exposed to sunlight. Tumors seem to be rare in these patients, and non-neurological abnormalities have been reported (34,47). Laboratory studies demonstrate decreased cell survival, reduced DNA repair synthesis, increased chromosome breaks, but normal sister chromatid exchange (34).

In Japan, most patients with XP belong to group A and the XP "variant." In Europe and in the United States, group C is the largest (43), followed by groups D and A (2). Combining all varieties, XP occurs in 1 in 250,000 in the general population of the United States and Europe (2,71), with the prevalence in Japan estimated as 1 in 40,000 (2). It has been described in all races (2). The degree of parental consanguinity is quite high (72).

Xeroderma pigmentosum is divided into seven complementation groups, A to G (vide supra). Bootsma et al (4), in 1998, compared the clinical and cell-biological characteristics of these groups, including in the XPD group the patient originally classified as XPH. XPA and XPC have relatively high frequency, XPD and XPF have intermediate frequency, and the other three are rare.

Research in understanding the XP mutations has progressed by cloning human DNA repair genes by using UV-sensitive Chinese hamster cells as recipients for DNA-mediated gene transfer. The human genes correcting the rodent repair defects are termed excision-repair cross-complementing, or ERCC, genes.

XPA, XPB, XPC, XPD, XPE, XPF, and XPG are involved in the different steps of nucleotide excision repair (7,92) (Fig. 13–121).



A

Abbreviations:

XPC - HHR23B complex: recognizes DNA damage

RNAPolⅡ - CSB: RNA polymerase - Cockayne syndrome B protein recognizing the DNA damage

TFⅡH Complex: a multiprotein factor (encoded by nine different genes and including XPB, XPD, and TTD-A) involved both in transcription and in DNA repair

XPA: DNA binding protein recognizing the DNA lesion

RPA: replication of protein A

XPB: bidirectional helicase incising the damaged strand

XPD: bidirectional helicase incising the damaged strand

TTD-A: protein with mutation associated with trichothiodystrophy A

XPF: protein excising the damaged oligonucleotide

XPG: protein excising the damaged oligonucleotide

Process of Nucleotide Excision Repair

Recognition of the site of DNA damage occurs either by the XPGHHR23B complex or by RNA polymerase (RNAPolⅡ) and Cockayne syndrome protein (CSB). Then DNA at the region of the lesion is opened by the action of RPA, XPA, and the bidirectional XPB/XPD helicases of TFⅡH. The damaged strand is incised on both sides of the injury by the repair-endonucleases XPF and XPG, followed by excision of the lesion-containing oligonucleotide and gap-filling DNA synthesis.

B

Fig. 13–121. *Xeroderma pigmentosum.* (A) Nucleotide excision repair (NER). (B) Legend for (A). (Modified from GS Winkler, JHJ Hoeijmakers, Nat Genet 20:106, 1998, and A Stary, A Sarasin, Cancer Surveys 26:155, 1996, with permission.)

The steps involved in nucleotide excision repair (NER) are as follows (7,92): The recognition of DNA damage can occur either by the XPC-HR23B complex (vide infra) or by RNA polymerase and Cockayne syndrome B protein (CSB) (Fig. 13–121). The initial steps involve also the DNA-binding proteins XPA and XPE. Subsequently, the DNA around the lesion is opened by the concerted action of RPA (replication protein A), XPA, and the bidirectional helicases XPB and XPD, which are components of the transcription factor TFIIH (Fig. 13–121). The damaged oligonucleotide region is then incised by the repair endonucleases ERCC1-XPF at the 5′ and XPG at the 3′ side. Following this, the lesion-containing oligonucleotide is excised. During all this process, the remaining single-strand template is protected by the single-strand binding protein RPA (Fig. 13–121). The gap is then filled and repaired with the action of DNA polymerase and ligase.

XPA is located at 9q34.1. It encodes a hydrophilic protein of relative molecular mass of 31,000. It has a zinc finger motif, which indicates that it interacts with DNA. This interaction is part of an enzyme complex that makes an incision near damaged sites (Fig. 13–121). Tanaka et al (80), in 1990, found that most Japanese patients with type A XP have a splice site mutation. Park and Sancar (64), in 1994, concluded from their studies that the XPA, ERCC1, and ERCC4 proteins form a complex that participates in both damage recognition and incision activities. Li et al (52), in 1995, demonstrated that the association between *XPA* and *ERCC1* is a necessary step in the nucleotide excision pathway.

States et al (77), in 1998, analyzed the mutation of XPA cell lines from 19 American and European patients. Patients with more severe disease, often with neurologic complications, had mutations in the DNA-binding region of XPA. Patients with milder skin disease had mutations in the C-terminus of the protein, which interacts with the TFIIH transcription factor.

XPB, xeroderma pigmentosum of complementation group B, has clinical and cytobiological characteristics of both XP and Cockayne syndrome (CS). The gene *XPB* has been shown to be the same as *ERCC3*, which was assigned to 2q21 (87) and was cloned in 1990 by Weeda et al (86). The nucleotide sequence predicted a protein of 782 amino acids comprising conserved motifs, strongly suggesting that the protein is a DNA repair helicase with a $3' \rightarrow 5'$ action (92) (Fig. 13–121). Weeda et al (88), in 1991, described the genomic architecture of the *XPB/ERCC3* gene. It consists of at least 14 exons spread over approximately 45 kb. In 1997, Weeda et al (89) assigned the defect of two patients with a mild form of trichothiodystrophy (TTD) to the complementation group B of XP. The *XPB* gene product is a component of the transcription factor TFIIH.

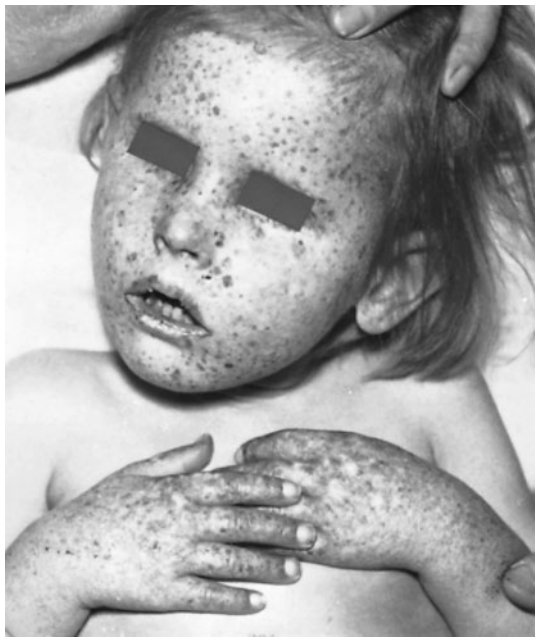
The *XPC* gene was mapped to 3p25 by Legerski et al (49). It encodes a highly hydrophilic protein composed of predicted 823 amino acids. Li et al (51) identified mutations in 5 XPC cell lines. *XPC* and *HHR23B* genes have products which form a tight complex (83) (Fig. 13–121).

The defect in XPD cells was found to be corrected by the *ERCC2* gene (19). This gene encodes a DNA repair/transcription helicase with a $5' \rightarrow 3'$ action (92) (Fig. 13–121). This helicase is also part of the TFIIH factor complex. TFIIH, a 9-subunit complex, has an essential function in two processes: initiation of transcription by binding to the promoters of protein-encoding genes and nucleotide excision repair (NER) (92) (Fig. 13–122). The NER system removes a wide variety of lesions, including UV-induced photoproducts, in a multistep "cut-and-paste" reaction involving 20–30 proteins (92). The XPB and XPD helicase subunits of TFIIH unwind the DNA, opening the helix locally, to form an open DNA intermediate necessary in both the transcription and repair processes (Fig. 13–121).

XPD provides a perplexing example of the complexity of genotype–phenotype relationships. Mutations that severely compromise the function of *XPD* are lethal. However, mutations with milder effects result in a heterogeneity of phenotypes, including at least three distinct disorders: xeroderma pigmentosum (XP), Cockayne syndrome (CS), or trichothiodystrophy (TTD) (61,92).

Coin et al (12), in 1998, provide a detailed account of the biochemical defects caused by the *ERCC2* mutations of XPD. An important effect appears to be the interaction of XPD with p44, which is still another TFIIH subunit and which stimulates the helicase activity of XPD. Mutations in the XPD C-terminal domain, as found in most patients, prevent the interaction with p44, resulting in a decrease in XPD helicase activity and explaining the nucleotide excision repair (NER) defect.

There appear to be 2 types of XPE: a DNA damage binding (DDB) protein-positive form and a DDB protein-negative form. Keeney et al (41), in 1993, purified the DDB protein. It appeared that it is a



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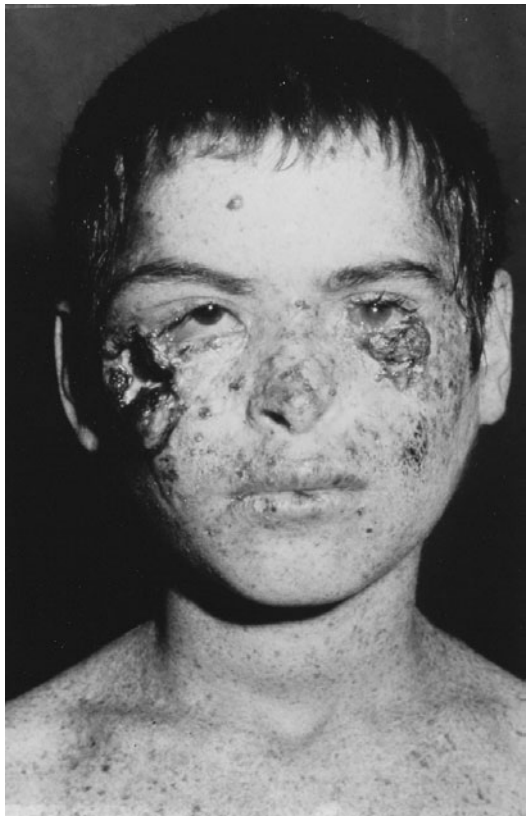


B

Fig. 13–122. *Xeroderma pigmentosum*. (A) Note skin lesions. (B) Note atrophic scars and a variety of skin tumors. (A courtesy of OP Hornstein, Erlangen, Germany.)

heterodimer, with polypeptides of 124 and 41 kD. Mutations in the smaller component of the heterodimeric protein were demonstrated by Nichols et al (56), in 1996.

In 1996, Sijbers et al (75) isolated a human gene that corrected the repair defects of XPF. The gene, *ERCC4*, encodes a 905-amino acid polypeptide. The ERCC4, or XPF protein, was purified from mammalian cells in a tight complex with ERCC1. This complex is an endonuclease responsible for the 5′ incision during repair (Fig. 13–121). The *ERCC4* gene map locus is at 16p13.2–p13.1 (75). Sijbers et al (75,76), in 1996 and 1998, identified a 4-nucleotide deletion and a point mutation in XPF patients.

XPG has one of the smallest series of cases. Norris et al (58) described patients with mild cutaneous changes but no UV-induced skin tumors. *XPG* and *ERCC5* were found by Nounspikel and Clarkson (59) as well as Shiomi et al (74) to be identical. Habraken et al (25), in 1994, demonstrated that XPG is a single-strand-specific DNA endonuclease, involved in nucleotide excision repair. They suggested that XPG nuclease acts on the single-stranded region created as a result of the combined action of the XPB and XPD helicases at the DNA damage site. O'Donovan et al (62) showed further that XPG cleaves the damaged DNA strand on the 3′ side of the lesion during excision repair (Fig. 13–121).

Nounspikel et al (60) demonstrated that patients with the combined phenotype XP-G/CS have mutations that would produce severely truncated XPG proteins. In contrast, certain XPG patients without CS were able to make full-length XPG protein, but with a missense mutation that inactivated its function in nucleotide excision repair.

Some patients with xeroderma pigmentosum have normal DNA repair rates. These belong to the "variant" form. Excision repair is normal, but postreplication repair is defective (50). It is characterized by a defect in conversion of newly synthesized DNA from low to high molecular weight after UV irradiation.

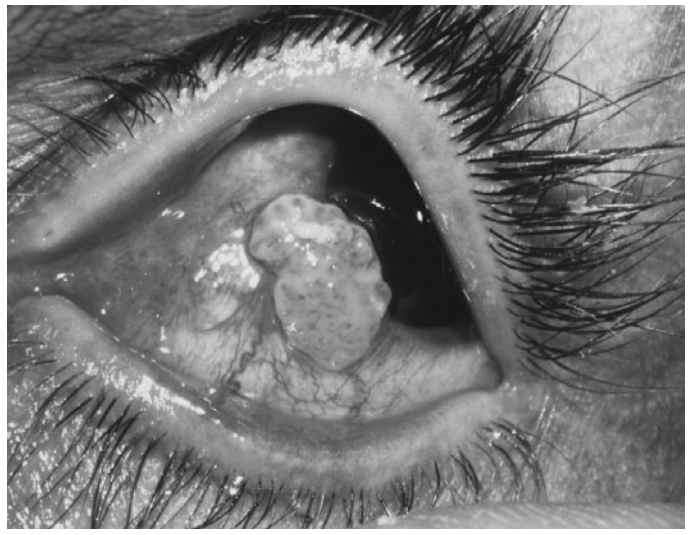
Face and skin. Marked sensitivity to sunlight, especially wavelengths from 2800 to 3100 Å, is noted early in life, following minimal sun exposure. The majority of children with the various types of XP experience severe sunburn reactions which taper off by adulthood. The skin not exposed to the sun is generally within normal limits. The areas exposed to the sun first develop freckles, generally before the second year of life (17,18,21,72,95,96). With progressive exposure to the sun, the freckles become larger and vary from light to dark brown in color (Fig. 13–122). In addition, macular areas of hypopigmentation occur, resulting in a "salt-and-pepper" appearance of the skin. The second stage of skin involvement is characterized by atrophy and telangiectasia with the development of scaly patches and small spiderlike hemangiomas. Skin atrophy on the face can be so severe as to interfere with normal opening of the mouth or eyes. Loss of scalp hair is frequent (95). Some patients, especially those with severe neurological manifestations, present loss of subcutaneous fat. This seems to be a generalized process not related to sun exposure (2). Reaction to sunlight, ranging from mild to severe, varies from patient to patient. Those presenting acute sensitivity are more prone to develop neurological abnormalities (2). The third stage is the development of actinic keratoses, papillomatous growths, and neoplasms as early as 2 years of age (43). The neoplasms encompass both ectodermal and mesodermal tumors: keratoacanthomas (72), squamous cell carcinoma, basal cell carcinoma, melanoma (53), fibrosarcoma and angiosarcoma, as well as benign lesions such as angiomas and fibromas (2). The most frequent neoplasms are basal cell carcinoma followed by squamous cell carcinoma and melanoma. The tumors tend to arise in areas of solar keratoses. This specificity indicates a direct mutagenic effect of sunlight and possibly other carcinogens (6).

Basal and squamous cell carcinomas have been reported in 45%, and melanoma in 5% (47). In about half of these cases, the melanomas are multiple (82). However, the frequency of melanoma has varied from 0% in Japanese series (79) to around 50% in the United States (70). The latter probably represents a highly skewed sample. Sixty-five percent of the melanomas and 97% of the basal and squamous cell carcinomas arise in the face, head, and neck (47). Melanoma and its metastases have been reported to undergo spontaneous regression in some patients (53). The propensity to develop skin neoplasms varies with the complementation group. Patients in group A tend to present basal cell carcinomas very early in life, whereas patients with the XP "variant" develop the same tumors after the second decade (43). In general, more than 50% of the patients develop cutaneous neoplasms before age 10, in contrast to the general population in which over 50% of patients with skin neoplasms are over 60 years old (46). There is marked affinity for patients in group A to develop multiple squamous cell carcinomas and, with less frequency, basal cell carcinoma, and, rarely, malignant melanoma. Similarly, patients in complementation group E tend to develop basal cell carcinoma in large proportions. The D group is more prone to have multiple melanomas. This will explain the fact that melanomas in Japanese patients are extremely rare, because in Japan group D is very rare (18,37). Heterozygotes are clinically normal and, in general, do not present sun sensitivity, but skin tumors seem to be four times higher than in the general population (78).

Eyes. Ocular involvement occurs in 40% (47). Most patients have marked photophobia and conjunctivitis with profuse lacrimation (72,95). The bulbar conjunctiva may exhibit pigmentation and telangiectasia. With severe involvement, the eyelids often lose their lashes, and ectopion, entropion, or symblepharon may complicate the clinical picture (2,16,17,45,47). Squamous cell carcinoma and melanoma of the conjunctiva, ulceration of the cornea, and iritis with synechia or iris atrophy have been described (21,29,84) (Fig. 13–123).

Central nervous system. Approximately 20% have neurologic abnormalities, the onset generally being after age 5 (47). Neurological abnormalities are observed largely in patients from complementation groups A, B, D, and G. Patients in group A tend to develop neurologic problems before age 7, whereas those in group D exhibit neurologic damage after this age (45). Only one patient from group C has presented severe CNS complications (27). This patient also had systemic lupus erythematosus. Rarely, patients from the other groups have CNS manifestations (6). The majority are in group A, with the more severe cases classified as De Sanctis–Cacchione syndrome (37,57). Clinically there may be spastic-ataxic gait and athetoid movements of the head and arms of variable degree (69). Areflexia, apparently due to lower motor neuron involvement, has been described (71). Pyramidal and extrapyramidal signs are common, and speech is often disturbed (14). Sensorineural hearing loss has been noted in several cases (47). Patients with De Sanctis-Cacchione syndrome present marked mental retardation and retarded physical development. The mental retardation is progressive and becomes evident during the first year of life. Abnormal electroencephalographic changes

Fig. 13–123. *Xeroderma pigmentosum*. Squamous cell carcinoma arising on palpebral conjunctiva.



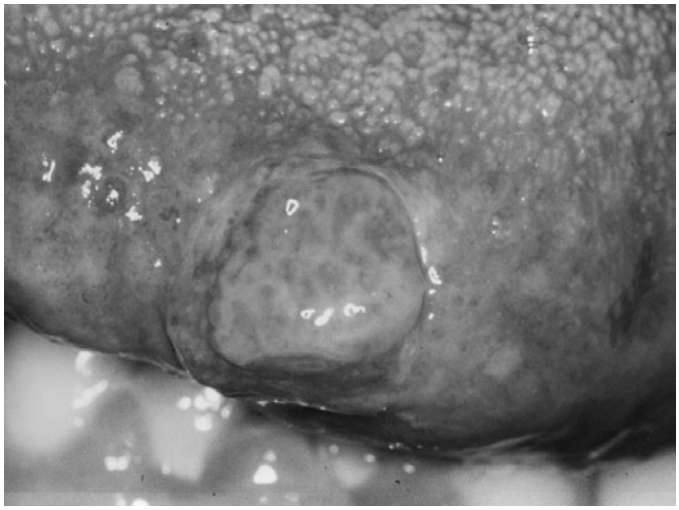


Fig. 13–124. *Xeroderma pigmentosum*. Squamous cell carcinoma arising on tongue tip. (From H Plotnick and A Lupulescu, J Am Acad Dermatol 9:876, 1983.)

(diffuse dysrhythmia with poorly developed alpha rhythm and with occasional paroxysmal burstlike slow-wave discharges) have been noted (10). Microcephaly, small brain, and diffuse mild cerebral and olivopontocerebellar neuronal loss have been found at autopsy (10,69,81). Nonaffected relatives exhibit a higher incidence of mental retardation and microcephaly than the general population (90). Brain atrophy, ventricular dilation, marked cortical atrophy, and thickening of the calvaria with excessive pneumatization of the frontal sinuses have been found by computed tomography in patients with De Sanctis–Cacchione syndrome (26,28). Peripheral neuropathy has been described and several nerve biopsies have suggested severe damage in both myelinated and unmyelinated fibers (26).

Oral manifestations. Areas of hyperpigmentation occur on the lips and anterior tongue (2). Squamous cell carcinoma of the lips, developing as early as age 14 (95), is frequent. Similar neoplasms of the tip of the tongue have been described (29,65,85,96). A 1987 survey of the literature (47) showed a total of 13 XP patients with squamous cell carcinoma of the tip of the tongue, two tumors arising in the gingiva and one in the palate (Fig. 13–124). Nearly 50% were below 14 years of age. Patients as young as 3 years of age have been reported with malignant oral neoplasms (46). These findings contrast with those in the general population of the United States, in which less than 1% of patients with oral or pharyngeal cancer are younger than 20 years (13).

A so-called "cheilo-nasal prominence" form of XP, characterized by profuse involvement of lips and nose starting in early childhood, has been described by Kraemer and Slor (45). This represents complementation group C, with marked actinic cheilitis, which eventually develops into carcinoma.

Other findings. Nuclear atypia of hepatic and pancreatic cells (78) and gonadal hypoplasia (14,33) have been reported.

Histologic features. Skin changes consist of hyperkeratosis, acanthosis, and areas of epidermal atrophy (72). A chronic inflammatory infiltrate of the epidermis can be observed, as well as abnormal accumulation of melanin in the basal cell layer. With increasing age, these changes become accentuated and eventually neoplasia occur. The histopathology of the neoplasms is identical to that of the same neoplasms arising in the general population.

Electron microscopic studies of sun-exposed and nonexposed skin reveal various abnormalities in melanin synthetic activity as well as phagocytosis of melanosomes by fibroblastlike cells (24,67).

Differential diagnosis. To be excluded are *Cockayne syndrome, Bloom syndrome*, and *Rothmund-Thomson syndrome*, drug-induced and allergen-induced photosensitivity, as well as erythropoietic protoporphyria light eruption (Hutchinson summer prurigo). Cockayne syndrome and xeroderma pigmentosum have been reported to occur simultaneously in two patients (55,71). One patient belonged to complementation group B and the other to group H. Thrush et al (81) reported sibs with an unclassified form of XP characterized by progressive dementia, chorea, sensorineural hearing loss, corticospinal tract degeneration, peripheral neuropathy, and skeletal abnormalities.

Laboratory aids. Autoradiographic determination of UDS is used to demonstrate DNA-excision repair of UV damage to DNA. Autoradiographs show a positive reaction in the nuclei of UV-irradiated cells after incorporation of tritium-labeled thymidine during the non-S phase. If fused fibroblasts from two different XP patients exhibit the reaction, they belong to two different complementation groups (2).

Fibroblasts from patients with XP have 10%–20% of normal ability to repair DNA probably due to an abnormal endonuclease activity (71). Increased chromosomal breakage has been found in fibroblasts, but not in lymphocyte cultures (67). Abnormalities in C and D chromosome groups (22) have been found in lymphocytes and cultured nontreated fibroblasts from patients with XP. Sister chromatid exchanges (SCE) are increased in cultured lymphoblastoid cells and fibroblasts following UV radiation (39). The number of SCEs has been found to correlate with the onset, severity, and prevalence of clinical symptoms and neoplasia. This reflects the mutation rate and the mutagenicity induced by UV radiation (39). However, it should be pointed out that similar changes occur in Cockayne syndrome, a disorder not prone to cancer production (73). Immunologic studies have demonstrated that some patients exhibit delayed rejection of skin grafts and reduced induction of lymphocytes by PHA. A decrease in T3-positive lymphocytes has also been noted (94). Elevated IgE level has been noted (68).

Prenatal diagnosis is possible (3,66,68,70). UDS studies after UV radiation in cultured fibroblasts obtained from obligate carriers have generally shown normal DNA repair levels (47,66,91). Reduced repair activity in heterozygotes has also been reported (5,15). There is a higher-than-expected (about 80%) association with blood group O. PCR technique can be used in lieu of complementation tests (44).

Sural nerve biopsy of two sibs with type A showed marked reduction in the number of large and small myelinated fibers (63).

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Endocrine-candidosis syndrome (candidosis, idiopathic hypoparathyroidism, and hypoadrenalcorticism)

The association of mucocutaneous candidosis with polyglandular autoimmune disease, especially idiopathic hypoparathyroidism and idiopathic hypoadrenalcorticism, has been known for many years, the first reference probably being that of Thorpe and Handley (40) in 1929. However, it has required almost five decades for analysis of enough cases to see recognizable patterns of occurrence.

The syndrome is manifested as variable combination of (in approximate order of decreasing frequency) superficial mucocutaneous candidosis, hypoparathyroidism, hypoadrenocorticism, ovarian atrophy, keratoconjunctivitis, alopecia, intestinal malabsorption, pernicious anemia, diabetes mellitus, hepatitis, and thyroiditis (7,16,18,39).

Neufeld et al (29) divided autoimmune polyglandular syndromes into three distinct types, plus a miscellaneous type. Type I includes at least two of the following: chronic mucocutaneous candidosis, acquired hypoparathyroidism, and idiopathic hypoadrenalcorticism with or without autoimmune disease. It is also known as APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy). The complete triad is present in only one-third of the cases. Type II includes idiopathic hypoadrenalcorticism plus autoimmune thyroid disease and/or insulin-requiring diabetes, but no hypoparathyroidism or chronic mucocutaneous candidosis. It subsumes the so-called Schmidt syndrome (14). In contrast to type I, which has early onset (12 years), type II typically becomes evident in midlife (30 years). Type III patients manifest autoimmune thyroid disease *without* Addison disease but with at least one associated organ-specific autoimmune disease, such as insulin-dependent diabetes, pernicious anemia, vitiligo, and/or alopecia. We will not be concerned with type III disease here.

The cell-mediated immune defects may well be unique. In nearly all cases, there is limited ability of lymphocytes to proliferate in response to *Candida* antigen. Response to mitogens and other antigens is essentially normal. It is possible that the defect is mediated by a humoral factor in type I patients (5,8,20,22,23,42). At least one patient has died of fulminating chicken pox (13). There are several excellent reviews of these autoimmune syndromes (10,13,16,22,29).

Candidosis is usually the first component to appear, most observers reporting its presence during the first 6 years of life. It is followed from 3 months to 13 years later by the other components. Idiopathic hypoparathyroidism and hypoadrenalcorticism become manifest most frequently during the prepubescent period; the former has a mean of about 5 years, the latter at about 8.5 years.

Ahonen et al (4), in 1990, reported data on 68 patients from 54 families, ranging from 10 months to 53 years. They emphasized the broad clinical spectrum and mentioned that some of the manifestations did not appear until the fifth decade. Candidiasis was the initial manifestation in 60% of the patients and was present in all patients. Hypoparathyroidism was present in 79%, adrenocortical failure in 72%, and gonadal failure in 60% of female patients over 13 years and in 14% of male patients over 16 years of age.

Zlotogora and Shapiro (47), in 1992, reported on 19 families from an Iranian Jewish community with 23 persons affected with type I. Hypoparathyroidism was found in 96%, and 91% were diagnosed by the age of 20 years. The prevalence of the condition among Iranian Jews was estimated to be between 1:6,500 and 1:9,000, which is comparable to the high frequency among Finns. However, the Iranian Jews showed relative rarity of candidiasis and absence of keratopathy.

Heredity. Whereas type I has autosomal recessive inheritance (3,5, 12,24,31,35,39,44–46), type II appears to be HLA linked (B8, DW3, DR3) and exhibits familial aggregation, but does not appear to have single gene inheritance (10,29). A high frequency of type I has been found in Finland and among Iranian Jews (47).

Aaltonen et al (1,2), in 1994 and 1997, mapped the gene of APECED to 21q22.3. Even though Björses et al (6) provided independent evidence for linkage of the Iranian Jewish variety to the same chromosomal region, the presence of different haplotypes suggested a variety of mutations in the same gene. The AIRE protein, located in the cell nucleus, is mutated (6).

In 1997, Nagamine et al (27) and the Finnish-German APECED Consortium (11) independently isolated the gene responsible for APECED and designated it *AIRE* (*a*uto *i*mmune *r*egulator). The gene consists of 14 exons and its protein contains motifs suggestive of a transcription factor including 2 zinc finger (PHD-finger) motifs. Nagamine et al (27) found a mutation in the Swiss (arg 257-to-ter) and another in the Finnish (lys 83-to-glu) APECED patients. The Finnish-German Consortium (11) discovered 5 *AIRE* mutations, one of which was the common Finnish mutation.

Endocrine systems. Idiopathic hypoparathyroidism, eventually present in about 80%, is commonly asymptomatic initially. Serum calcium is reduced and serum phosphorus is elevated in the absence of significant disease of the genitourinary and gastrointestinal systems. Tetany is not evident unless calcium levels are significantly reduced. Furthermore, parathormone injection results in increased serum calcium and in elevated urinary phosphorus excretion. At necropsy, absence of the parathyroid glands or their replacement with fat has been noted (16).

Hypoadrenalcorticism is found in about 65% of type I patients. Often initially silent, it appears soon after the signs of hypoparathyroidism (29). Lassitude, anorexia, progressive weakness, hypotension, and progressive pigmentation of the skin and mucous membranes signal its onset.

Laboratory findings confirm the low serum sodium and high potassium levels. Death from adrenal crisis may result, and necropsy shows adrenocortical atrophy of the "cytotoxic type."

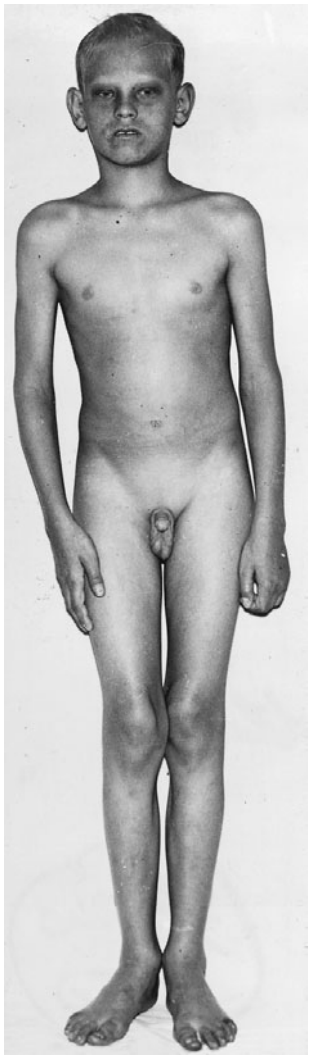
Autoimmune thyroid disease, also initially subtle, has been diagnosed in only 10% of type I cases but in 70% of type II examples (29). It has been shown to be primary, since thyroid-stimulating hormone (TSH) does not produce a rise in thyroid-131 uptake or alter the protein-bound iodine levels.

Insulin-requiring diabetes mellitus is found in only 2%–4% of type I cases, but in over 50% of type II cases (29). Diabetes insipidus has been reported in sibs with the disorder (29). The relation of Candida infection to the endocrine glands is not known. It has been suggested that candidosis is a superficial expression of undetermined abnormalities already present in the host that favor the development of the infection as well as the endocrinopathies.

Primary gonadal failure (almost exclusively ovarian) has been reported in 10%–15% of type I cases and in 3%–4% of type II patients (7,9,29,35).

Skin and skin appendages. The skin is dry, and the hair of both body and scalp usually brittle and diminished (Fig. 13–125). Eyebrows and axillary and pubic hair are remarkably sparse. Total alopecia may develop spontaneously in 25%–30% of type I cases (18,29). Fingernails and toenails are frequently thin, ridged, and brittle, and often are the site

Fig. 13–125. *Endocrine-candidosis syndrome*. Note generalized skin pigmentation, especially marked over face, midtrunk, and knees. (From JA Whitaker, J Clin Endocrinol 16:1374, 1956.)



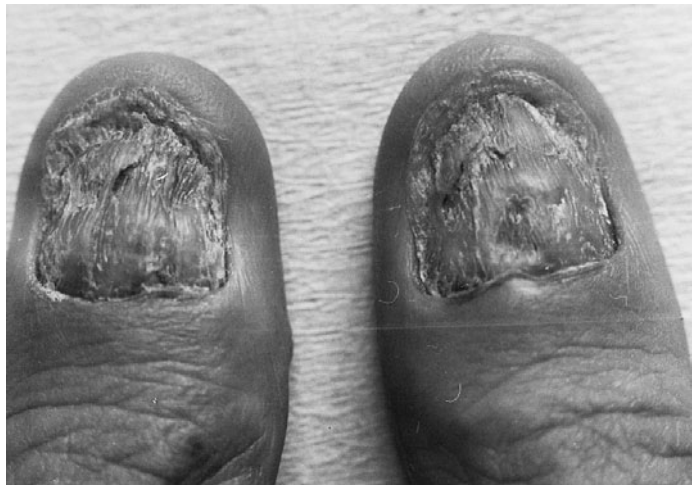


Fig. 13–126. *Endocrine-candidosis syndrome*. Candidosis of fingernails. (From KH Sjöberg, Acta Med Scand 179:157, 1966.)

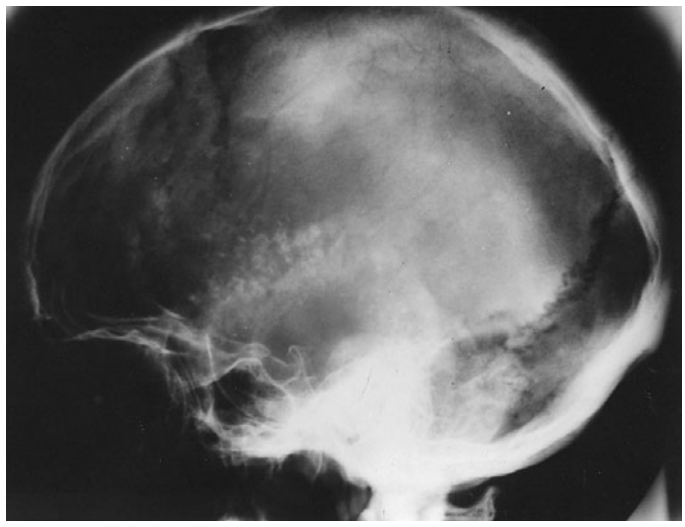
of *Candida* infections (Fig. 13–126). If infected, the nails become brown, irregular, and thickened with a crumbled outer edge. Vitiligo is present in 10% of type I patients and in 5% of type II patients (12,29). Premature graying of the hair has also been noted.

Central and peripheral nervous system. Increased cerebrospinal fluid pressure, associated with papilledema, intracranial calcification, epileptiform seizures, and mental retardation have been noted (13,32,41) (Fig. 13–127). Muscle twitchings and cramps, tetany, abdominal pain, paresthesias, and rigidity are seen. The neurologic findings have been especially well reviewed by Jordan and Kelsall (19).

Ocular findings. Several patients have manifested photophobia, blepharospasm, recurrent blepharitis, corneal pannus, keratoconjunctivitis, corneal scarring, loss of eyebrows and/or eyelashes, and cataracts (13,18,29,43) (Fig. 13–128).

Gastrointestinal findings. Malabsorption has been noted in 25% of type I cases (29). Autoimmune chronic active hepatitis occurs in 10%–15% of type I cases, but not in type II cases (9,17,29,34,45).

Fig. 13–127. *Endocrine-candidosis syndrome*. Skull radiograph exhibiting extensive basal ganglion calcification. (From JDM Gass, Am J Ophthalmol 54:660, 1962.)



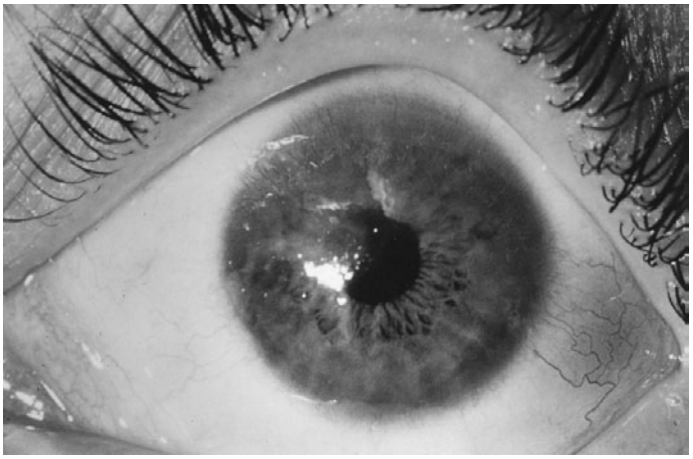


Fig. 13–128. *Endocrine-candidosis syndrome*. Keratoconjunctivitis. Note peripheral corneal vascularization and irregular, slightly raised, confluent nodular opacities in midperiphery of cornea. Lower paracentral cornea is not involved. (From JDM Gass, Am J Ophthalmol 54:660, 1962.)

Blood findings. Pernicious anemia is found in about 15% of type I cases but very rarely in type II patients (29).

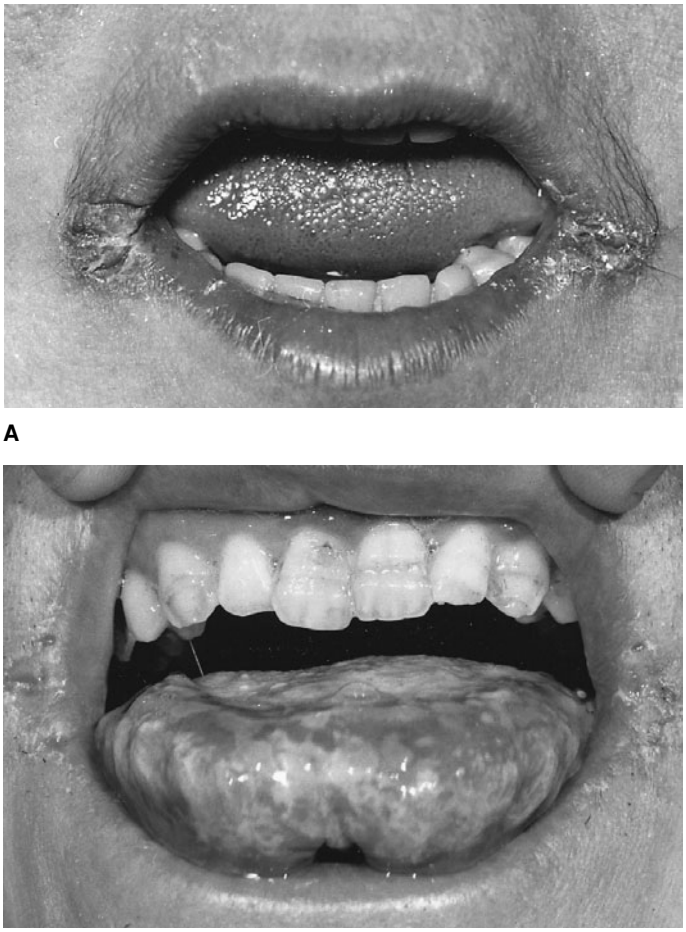
Oral manifestations. Candidosis, present in about 75% of type I patients (26,29,33), may be superficial or deep seated and may involve the lips, tongue, buccal mucosa, palate, and larynx with thick, creamy-white plaques (Fig. 13–129). The mucosa between the plaques is often hyperemic, and the tongue may be smooth and devoid of papillae. Perleche, or angular stomatitis, may extend over a considerable portion of the perioral skin. Similar involvement of the anal and vaginal mucosae has been described.

With the advent of Addison's disease, areas of splotchy melanin pigment are seen in the mouth, especially on the buccal mucosa and palate.

The teeth are chalky with pitted crowns or transverse hypoplastic bands of enamel in 80% (13,23,26,28,37,38) (Fig. 13–129B). Involvement, however, is usually of mild degree (15,16,19,45) and appears to be independent of the hypoparathyroidism (26), probably being the result of autoimmune abnormalities. Dental age is probably normal (26). Late dental eruption has been found in some patients (19,35) but not in others (26). Impacted teeth (26,37) have also been found. The occurrence of squamous cell carcinoma of the oral cavity has been reported (25,35).

Differential diagnosis. Because of the wide spectrum of the syndrome, differential diagnosis must include the differential diagnosis of each of its components. This runs an exceedingly wide gamut.

Oral and perioral candidosis, possibly as a secondary factor, may also be seen in association with an underlying malignant process (leukemia, lymphoma, iatrogenically prolonged antibiotic or corticosteroid therapy). It is also seen in acrodermatitis enteropathica and in zinc deficiency. Chronic mucocutaneous candidosis is also seen in association with primary immunodeficiencies, both those with predominantly T lymphocyte defects (AIDS, severe combined immunodeficiency. DiGeorge sequence), and occasionally with other disorders (myeloperoxidase deficiency, chronic granulomatous disease). Chronic mucocutaneous candidosis can also occur by itself in a late-onset or familial form or it can be found in association with thymoma with or without myasthenia gravis (21,36). An autosomal dominant endocrine-candidiosis syndrome that is the same as *Witkop syndrome* was reported by Okamoto et al (30). Both T and B cells were reduced. Autoantibody abnormalities were not detected, but adrenal deterioration was noted. Pisanty and Garfunkel (32) reported five families in which hypoparathyroidism and candidosis were found with mental retardation. It was not determined whether this autosomal recessive syndrome is the same as endocrine candidosis, type I.



A

B

Fig. 13–129. *Endocrine-candidosis syndrome*. (A) Marked angular cheilosis due to monilia. (B) Note enamel deficiency related to hypoparathyroidism and monilial granulomas of tongue. (A courtesy of W Reither, München, West Germany.)

Laboratory aids. There are no specific diagnostic aids for the syndrome other than those used in the diagnosis of the individual components. Laboratory examinations to determine calcium and phosphorus levels, tests for kidney function, and the Ellsworth-Howard tests and levels of serum parathormone are necessary to establish the diagnosis of idiopathic hypoparathyroidism. Chvostek and Trousseau signs are positive when the calcium level is sufficiently low. Calcium and phosphate levels should be checked every 6 months after the diagnosis of mucocutaneous candidosis is made. Hypoadrenalcorticism is established on the basis of the clinical findings, low serum sodium and high potassium levels, low plasma cortisol and/or aldosterone levels, and adrenal antibodies. Sodium and potassium levels should be periodically checked after the diagnosis of hypoparathyroidism has been established. Hypothyroidism is established on finding low serum thyroxine and high serum thyrotropin. It, like the diabetes, is often overlooked.

Blood should be examined for evidence of pernicious anemia. Ophthalmologic study should be carried out for corneal surface abnormalities by use of rose bengal, fluorescein, or Schirmer testing.

Immunologic abnormalities should be investigated: autoantibodies (both organ and nonorgan specific), cell-mediated immunity, and HLA linkage (42,46).

In family studies, or for prenatal diagnosis, molecular testing of the specific mutation may be used for the diagnosis of type I (27).

References [Endocrine-candidosis syndrome (candidosis, idiopathic hypoparathyroidism, and hypoadrenalcorticism)]

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Epidermolysis bullosa

Epidermolysis bullosa (EB) includes several hereditary vesicular disorders that involve the skin and often oral and other mucosas. The vesicles usually arise at points of trauma. For some types, however, heat may be the precipitating factor, or blisters may arise spontaneously.

The name "epidermolysis bullosa" is technically improper because cytolysis of the epidermis is observed in only three or four of the subtypes. Nevertheless it is preserved because of its many years of usage.

EB is presently classified according to various combinations of inheritance, scarring, and location of bullae. Because many of the clinical manifestations in the various subtypes of EB can be similar if not identical, it is imperative that proper typing of patients be accomplished with electron microscopic, immunofluorescent, and immunohistochemical studies (52a,59,64).

Recent progress has been made in understanding the molecular basis of the various types of EB. This progress was achieved by studying the structural features of the epidermis and dermal–epidermal junction. The molecular cloning of genes encoding proteins critical for the integrity of these cutaneous layers has helped in this process, thus explaining also many of the clinical manifestations (28, 47) (Fig. 13–130). The interested reader is referred to the works and reviews of Bergenholtz and Olsson (11), Haber et al (64), Gedde-Dahl and Anton-Lamprecht (59), Gedde-Dahl (58), Schnyder (134), Abahussein and Al-Zayir (1), Bruckner-Tuderman (17,18), Cooper and Bauer (35), Fine (48,49,53), Tabas et al (140), Christiano and Uitto (28), Bonifas et al (13), Hovnanian and Christiano (70), Marinkovich et al (91), Nomura et al (109), and, especially, Fine et al (52a).

The present classification of EB is based primarily on the level at which the cleavage that forms the bulla takes place. This is combined with the resultant clinical signs (e.g., scarring) and the type of inheritance (76). Thus, the basic classification is as follows (see also Table 13–6):

Type I: Intraepidermal forms, characterized as nonscarring varieties having autosomal dominant, recessive (vide infra), and X-linked forms.

Table 13–6. Epidermolysis bullosa[a]

Type	Inheritance	Gene map locus	Onset	Skin	Face	Oral mucosa	Teeth	Corneal erosions	Nails	Hands	Feet	Seasonal variation	References
I. *Intraepithelial blister formation (simplex - EBS)*													
A. *Major variants of nonscarring EBS*													
1. Weber-Cockayne variant	AD	12q13 17q1–q21	First to third decade	EB of hands and feet; scarring	No	9% intraoral blistering	No	No	Dystrophy	Yes	Yes	Summer	13,47a,51,119
2. Koebner variant	AD	12q13 17q12–q21	Birth to third year	EB simplex, generalized; scarring (24.1%)	±	23.1% intraoral blistering	No	No	Dystrophy	Yes	Yes	Warm weather	25,27,47a,51, 72
3. Herpetifomis, Dowling-Meara variant	AD	12q13 17q12–q21	First month	Herpitiform lesions Scarring (55.8%) Milia (68.8%) Hyperkeratosis palms and soles	Yes	62.5% intraoral blistering	Some	Some	Dystrophy 27.7%	Yes	Yes	No	45,47a,51,84, 104
B. *Minor variants of nonscarring EBS*													
1. EBS with anodontia/ hypodontia (Kallin syndrome or Nielsen-Sjölund syndrome)	AR			Blisters common Childhood alopecia with brittle hair Localized to hands and/or feet		Erosions	Anodontia or hypodontia		Thickened or curved	Yes	Yes		51,101
2. EBS with mottled pigmentation	AD	12q13	Birth to infancy	2–5 mm hyper- or hypopigmented spots	No	No	No	No	Longitudinally curved	Yes	Yes	No	18,51 52,73,140
3. EBS with limb-girdle muscular dystrophy (EB-MD)	AR	8q24	Birth	Generalized Scarring, alopecia		Frequent	Rarely defective enamel	Rare	Dystrophy common	Yes	Yes		26,39, 85,110,132
4. EBS Ogna variant	AD	8q24	Early childhood	Generalized, especially hands and feet	No	No	No	No	Onychogryposis of great toes	Yes	Yes	Summer	51,106
5. EBS, Mendes da Costa variant, macular	XR	Xq27.3–qter	First to third year	Mainly extremities	No	No	No	No	No	Yes	Yes		51,86a,98a,144a
6. EBS, recessive	AR	17q12–q21		Generalized	No	No	No	No		Yes	Yes		69
7. EBS, superficialis	AD		Birth/ infancy	Generalized or extremities		Common	Conjunctival vesiculation	Common					51
II. *Junctional epidermolysis bullosa (JEB) with hemidesmosome defect (atrophicans group)*													
A. *Nonscarring JEB, major variants*													
1. Generalized, with atrophy, gravis (Herlitz)	AR	18q11.2 1q32 1q25–q31	First days	Blisters, erosions, crusts, scarring, atrophy	Yes	Yes	Yes	Rarely	Yes, dystrophic or absent	Yes, at infancy	Yes, at infancy	No	20,28, 51,76,114–116,143
2. Generalized, atrophic, benign epidermolysis bullosa (GABEB) (Mitis or Disentis)	AR	1q32 10q24.3	At birth	Blisters. Scarring common but focal	No	Yes	Yes	No	Yes, dystrophic or absent	Yes	Yes	Summer	51,91,110

3. Generalized, inversa variant	AR	1q31	First days		No	Rarely	Yes	Yes	Yes	No	No	No	28,51,58
4. Junctional EB with pyloric atresia (EB-PA) (Carmi syndrome)	AR	17q11–qter		Aplasia cutis congenita, axillary pterygia	Ectropion Ear and nose deformity	Variable involvement	No	No	Variable involvement	Contracted fisted hand	Arthrogryposis	No	54,83,88, 110,117
B. *Nonscarring JEB, minor variants*													
1. JEB, localized, minimus (with atrophy)	AR		Birth	Blisters, atrophy present		Common	Enamal hypoplasia	No	Absent				51
2. JEB, localized, progressive	AR		5–8 years	Blisters. Atrophy variable	No	Present	Enamel hypoplasia	No	Dystrophic or absent	Mild finger contractures	Yes	No	51
3. JEB, cicatricial variant	AR		Birth	Blisters. Scarring and atrophy common, scarring alopecia		Common	Enamel hypoplasia	Infrequent	Absent	Present			51,60
III. *Dermolytic blister formation (dystrophic group) with scarring*													
A. *Major variants*													
1. EB dystrophica albupapuloidea, Pasini variant	AD	3p21.3	Birth	Blisters, milia, scarring, atrophy	Yes	Mild erosions	No	No	Dystrophic or absent	Yes	Yes	No	51
2. EB dystrophica, Cockayne-Touraine variant	AD	3p21.3	Birth to 5th year	Blisters, milia, scarring atrophy	No	Rare	No	No	Dystrophic or absent	Yes	Yes	No	24,41, 51,81,119
3. EB dystrophica, localized (Bart syndrome type)	AD	3p21.3	Birth	Congenital localized absence of skin; blistering	Yes				Dystrophy or absence	Yes	Yes		33,51
4. EB dystrophica, gravis Hallopeau-Siemens variant	AR/AD	3p21.3	Birth	Blisters, milia scarring, atrophy	Yes	Severe erosions, scarring, microstomia, ankyloglossia	Caries	Rare	Absent	Severe mitten deformities and contractures		No	32,51,57, 63,71
B. *Minor variants*													
1. EB dystrophica, localized (minimus)	AD		Early childhood	mild or absent lesions after early childhood		No			Yes	Acral distribution			51
2. EB dystrophica, localized	AR	3p21.3											55
3. EB dystrophica, pretibial	AD	3p21.3	Childhood or adolescence	Pretibial scarring and atrophy	No	No	No	No	Yes		No	No	30,51,99
4. EB dystrophica, inverse variant	AR		Neonates	Neck, groin, axilla, blisters, scarring atrophy	No	Yes	No	No	Variable	No	No	No	51
5. EB dystrophica, centripetal variant	AR		Birth	Centripetal spread		No		No	Dystrophic or absent				51
6. EB dystrophica, mitis	AR		Birth	Generalized		Mild		No	Dystrophic or absent				51
7. Transient bullous dermolysis of the newborn	AD		Birth, amelioration after age 1 year	Blistering	Yes	Yes				Yes	Yes		51
IV. *Acquired phenocopy of dystrophic EB (EB acquisita)*			Adult		No	Slight	No	No	Yes	Yes	Yes	No	

[a] Classification according to consensus report by the Subcommittee on Diagnosis and Classification of the National Epidermolysis Bullosa Registry (53).

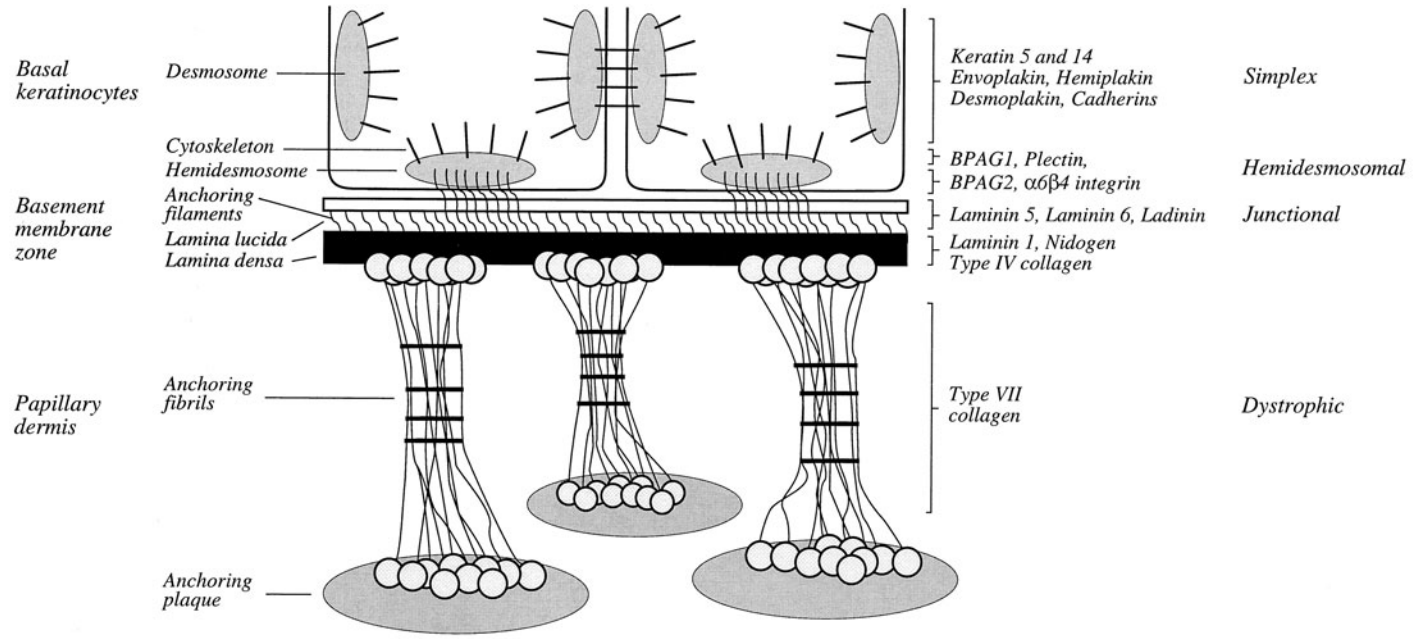


Fig. 13–130. *Epidermolysis bullosa*. The complexity of the cutaneous basement membrane zone. The figure depicts basal keratinocytes at the lower part of the epidermis which is separated from the underlying papillary dermis by a dermal-epidermal basement membrane. Ultrastructurally recognizable attachment complexes are indicated on the left, while the specific structural components within each layer are indicated on the right. Also note the level of tissue separation within different subgroups of epidermolysis bullosa as shown on the right. (Modified from J Uitto and AM Christiano, J Clin Invest 90:687, 1992, with permission.)

Type II: Junctional forms, characterized primarily by skin atrophy, with autosomal recessive inheritance.

Type III: Dermal forms, characterized by atrophy and scarring, with autosomal dominant and recessive varieties.

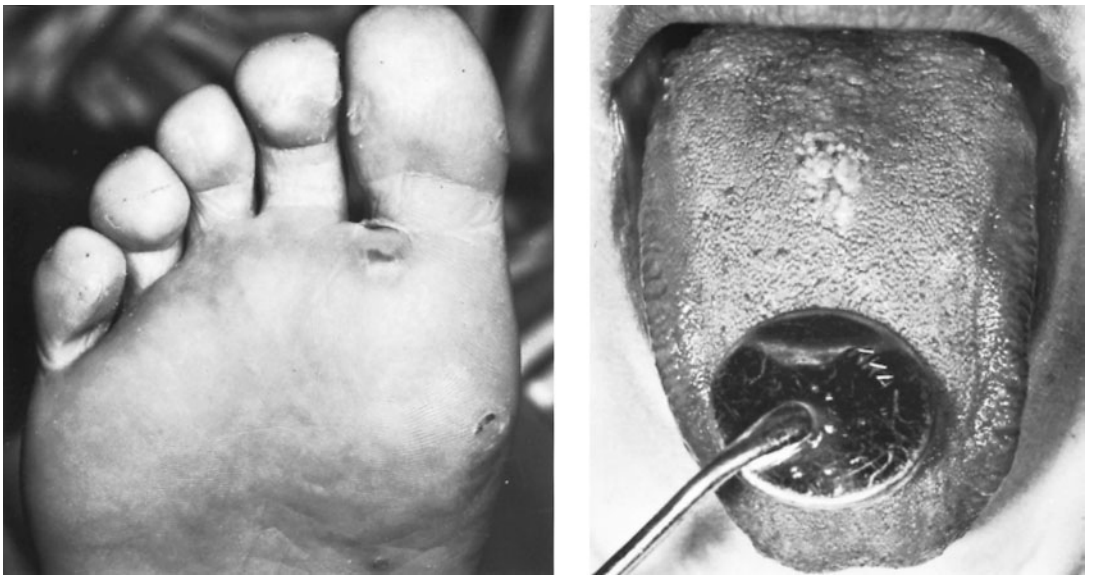
Type IV: Acquired (nonhereditary) variety known as EB acquisita.

Here, in the text, only those types presenting oral mucosal and/or dental manifestations will be described. A more complete list is presented in Table 13–6.

EB simplex Koebner type

Systemic manifestations. Sites of friction or trauma are most frequently involved. Nails are affected in about 20%. Healing does not result in scarring and/or pigmentation. The disorder, which usually appears neonatally or during infancy when the child begins to crawl, involves principally feet, hands, and neck, but rarely ankles, knees, trunk, and elbows (Fig. 13–131). After the third year of life, usually only hands and feet are affected. The nails are normal. The condition generally improves

Fig. 13–131. *Epidermolysis bullosa, dominant simplex type*. (A) Nonscarring blisters of feet. (B) Oral vesicles seen in about 2% of patients.



A B

markedly at puberty. Heat also seems to be an important precipitating factor in blister production (19). This type of EB must be differentiated from the Weber-Cockayne type, in which only the feet are affected. This latter form of EB more commonly (70% vs. 40%) appears at less than 1 year of age, and does not present oral involvement. It should be differentiated also from the Dowling-Meara type, in which serous and hemorrhagic blisters occur on any part of the body, but most frequently on the palms and soles, around the mouth, and on the trunk and neck (45).

Oral manifestations. Occasional intraoral blister formation is seen. The lesions are not as pronounced as those in the more severe types of EB. They can occur at any intraoral location. Tooth alterations are not present (58,63) (Fig. 13–131B).

Histologic study reveals cleavage through the basal layer, with nuclei on the blister floor, i.e., above the PAS-positive basement membrane. Adjacent to areas of separation, the basal cells are vacuolated, with displacement of the nucleus to the epidermal end of the cell. These alterations have been confirmed ultrastructurally (113,126). No histochemical abnormality has been observed (87).

Inheritance and genetics. Inheritance is autosomal dominant. Linkage of epidermolysis bullosa simplex to keratin gene loci has been reported (99). These phenotypes are caused by mutations in either the keratin 5 gene (*KRT5*) at 12q13 (74) or the keratin 14 gene (*KRT14*) at 17q12–q21 (25,27,74). (Fig. 13–130). The Koebner type of EBS is not fundamentally distinct from the Dowling-Meara type, which is also caused by mutations in keratin 5 or 14 genes (45,85,110). However, the Dowling-Meara type is severe and reveals, by electron microscopy, the presence of large cytoplasmic clumps of tonofilaments (4). Clinical severity is related to the location of point mutations within the keratin polypeptides. Point mutations in the most severe forms have been clustered in the highly conserved ends of K5 or K14 (85).

EB simplex with muscular dystrophy (MD-EBS). Several authors (52,81,108) have described an autosomal recessively inherited EB simplex with muscular dystrophy of the limb-girdle type (52,108) or congenital myasthenia gravis. It has been suggested that myasthenia gravis is an independent finding (52). Appearing at birth, the disorder becomes generalized but more severely involves the extremities. Milia are common. Oral mucosal involvement is frequent. A mild atrophic scarring has been seen in most patients.

In 1996, Gache et al (55) found that skin samples from MD-EBS patients did not react with 3 antibodies of the intermediate filament-associated protein plectin (Fig. 13–130). Moreover, plectin was not detected in skeletal muscles of these patients. Gache et al (55) also observed deficient immunoreactivity against the hemidesmosomal protein HD1. It is strongly suggested that plectin and HD1 are closely related and that defective expression of plectin results in an aberrant anchorage of cytoskeletal structures in keratinocytes and muscle fibers, leading to cell fragility. It has been also postulated that plectin functions in muscle as a putative attachment protein mediating binding of actin to membrane complexes. This would explain the cutaneous fragility and muscular weakness in these patients (44,57,118,138).

Inheritance and genetics. Inheritance is autosomal recessive. The disease segregates with markers in the 8q24.13-qter region where the plectin gene maps (Fig. 13–130). Various mutations and deletions in the *plectin* gene have been reported (26,86,100,115,118,125,138,147). A protein truncation test has been used for the detection of premature termination codon mutations (39).

EB atrophicans generalisata gravis (Herlitz type)

Systemic manifestations. This type of EB, inherited as autosomal recessive, was originally described by Herlitz and Pearson under the name of EB letalis. As a number of infants with this form survive into adulthood, the term *letalis* should be discarded. Because affected infants have survived the first months of life, it may be assumed that in the past several cases have been misdiagnosed (37).

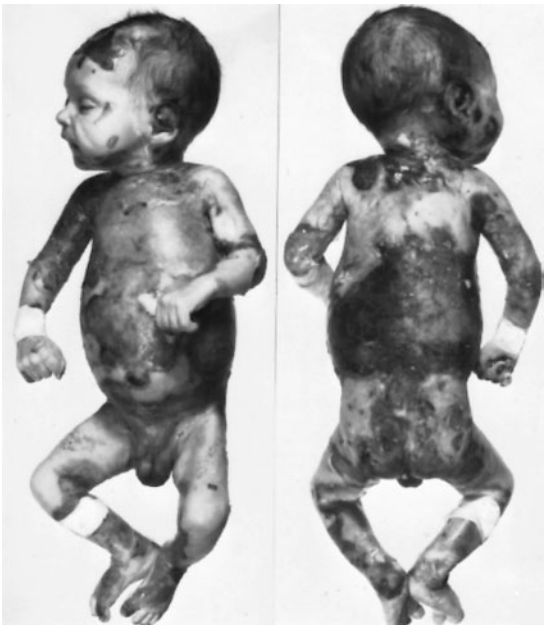


Fig. 13–132. *Epidermolysis bullosa, recessive letalis type*. Extensive skin involvement. (From EB Brain and JS Wigglesworth, Br Dent J 124:255, 1968.)

Usually the vesicles, often hemorrhagic, are noted at the base of the fingernails within the first few hours of life. The nails soon become loose and are shed (62). This is followed by involvement of the trunk, umbilicus, face, scalp, and extremities. The palms and soles are never affected. There seems to be an absence of reaction to traumatic provocation. A number of affected infants die within the first few months of life, usually from secondary septic infections (Fig. 13–132). The patients who survive do not present fusion of the digits. Their hands and feet are affected only to a minor degree (64). Anemia, growth retardation, and nail dystrophy are frequently present (59,64). With age, the healing process is retarded or arrested, leaving large excoriated areas.

Light microscopic examination demonstrates epidermal–dermal cleavage that follows the rete ridge contour. Inflammatory changes are not originally present (89,127). Vesicles at the dermoepidermal junction in the stratum germinativum of intact skin have been demonstrated (11,87).

Electron microscopic appearance, originally reported by Pearson (113), demonstrated separation between the plasma membrane of the basal cell and the basement membrane. The basic defect is hypoplasia of hemidesmosomes and lack of the subbasal dense plate (Fig. 13–130) (66,67).

A late-onset variety of junctional epidermolysis bullosa associated with mental retardation has been reported as a distinct autosomal recessive syndrome (104).

The cumulative risk of death in junctional epidermolysis bullosa is 37.4% by 1 year of life and 45.6% by age 5 years. Then it remains at that level through at least age 40, suggesting that the risk of mortality in junctional EB is primarily of concern during infancy and childhood (49).

Oral manifestations. Bullae, which are remarkably fragile and hemorrhagic, are found in nearly all patients, especially at the junction between the hard and soft palates (8). Oral ulcerations as well as blistering can be observed at birth or shortly thereafter (67). Hypoplastic and pitted enamel affecting principally the molars is also seen. Enamel formation is abnormal, leading to extensive caries (22). Histologic study reveals cleavage between the epithelium and connective tissue. The cells of the basal layer seem quite palisaded as a result of extracellular vacuolization. Perioral and perinasal crusted and granular hemorrhagic lesions tend to

develop between the sixth and the twelfth months of life (59,64,156). These lesions are believed to be pathognomonic for the Herlitz type of EB in older patients (113).

Arwill and coworkers (8) ultrastructurally investigated skin as well as oral mucosa in four cases of the Herlitz form. In contrast to those in the normal infant, the gingiva and skin exhibited fewer hemidesmosomes and tonofilaments. The initial changes consisted of edema of the subepithelial connective tissue, degeneration of mitochondria, and electron-opaque perinuclear zone that, upon dissolution, frees remnants of tonofibrils and mitochondria and widens intercellular spaces between epithelial basal cells. Although the desmosomes remained intact, minute vesicles were found between the basement membrane and the basal cell membrane in the intermediate zone. The lamellated pattern of the hemidesmosomes disappeared, replaced by a granular substance. The hemidesmosomes show abnormal association with the keratin filament network in junctional forms of epidermolysis bullosa (101).

Arwill and colleagues (7) appear to have been the first to have performed microscopic and microradiographic studies on the teeth in the Herlitz form of the disease. The enamel, lamellar in appearance, varied in thickness from 50 to 400 μm, the outer and inner zones being more markedly mineralized than the intermediate zone. Outside, and at varied distances from the surface, were free globular structures exhibiting variable mineralization. The cervical enamel was more highly mineralized than the incisal edge. In the permanent teeth there was folding at the dentinoenamel junction, which was normal in the deciduous teeth.

Decalcified sections showed intense proliferation of dental lamina and inner and outer enamel epithelium. The latter also manifested metaplasia to stratified squamous epithelium. Numerous vacuoles containing epithelium were observed. The enamel stroma was hyalinized, lamellar, and, at times, globular. Vascular proliferation was marked about the tooth germs, and hemorrhage was noted in the dental sac and stellate reticulum.

Brain and Wigglesworth (15) also investigated the deciduous dentition of an infant with the Herlitz form of EB, noting that the enamel was only 40 μm thick. There was no organized prism structure, and some parts appeared laminated. Globules resembling enamel were distributed between the hypoplastic layer of enamel and the outer enamel epithelium. The reduced enamel epithelium was extensively disorganized. Vesiclelike structures were present adjacent to tooth crowns.

Inheritance and genetics. The inheritance is autosomal recessive. In 1991, Carter et al (23) characterized a human keratinocyte extracellular matrix (ECM) glycoprotein complex termed *epiligrin*. Later, it was found that epidermolysis bullosa atrophicans generalisata gravis (Herlitz type) is caused by mutations in any one of 3 polypeptides of laminin 5 (Fig. 13–130). These are the laminin 5 α3, β3, and γ2 chains, according to the nomenclature of Burgeson et al (20).

Kivirikko et al, in 1995 (78), reported a homozygous nonsense mutation in the α3 chain gene of laminin 5 (LAMA3) in lethal (Herlitz) junctional epidermolysis bullosa. McGrath et al, in 1996 (97), studied a newborn with first-cousin parents of Pakistani origin. The proband had extensive blisters and erosions. Electron microscopy of the skin revealed scanty, rudimentary hemidesmosome-anchoring filament complexes and tissue separation within the lamina lucida. A homozygous nonsense mutation was found by molecular studies. In 1995, Vidal et al (151) found a homozygous single bp deletion in the transcripts encoding the 2 isoforms of laminin α3A and α3B in a patient with Herlitz junctional epidermolysis bullosa.

Pulkkinen et al, in 1994 (115), also found homozygosity for a nonsense mutation in the *LAMB3* gene in a patient with Herlitz junctional epidermolysis bullosa. A year later, in 1995 (117), they elucidated the exon/intron organization of the human *LAMB3* gene. In 1996, Kivirikko et al (79) examined 14 families with Herlitz type. In over 50% of the mutant *LAMB3* alleles they found two recurrent nonsense mutations (79,119). Compound heterozygosity for nonsense and missense mutations in the *LAMB3* gene has been reported in nonlethal junctional epidermolysis bullosa (98). Maternal uniparental disomy of chromosome 1 with reduction to homozygosity of the *LAMB3* locus has also been reported (121).

Finally, based on the new nomenclature for laminin chains and their isoforms (20), the *LAMNB2* or *LAMC2* gene coding for the γ2 chain was found to be mutated in certain patients with the Herlitz type of junctional epidermolysis bullosa (2,9,116,120).

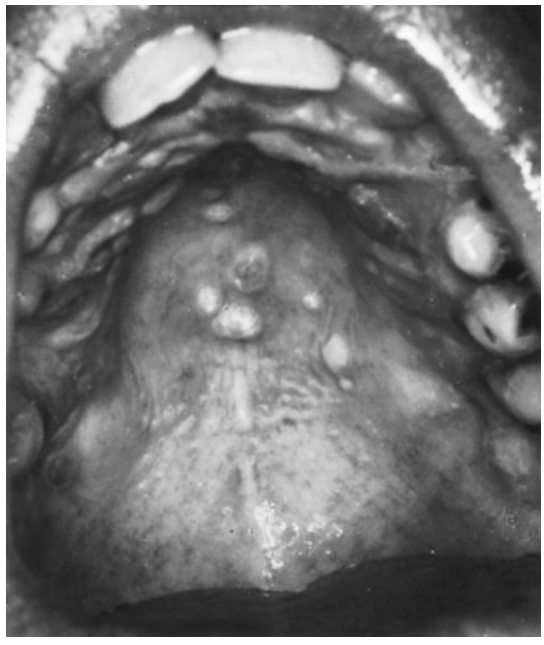
While the molecular basis of many of the classic forms of junctional EB is now well understood on the basis of laminin 5 mutations, there is a group of patients in which blisters form in and around the hemidesmosome (HD) (28). The hemidesmosomes are attachment structures critical for the stable association of epidermis and dermis. (Fig. 13–130). They extend from the intracellular compartment of the basal keratinocytes to the lamina lucida in the upper portion of the dermal–epidermal basement membrane (28). Five major components of HD have been identified. These are polypeptides named HD1-HD5 (28). HD1 is considered to be closely related to plectin (55). HD2 and HD4 are bullous pemphigoid antigen BPAG1 and BPAG2/COL17A1, respectively (Fig. 13–130). HD3 and HD5 correspond to the β4 and α6 of integrins, respectively. BPAG2/COL17A1 and $\alpha 6\beta 4$ integrin mutations are responsible for generalized atrophic benign EB and junctional EB with pyloric atresia, respectively (see Table 13–6).

Based on mutation analysis, prenatal diagnosis (34,92,95,96,123, 142,149) and preimplantation genetic diagnosis (38) have been performed in families at risk for Herlitz junctional epidermolysis bullosa.

Dominant dystrophic (hypertrophic) form (Cockayne-Touraine type). This form of epidermolysis bullosa is characterized by flat, pink, scar-producing bullae of the ankles, knees, hands, elbows, and feet, in decreasing order of frequency (41). Milia are common but less numerous than in the recessive dysplastic type. The nails are usually (80%) thick and dystrophic. In contrast to recessive dystrophic cases, the conjunctiva and cornea are never involved. Approximately 20% show changes before the age of 1 year (109). Improvement seems to occur with age. Hyperhidrosis of palms and soles may also occur.

Oral manifestations. The consensus favors the view that teeth are not affected. Touraine's often-quoted statement (144) that 20% manifest oral bullae would appear to be essentially substantiated by other studies (41), but series have been small. Oral milia were noted by Andreasen and associates (3). (Fig. 13–133). These milia are not retention cysts, but epidermoid cysts that originate from detached islands of epithelium in areas of earlier bulla formation.

Fig. 13–133. *Epidermolysis bullosa, dominant dystrophic type*. Milia of palate. (From JO Andreasen et al, Acta Pathol Microbiol Scand 63:37, 1965.)



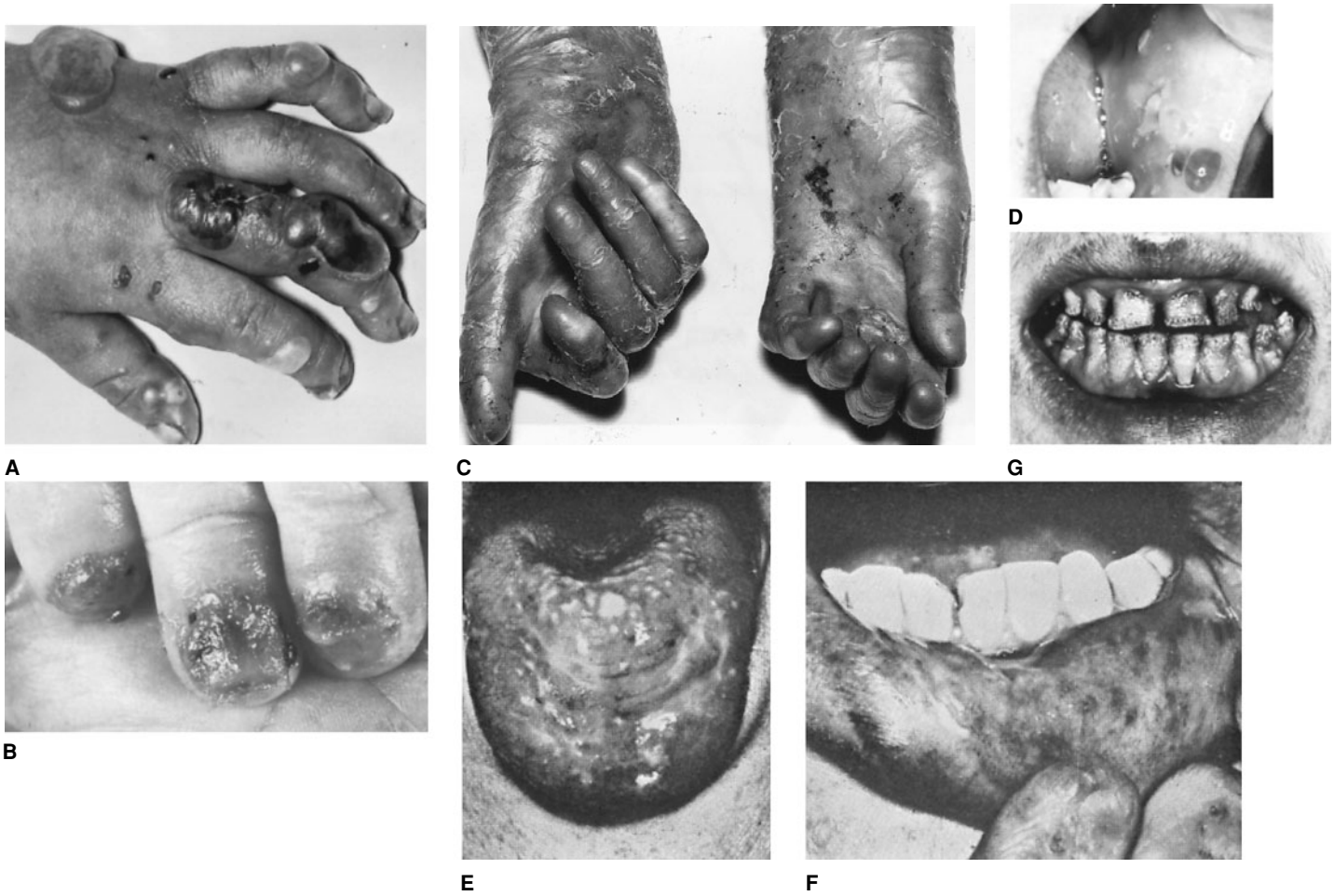


Fig. 13–134. *Epidermolysis bullosa, recessive dystrophic type*. (A) Extensive blister formation of hand. (B) Destructive lesions of fingernails in newborn. (C) Severe involvement of hands. Note dystrophy of nails. (D) Bullae of buccal mucosa. (E) Dorsum of tongue exhibiting numerous scars and complete loss of papillae. Often mobility is limited. (F) Labial mucosa showing extensive scarring. Also note nail dystrophy. (G) Pitted enamel. (A courtesy of A Lodin, Stockholm Sweden. C,E and F from D Winstock, Br J Dermatol 74:431, 1962. G from OE Rodermund, Dermatol Wochenschr 153:350, 1967.)

Inheritance and genetics. Inheritance is autosomal dominant. Many extensive families have been reported (24,124). It is possible that Cockayne-Touraine, Pasini, and Bart types represent different expressions of the same mutant gene (14). Kon et al (82) reported novel glycine substitution mutations in COL7A1, revealing that the Pasini and Cockayne-Touraine variants of dominant dystrophic epidermolysis bullosa are allelic.

Scarring EB with dermolytic blisters (Hallopeau-Siemens type). The extensive studies of Gedde-Dahl (58) and Gedde-Dahl and Anton-Lamprecht (59) suggest that this group of disorders has very significant heterogeneity.

Bullae are usually manifested at or shortly after birth, arising at sites of pressure or trauma or appearing spontaneously (Fig. 13–134). In infants, the most commonly affected areas are feet, buttocks, scapulas, elbows, fingers, and occiput. In older children, hands, feet, knees, and elbows are most often involved. When a bulla ruptures or its roof peels off, a raw painful surface is evident. The fluid contained in the bulla is at first sterile but may become secondarily infected and bloody. Upon healing, the bullae often are followed by keloidal scars, causing contraction. They are frequently associated with miliumlike cysts. The scars may lead to loss of bony structures or to interference with growth and resultant dwarfism. Formation of clawhand and the enclosure of the hand in a glovelike epidermal sac have been noted frequently (16,155) (Fig. 13–134A). The Nikolsky sign is often present. The nails may be extremely involved, often being dystrophic or absent (58) (Fig. 13–134B,C). Hyperhidrosis of palms and soles is an inconsistent finding but may be marked. Hair may be deficient.

The eyes have been subject to a number of changes: essential shrinkage of conjunctiva, nonspecific blepharitis, symblepharon, conjunctivitis, and keratitis with corneal opacity and vesicle formation (58).

Hoarseness and, rarely, aphonia and dysphagia may occur as a result of bullae of the larynx or pharynx. Laryngeal stenosis may eventuate from scarring. Involvement of the esophagus may result in complete obstruction (10,68).

Changes are essentially limited to the hands, feet, and esophagus. The esophagus (most often the upper half) may become segmentally stenotic in childhood, with consequent dysphagia (10,152). The metacarpals become slender and overconstricted and distal phalanges become pointed and claw-like (16,155).

By ages 25 and 35, 23.7% and 51.0%, respectively, of patients with the Hallopeau-Siemens variant have developed at least one squamous cell carcinoma (112). In addition, the cumulative risk of malignant melanoma in this variant was found to be 4.1% by age 12 (49). Angiosarcoma has also been reported as a complication (133).

Little increased risk of death occurs in recessive dystrophic EB patients until after the age of 20. By age 40, however, the risk of death is 33.3%, coinciding with the timing of squamous cell carcinomas in this patient population (49).

Oral manifestations. Although a considerable number of authors have remarked on the teeth having hypoplastic enamel with great susceptibility to dental caries, delayed eruption, and frequent retention, there is little documentation concerning frequency of these manifestations (40,77,93,154). We share with Rodermund (129) the belief that there is no correlation between the degree of cutaneous involvement and the degree of dental involvement. Pockmarked enamel was handsomely illustrated by Rodermund (129) (Fig. 13–134G). Excellent histologic studies of unerupted teeth have been published by Delaire and colleagues (43) and by Arwill and coworkers (7). Both groups noted hypoplasia of enamel with absence of prismatic structure. Extracted teeth were examined by Crawford et al (37), who found accentuation of enamel tuft formation extending from the dentinoenamel junction to the enamel surface. Additionally, irregular dentinal foldings and indentations were found at the dentinoenamel junction.

Oral mucosal involvement occurs soon after birth, vesicles apparently forming from the negative pressure involved in the sucking reflex (Fig. 13–134D) (157). Although oral bullae are said to occur in a least 16%, our impression is that the percentage is much higher. The lingual mucosa appears thick, gray, and smooth and may become bound down (Fig. 13–134E,F). Repeated blistering with scar formation may lead to ankyloglossia, tongue atrophy, elimination of buccal and vestibular sulci, and perioral stricture (12,37) (Fig. 13–134F). Severe periodontal disease with alveolar bone resorption had also been noted (40). Even routine dental management may cause the eruption of bullae on lips and oral mucosa (12). Diminished oral opening following scarring after blistering as well as ankyloglossia due to the same cause have been reported (12). The slightest abrasion from normal tooth brushing may cause serious sequelae. Other oral changes, the frequencies of which have not been established, are atrophy of the maxilla with resultant relative mandibular prognathism, increased mandibular angle (16), and oral carcinoma (80,128,132). Histopathologic changes in the oral mucosa were well demonstrated by Arwill and associates (6). The bullae occur below the PAS-positive basement membrane (87). Hemidesmosomes and tonofibrils are absent or decreased in numbers. Lowe (87) also noted an increase in elastic and pre-elastic fibers in the corium. Hitchin (69) described defective cementum.

Inheritance and genetics. Inheritance is autosomal recessive or dominant. In 1993, Hovnanian and Christiano (70) and Uitto et al (146) demonstrated linkage between a PvuII polymorphic site of the COL7A1 and dystrophic epidermolysis bullosa (Fig. 13–130).

Type VII collagen appears to be restricted to the basement membrane zone beneath stratified squamous epithelia. Within the cutaneous basement membrane zone, type VII collagen localizes to the lamina densa and sublamina densa areas in the upper papillary dermis (57,103). The severe autosomal recessive dystrophic form has been found to be associated with type VII collagen deficiency (17).

Christiano et al (29–31) found mutations in type VII collagen in patients with recessive dystrophic epidermolysis bullosa in the Bart form (103). Later, in 1996 (32,33), they stated that the COL7A1 gene is unique among the collagen genes in that different glycine substitutions can result in a spectrum of dystrophic epidermolysis bullosa phenotypes and patterns of inheritance. Hovnanian et al (73), in 1997, characterized 21 mutations in the COL7A1 gene, 18 of which had not been previously reported, in patients from 15 unrelated families with recessive dystrophic epidermolysis bullosa (RDEB). Fourteen of the 21 mutations created premature termination codons and consisted of nonsense mutations, small insertions, deletions, and splice site mutations. An additional 7 mutations predicted glycine or arginine substitutions in the collagenous domain of the molecule. Genotype–phenotype correlations suggested to Hovnanian et al (73) that the nature and location of these mutations are important determinants of the phenotype. Hammami-Hauasli et al, in 1998 (65), studied naturally occurring COL7A1 mutations and showed that some, but not all, glycine substitutions in collagen VII interfere with biosynthesis of the protein in a dominant negative manner. Three point mutations in exon 73 caused glycine substitutions in the triple helical domain of collagen VII and interfered with its folding and secretion. In contrast, the glycine substitution in another segment of the triple helix remained phenotypically silent. Thus, collagen VII is a remarkable exception among collagens in that the biologic consequences of the glycine substitutions depend on their position within the triple helix.

Hovnanian et al (72) reported DNA-based prenatal diagnosis of generalized recessive dystrophic epidermolysis bullosa in pregnancies at risk for recurrence.

Oral manifestations of other forms of EB. *Epidermolysis bullosa acquisita* rarely presents oral manifestations, but they have been described (107). This form of EB is nonhereditary and manifests in adulthood with blister formation, especially in areas of trauma. It may be associated with other systemic diseases, such as amyloidosis, multiple myeloma, diabetes mellitus, and inflammatory bowel disease. The last association may represent a gastrointestinal cutaneous syndrome with immune pathogenesis (143).

Scarring or cicatricial junctional type of EB has autosomal recessive inheritance. Patients present at birth with skin blisters and lack of nails. There is marked disfigurement, especially of hands and feet. The skin blisters heal with scar formation, producing marked atrophy, especially around the nares. Occasionally a diminished oral opening is noted. Patients present intraoral blisters that are found at any site but are not as profuse or as severe as those in some other forms of EB. All patients with this condition have been reported either as having extensive dental caries or as being edentulous. Further studies are needed to assess whether there is some form of enamel defect present. Since this type of EB has definite ectodermal alterations (anonychia), an enamel defect is within the realm of possibility (62).

EB nonscarring atrophicans generalisata mitis (R-EBA-MITIS), epidermolysis bullosa junctionalis, disentis type, inherited as an autosomal dominant disorder, presents oral and dental alterations. Oral mucosa can be the site of blisters, especially trauma-related; nodular excrescences on the palate and gingiva have also been reported (61). Teeth can present pitting of enamel, conducive to extensive caries (113).

A possible new variety of EB has been reported by Nielsen and Sjölund (106): *epidermolysis bullosa, late-onset localized junctional, with mental retardation, in two sisters*, offspring of nonconsanguinous parents. These patients presented hemorrhagic blisters localized to hands and feet associated with partial alopecia, onychogryposis, anodontia, and an amelogenesis imperfecta-like condition. Light microscopy showed intraepithelial bullae formation. No EM studies were reported.

Epidermolysis bullosa associated with pyloric atresia has also been described. Autosomal recessive inheritance has been found (19,21, 36,42,83,84,91,102a). The gene has been mapped to 17q11–qter. Mutations in the a6 and b4 integrin chain genes have been reported (115,122, 130,141,150) (Fig. 13–130). These patients not uncommonly have erosions and/or subepithelial cleavage in the respiratory, gastrointestinal, and urinary tracts. Obstruction of the ureterovesical junction and a high incidence of a peculiar form of aplasia cutis congenita may also occur. Prenatal diagnosis has been accomplished microscopically (105). Direct first trimester molecular prenatal diagnosis of junctional epidermolysis bullosa with pyloric atresia has been reported (114,136).

Differential diagnosis. Recognition of EB is seldom difficult, even without assessing its entire clinical, genetic, and histologic character. In infants and children, the syndrome may be occasionally confused with conditions such as bullous impetigo (so-called pemphigus neonatorum), Ritter disease, porphyria congenita, congenital syphilis, or juvenile bullous dermatitis herpetiformis. In older patients, differential diagnosis includes pemphigus, drug eruptions, dermatitis herpetiformis, and bullous erythema multiforme.

It has been noted that in EB, pulling up a strip of cellophane adhesive tape will cause the top layers of the skin to adhere to the tape. The phenomenon is not seen in Ritter disease or in generalized impetigo. The lesions of porphyria are generally confined to chronically sun-exposed areas. Only the exposed skin is fragile; epidermolysis bullosa shows no localization of skin fragility.

The differential diagnosis should include *Kindler syndrome* characterized by bullae formation since birth on pressure areas that, on healing,

leave atrophic scars. In addition, affected individuals present severe photosensitivity and poikiloderma. The oral mucosae are atrophic and present multiple white macules (137).

Laboratory aids. Microscopically, the bullae are intraepidermal in the nonscarring forms, at the level of the epithelial dermal junction in the trophic forms and subepithelial or intradermal in the scarring forms. Unfortunately light microscopy is not useful in differentiating among the severe types of EB. Periodic acid-Schiff (PAS) stain is useful in subdividing the various types of EB according to the location of the basement membrane, but is unreliable because during the process of blister formation there will be retraction in the actual position of the basal membrane. The basal membrane remains attached to the dermis in EB simplex and junctional types, whereas it remains adherent to the epidermis in dystrophic types of EB.

Ultrastructural examinations are essential for an accurate diagnosis of EB types; neither regular light microscopy nor clinical presentation is sufficient or adequate for proper diagnosis.

Tonofilaments, which are the intercellular bindings of basal cells, have been shown to be defective in intraepidermal types of EB. Junctional types of EB are characterized by defects in anchoring filaments of hemidesmosomes, whereas primary or secondary destruction of the anchoring fibrils that extend from the basal lamina into the dermis are observed in the dermal types of EB (66).

Other pathogenetic mechanisms for certain types of EB include degradation of collagen through collagenase and gelatinase (131). Excessive secretion of collagenase by dystrophic fibroblasts from patients with simplex and dystrophic forms of EB has been reported (111).

Immunofluorescent mapping studies are used to differentiate among various types of EB by detecting the presence of four structural components within the skin basement membrane: bullous pemphigoid antigen, laminin, type IV collagen, and lamina densa antigen-1 (LDA-1). The diagnosis is made by identifying the location of these antigens and their relation to the level of cleavage in a freshly induced blister (50).

Prenatal diagnosis of the various types of EB is possible through fetoscopy with fetal skin sampling, electron microscopic studies (5), and immunofluorescent mapping (51). However, with recent advances in molecular diagnostics, the study of gene mutations after amniocentesis or CVS is the most reliable and safest method (28,46). Preimplantation diagnosis has also been accomplished (38).

At present, the definitive and precise diagnosis as well as the classification of epidermolysis bullosa are made on the basis of molecular studies of gene mutations (28).

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Hyalinosis cutis et mucosae (lipoid proteinosis, Urbach-Wiethe syndrome)

The syndrome, consisting of yellow nodular infiltration of skin and mucous membranes and intracranial calcifications, was first described by Siebenmann (54) in 1908. Other cases were reported in the 1920s, but credit is given to Urbach and Wiethe (60,61,65), who defined the condition and applied the terms "lipoidosis cutis et mucosae" and "lipoid proteinosis" (37). The history of the syndrome has been reviewed by Laymon and Hill (37) and Gordon et al (20). Approximately 200 patients have been described.

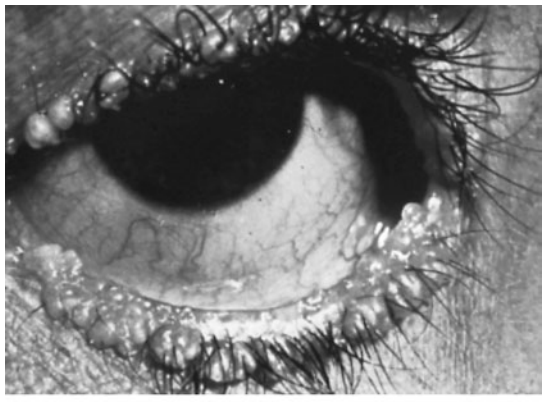
The syndrome is transmitted as an autosomal recessive trait (20). It has appeared in sibs (16,25,32,52,55,58,61); in about 20% of cases there has been parental consanguinity (6,7,35,38), Many patients have been of Dutch or German ancestry. Almost a quarter of all reported cases of lipoid proteinosis have been in residents of South Africa. Stine and Smith (56) estimated the coefficient of selection for the lipoid proteinosis gene to be 0.07 in the Afrikaner population of South Africa. They suggested that this may be a pleiotropic gene that has a dominant effect in selection, even though the clinical manifestations follow a recessive pattern.

Skin and skin appendages. Discrete or confluent yellow-ivory nodules, from pinhead to matchhead in size, are found on the face, neck, axillas, and hands early in life. However, late onset is possible (25a). The perineum and scrotum have also been involved (20). Some patients develop bullous lesions of the face and upper extremities that have sometimes been described as impetigenous (13,20,34,52); on healing, these lesions leave hyperpigmented, pitted, atrophic patches (14,20,31) (Fig. 13–135). Brown-yellow, wart-like, hyperkeratotic lesions occur on the knees, elbows, and interarticular surfaces of the fingers (4,14,20,31,44, 45,46,53) (Fig. 13–136). With time, there is generalized skin thickening.

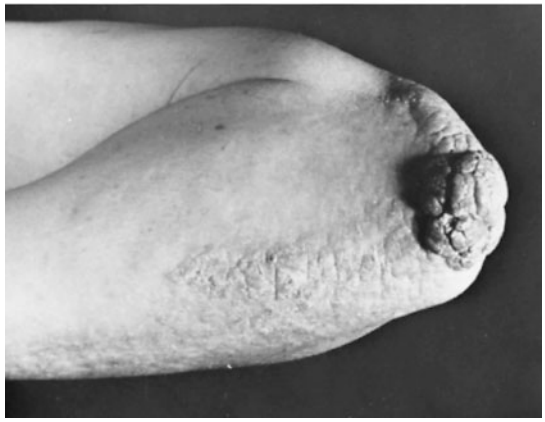
Diffuse or patchy alopecia of the scalp hair is common (6–8,21,23, 34,40,41,46,57,58).

Ophthalmologic abnormalities. Beadlike excrescences (moniliform blepharosis) are found on the upper and lower eyelid margins in almost all patients (30,31), followed in some cases by loss of cilia (23,37,46) (Fig. 13–136A). Fundus changes, consisting of sharp or poorly demarcated small, round, gray-white or yellow-white lesions were seen in 9 of 20 patients described by Heyl (26); in addition, vascular tortuosity was found. Finlay (14) described significant abnormalities in a 16-year-old legally blind patient who had visual problems since age 7. Other investigators noted drusenlike changes in patients as young as 23 and 34 years of age (49,51). On histologic examination, Marquardt (39) felt these lesions differed from classic drusen because they extended into the choriocapillaris. Histochemically they were identical to the skin lesions. Glaucoma was seen in several cases (18,39).

Fig. 13–135. *Hyalinosis cutis et mucosae*. Note numerous raised yellowish nodules. (From KH Holtz, Arch Klin Exp Dermatol 214:289, 1962.)



A



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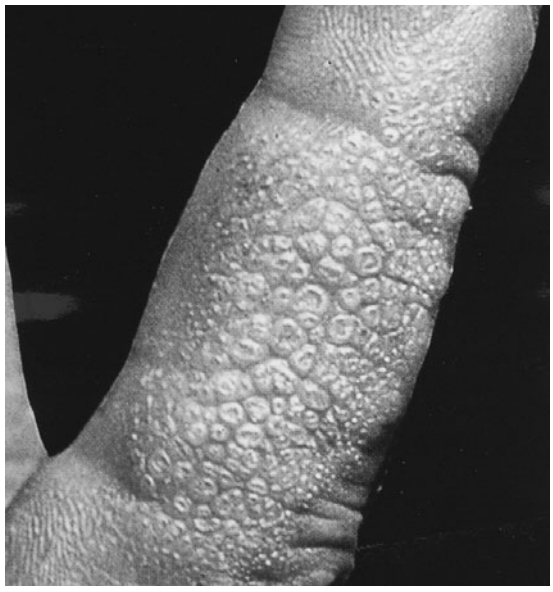
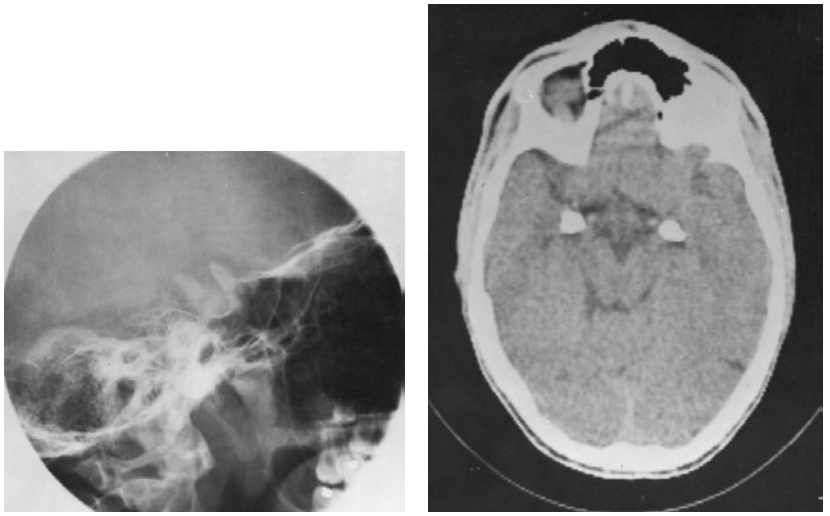


C

Fig. 13–136. *Hyalinosis cutis et mucosae*. (A) Beadlike excrescences among eyelid margins. (B) Verrucous lesions of elbow. (C) Verrucous lesions of fingers. (A from AR Rosenthal and JR Duke, Am J Ophthalmol 64:1120, 1967; B from RC Juberg et al, J Med Genet 12:110, 1975.)



A B

Fig. 13–137. *Hyalinosis cutis et mucosae*. (A,B) Radiograph and CAT scan showing calcification of hippocampal gyri. (From K Fochem et al, Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 138:265, 1983.)

Central nervous system. Bilateral intracranial calcifications, found in at least 70%, have been located in the hypothalamus (41) and above the pituitary fossa in the hippocampus, falx cerebri, or temporal lobes (7,14,19–21,32,36,37,41,44,52,62,64,68); these abnormalities are more often seen in individuals over 10 years of age (20). Calcification has been localized to the head of the caudate nucleus, globus pallidus, and amygdaloid nucleus (44). Adolphs et al (1) suggested that the human amygdala may be indispensable to recognize fear and multiple emotions in facial expressions. Seizures have been reported (7,26,37,38,44) (Fig. 13–137). Emsley and Paster (11) reported two patients with long-standing memory impairment, paranoia, and bilateral temporal lobe calcification.

Larynx and other mucosal involvement. The voice in almost all patients is hoarse from birth (14,21,30,63), infancy (15,53), or from the first few years of life (13,28,53), and a low-pitched cry has been described (9,44); these findings testify to early laryngeal involvement (8). Laryngoscopic examination reveals yellow-white plaques on the epiglottis, aryepiglottic folds, and interarytenoid regions (9,13,20,30,46,47). The cords are thickened (9,53,68) and nodular (17,22,68). Extension of the infiltration to the tonsils and pharynx may result in severe dysphagia (14,44,48) and dyspnea, necessitating tracheostomy (5,20).

Other mucosal surfaces, such as the vulva, esophagus, stomach, and rectum, are also affected (7,20,21,27,61). Wartlike lesions have been found in the main bronchi (45).

Oral manifestations. Oral manifestations have been summarized (4,29). Oral mucous membranes are extensively infiltrated with yellow-white, elevated granules and pea-size plaques, which usually appear before puberty and gradually increase in severity (29). The lower lip is usually more severely affected than the upper, and has a cobblestone appearance (Fig. 13–138A). Radiating fissures may appear at the angles of the mouth (13,34,37) and on the lips (67) and tongue (21,30).

The tongue becomes firm or woody, thick, large, and restricted in mobility (1,3,5,34,40). The dorsum loses its papillae (13,30,35,44,51). There is usually marked infiltration of the lingual frenulum, which becomes inelastic (5). Ulcers may develop (6,114,21,26,63,66) (Fig. 13–138B–D).

With infiltration of the buccal mucosa, the opening of the parotid duct may become stenotic, with ensuing retrograde parotitis (4,6,26,27,34, 37,38,44,45,57). The soft palate and uvula may also be involved (55) (Fig. 13–138E). Affected individuals may not be able to open their mouths widely (20).

Specific dental abnormalities have not been documented. However, patients have been described as having lost their teeth at an early age (14), perhaps due to dental caries, resulting from obstruction of the orifices of major salivary gland ducts, as well as hyalinization of minor salivary glands. Gingival hyperplasia may be present, due to diffuse deposition of hyaline-like material (48).

Differential diagnosis. Conditions to be considered include amyloidosis, colloid milium adenoma sebaceum, *pseudoxanthoma elasticum*, and porphyria cutanea tarda.

Laboratory aids. Several investigators noted an increase in $\alpha 2$ and γ globulin levels and a diminution in the concentration of albumins (20,21,32), but these changes have been denied by others (37).

On light microscopic examination of the skin, there is hyalinization of the superficial connective tissue, beginning about the small and medium-sized blood vessels and sweat glands. Concentric laminar thickening of the stroma around these structures is noted (12). Hyalinization later extends more deeply (2) (Fig. 13–139). Biopsy of oral mucous membranes has also shown hyalinization, which may replace mucous gland acini (21,55). Histochemical study (21) has revealed the presence of carbohydrate but little or no lipids. The hyaline material stains intensely with the PAS procedure (53,59), thus appearing to be a glycoprotein, either free or loosely bound to collagen (16,27,53). Ultrastructural studies have been carried out on the hyaline material (10,25,36,42,50). Several authors (42,44) have suggested that it represents an altered collagen. Ishibashi (33), by electron microscopy, determined that the hyalinization was an accumulation of type IV collagen and laminin. Concentric layers of basal laminae are seen surrounding blood vessels in an onionskin arrangement (20,42,43). Fat has been demonstrated in fibroblasts (7).

On biochemical analysis, Harper et al (24) found reduced amounts of collagen in skin; however, the proportion of type III to type I collagen was elevated. In addition, the amount of type V collagen was five times normal. Immunologic studies showed a patchy, diffuse, widely distributed type III collagen, with increases in types IV and V collagen (26,45). An abnormal pattern of collagen cross-linkage was also found. Fleischmajer et al (17) concluded that the hyaline material originated from overproduction of noncollagenous proteins.

Results of studies of Bauer et al (2) suggested that the disorder was a lysosomal storage disease; cultured fibroblasts displayed a three- to four-fold increase in total hexuronic acid. Studies of cultured fibroblasts by Shore et al (53) found a lipid content similar in quantity and distribution to that of control cells.

References [Hyalinosis cutis et mucosae (lipoid proteinosis, Urbach-Wiethe syndrome)]

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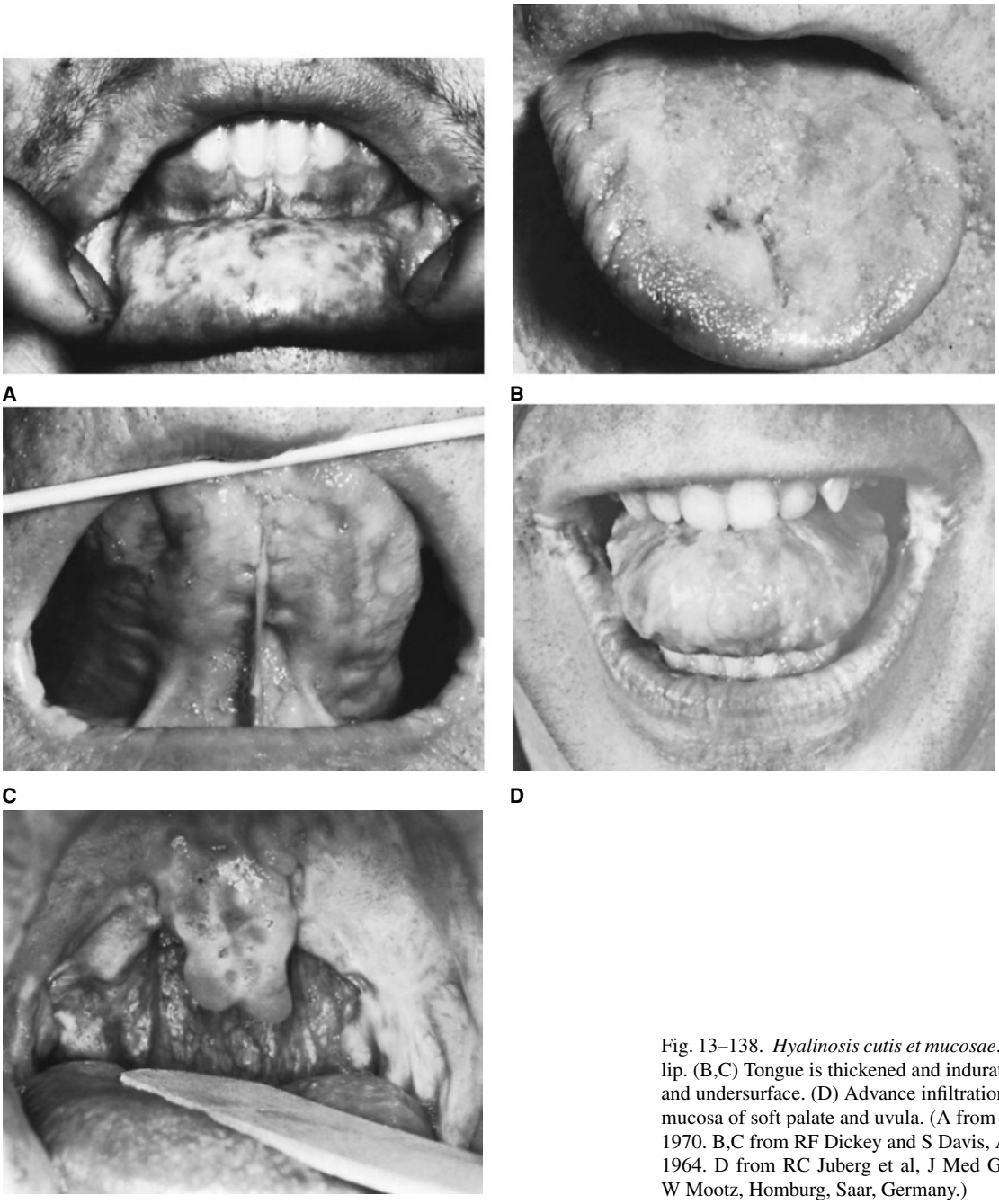

Fig. 13–138. *Hyalinosis cutis et mucosae*. (A) Extensive infiltration of lower lip. (B,C) Tongue is thickened and indurated with plaques on dorsum, sides, and undersurface. (D) Advance infiltration of tongue in adult. (E) Infiltrated mucosa of soft palate and uvula. (A from JA Kiepert, Aust Paediatr J 6:135, 1970. B,C from RF Dickey and S Davis, Ann Otol Rhinol Laryngol 73:287, 1964. D from RC Juberg et al, J Med Genet 12:110, 1975. E courtesy of W Mootz, Homburg, Saar, Germany.)

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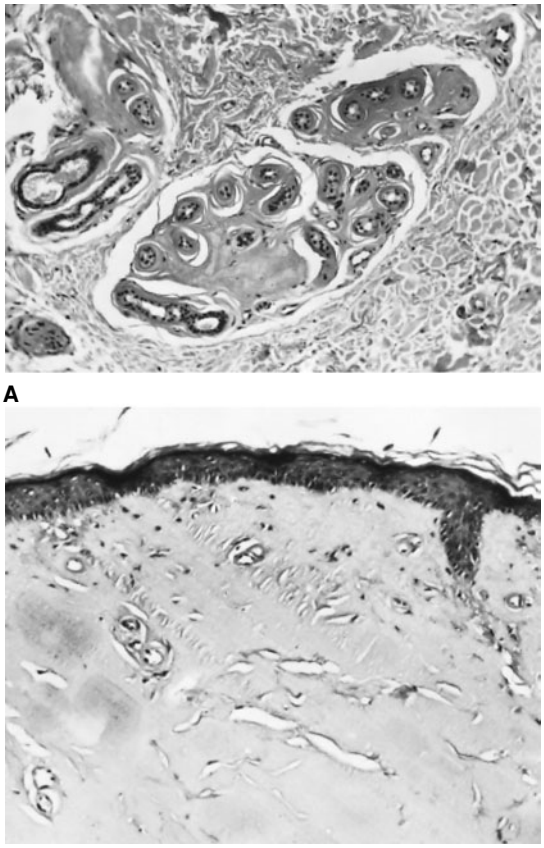

Fig. 13–139. *Hyalinosis cutis et mucosae*. (A) Deposition of hyaline material around sweat glands in lower dermis. (B) Amorphous deposits lying directly beneath epithelium. (A from R Shore, Arch Dermatol 110:591, 1974; B from AR Rosenthal and JR Duke, Am J Ophthalmol 64:1120, 1967.)

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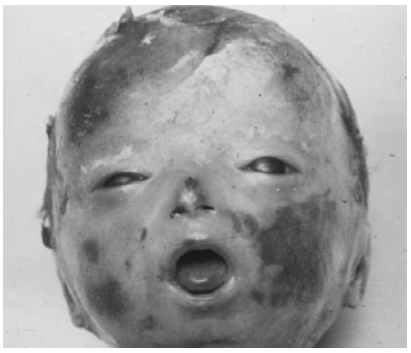

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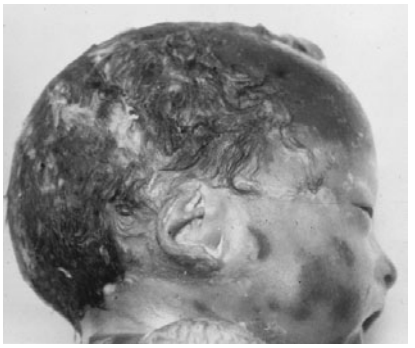


B

Fig. 13–140. *Restrictive dermopathy.* (A,B) Fixed facies with hypertelorism, small nose, low-set dysmorphic pinna, small tight mouth, and micrognathia.

Restrictive dermopathy (late fetal epidermal dysplasia, type II)

Witt et al (28) and Toriello (22), in 1986, defined a lethal syndrome characterized by rigid, tightly adherent skin with generalized joint contractures, unusual facies, pulmonary hypoplasia, abnormally large placenta, short umbilical cord, and skeletal alterations. Toriello et al (23) reported two earlier examples in 1983, and Lowry et al (14) and Schnur et al (20) probably described the same condition. Approximately 20 additional examples have been reported (4,5,7–10,12,13,15–19,21,25–28).

Inheritance is autosomal recessive (9,14,16,22). There may be a Hutterite type and a non-Hutterite type (2,6).

Prematurity (about 32 weeks), polyhydramnios, and decreased fetal movement late in pregnancy, and short umbilical cord are common features. Intrauterine growth retardation is severe. Death is usually due to pulmonary hypoplasia (8,9,14,28).

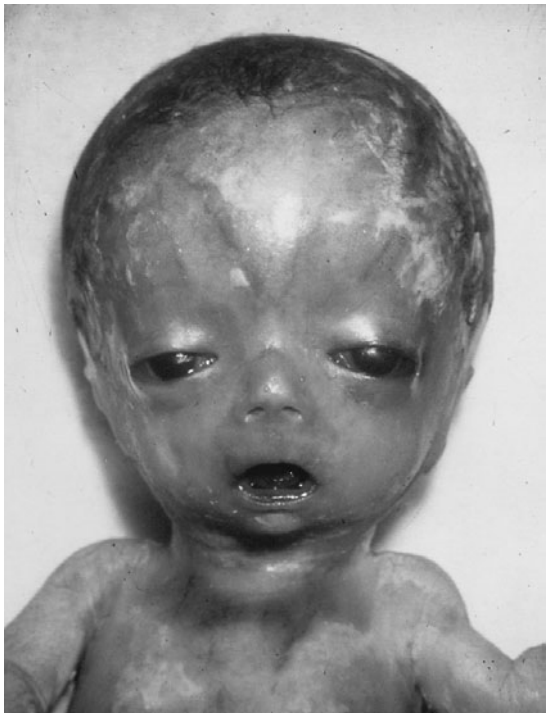
The fixed facies manifests hypertelorism, with or without ectropion, small thin nose, apparently low-set anomalous pinnae, small tight open O-shaped mouth, and micrognathia. The temporomandibular joint is fixed. Submucous cleft palate has been described (23) (Figs. 13–140 and 13–141A). Choanal stenosis (14,27) and usually natal teeth (27) have been documented.

The chest is small and barrel shaped with increased AP diameter. Breast buds are prominent. There are dorsal kyphosis and rocker-bottom feet (Fig. 13–142). The lungs are hypoplastic. The internal organs are otherwise normal.

Additional findings in individual patients included blepharophimosis, skin tear in the frontal neck and inguinal area, absent eyelashes, a wide ascending aorta, and dextrocardia (22).

In some examples, the skin has a rigid, thick, smooth, and shiny shell-like structure, whereas in others there are extensive erosions (Fig. 13–141B). Histologic skin changes include orthokeratotic hyperkeratosis, hypoplastic pilosebaceous structures and sweat glands, absence of dermal rete ridges, and thin dermis with collagen bundles aligned parallel to the epidermis (22,28). Fetal hyperkeratinization of the skin is probably the primary defect (3,11). Electron microscopy of the epidermis exhibits lack of keratin filaments and abnormal globular shape of the keratohyalin granules (9). Fibroblasts display increased expression of the alpha-1 and alpha-2 subunits of integrin, which are responsible for collagen binding (5), a finding not supported in one study (22).

Radiologic changes include wide fontanels and sutures, and overtubulation of all long bones with modeling defects of the proximal humeri and distal radii and ulnae (Fig. 13–143) (19). There is deficient ossification of the distal or midportion of the clavicles and generalized fixed flexion contracture at all joints, including fingers and mandible. The ribs are sometimes thin and dysplastic. The scapulae are abnormally shaped and positioned (19). The prenatal sonographic findings have been described (24).



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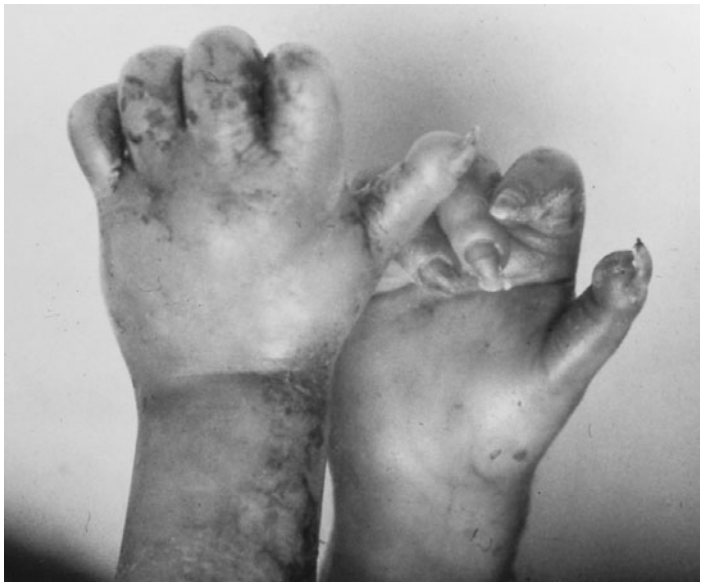

B

Fig. 13–141. *Restrictive dermopathy*. (A,B) Edematous rigid skin of facies, hands, flexion contraction of fingers. (A from C Pierard-Franchimont et al, J Pathol 167:223, 1992.)

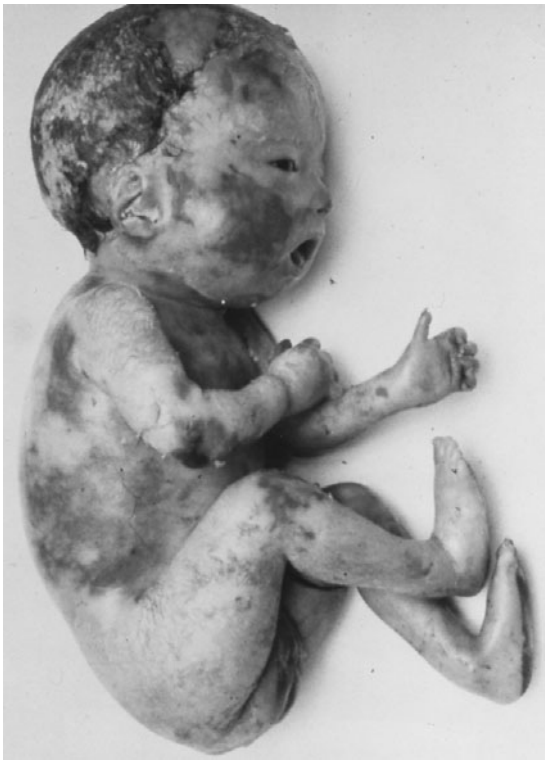

Fig. 13–142. *Restrictive dermopathy*. Note kyphosis and rocker-bottom feet.

Differential diagnosis includes sclerema neonatorum, scleredema, scleroderma, subcutaneous fat necrosis, stiff skin syndrome, Parana hard skin syndrome, *epidermolysis bullosa* with pyloric atresia, *fetal akinesia sequence*, and *Neu-Laxova syndrome*.

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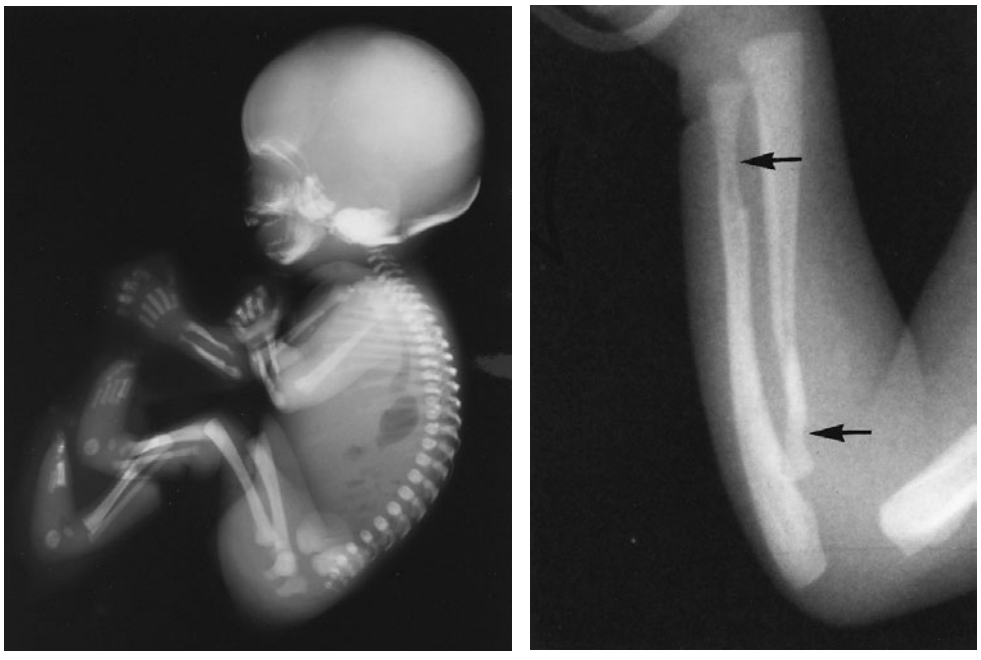

A B

Fig. 13–143. *Restrictive dermopathy*. (A) Note wide fontanels and sutures, modeling defects of radii and ulane. (B) Note bony defects in distal ulna and proximal radius. (B courtesy of HV Toriello, Grand Rapids, Michigan.)

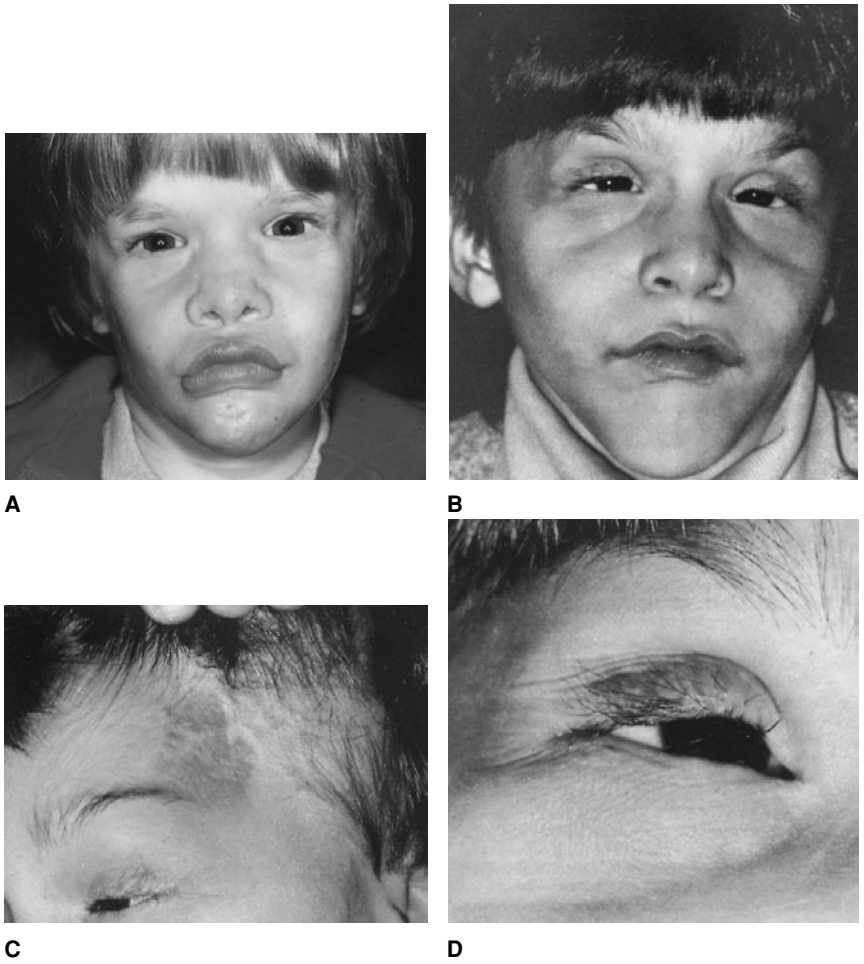

Fig. 13–144. *Setleis syndrome*. (A) Note coarse facies, thick nasal tip, fleshy vermilion, ample chin. (B) Compare with patient seen in (A). Note arched eyebrows. (C) Temporal "forceps marks." (D) Double row of upper eyelashes. (A from RD Clark et al, Am J Med Genet 34:354, 1989. B–D from DR Frederick, RM Robb, J Pediatr Ophthalmol Strabismus 29:127, 1992.)

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Setleis syndrome

Setleis syndrome is characterized by bitemporal scarring that resembles forceps marks, periorbital puffiness with wrinkling of facial skin, abnormalities of eyebrows and lashes, flat nasal bridge with bulbous nasal tip, and increased mobility of facial skin associated with severe redundancy of soft tissues (12,16,18). Nearly all patients have been from isolated towns in Puerto Rico. A few others have been of Basque, German, Italian, Japanese, and Arabic origin (1,2,4,5,13,14,20). Two sets of affected sibs and consanguinity indicate autosomal recessive inheritance (12). In 1992, Kowalski and Fenske (10) described two new patients and suggested that Setleis syndrome be classified as FFDD III (focal facial dermal dysplasia with additional features). They called FFDD II the autosomal recessive form of FFDD without additional features and referred to the autosomal dominant form as FFDD type I or Brauer syndrome. There has been some suggestion that the gene maps to 1p36.21 to 1p36.13 (19).

Craniofacial features. Features include "forceps marks" scarring bitemporally (rarely unitemporally), periorbital puffiness, eyebrows that angle sharply upward and outward but are deficient laterally, distichiasis of upper lids and astichiasis of lower lids (Fig. 13–144), flat nasal bridge, bulbous nasal tip, nasal septum extending below alae nasi, redundant skin and soft tissues, alopecia, thin scalp hair, low frontal hairline, and, in some instances, downslanting palpebral fissures (50%), epicanthic folds, chronic blepharitis, thick lips and cleft chin (6,12,16–18). Tsukahara et al (19) presented a follow-up on a previously reported patient and reported previously undescribed additional manifestations as an aberrant hair pattern and linear skin lesions on the forehead, short palpebral fissures, cone-shaped teeth, and pectus carinatum.

Other findings. Hypo- and hyperpigmentation of the skin have been recorded in 65% (7). Abnormal palmar creases have also been noted in 35% (12).

Differential diagnosis. A disorder known as focal facial dermal dysplasia has been documented with autosomal dominant inheritance (3,8,11,15). Real forceps marks, of course, are not accompanied by other features of Setleis syndrome. Ward and Moss (21) suggested that Setleis syndrome (FFDD III) and Brauer syndrome (FFDD I) are a single disorder. A similar opinion was also expressed by Kaplan et al (9). We agree.

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Goeminne syndrome

Goeminne (1) described a family in which males had congenitally progressive muscular torticollis with facial asymmetry, multiple spontaneous keloids that appeared at puberty, cryptorchidism, chronic progressive pyelonephritis with hypertension, varicose veins of the legs, and multiple pigmented cutaneous nevi (Fig. 13–145). Female carriers were less severely affected. The literature on the familial occurrence of each component was extremely well reviewed by Goeminne (1). The gene has been mapped at Xq28, distal to the G6PD locus. It probably represents the most distal gene on the X chromosome (3). Sands (2) reported minor stigmata in a female with translocation involving this area of the X chromosome.

Fig. 13–145. *Goeminne syndrome*. Facial asymmetry, torticollis, numerous keloids of arms and thorax. (From L Goeminne, Acta Genet Med Gemellol (Roma) 17:439, 1968.)

References (Goeminne syndrome)

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Tongue atrophy, linear skin atrophy, scarring alopecia, and anonychia

The syndrome was independently described by Sequeiros and Sack (2) and Cohen et al (1) in 1985. The patients were isolated examples, the first being one of monozygous twins. All three were premature. Hence, it can be assumed that the condition is not a single gene disorder but may result from some form of intrauterine injury.

The condition is characterized by skin atrophy with linear alternation of depressed scarlike areas and intervening ridges of essentially normal skin. At birth the involved skin areas are friable, with a vesiculobullous eruption followed by gradual scabbing. Symmetrical reticulated scarring involves at least 75% of cutaneous surfaces. Scars on the trunk and head are cobblestonelike and, in some areas, are oriented along skin cleavage lines. On the limbs, the reticulated pattern follows the long axes of the extremities. The palms, soles, and face are not involved. Scarring alopecia and congenital absence of one or more toenails are evident. Abnormal sweating, heat intolerance, and febrile convulsions were seen in all three patients. A scarlike lesion of the dorsum of the tongue was found in two of the three (Fig. 13–146).

Histologically, all showed thickening of the dermis, increase in collagen density, or decrease in elastic fibers. The skin lesions look somewhat like those of *Bazex syndrome*.

References (Tongue atrophy, linear skin atrophy, scarring alopecia, and anonychia)

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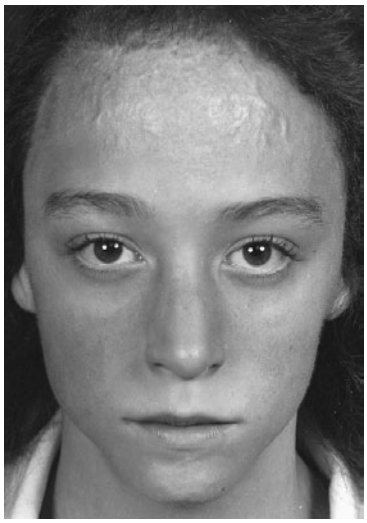
Keratitis-ichthyosis-deafness syndrome (KID syndrome)

Burns (6), in 1915, reported a syndrome characterized by congenital atypical ichthyosiform erythrokeratoderma, palmoplantar keratosis, and sensorineural hearing loss. At least 30 cases have been reported. Some have been well documented (1–3,5,8,9,15,18,19,22,24,26,32,33,38, 39,42,45,47–49) and others less well (6,11,16,20,28,35,46). Nearly all have been isolated, but examples have been noted in two generations (31). There is no sex predilection. Skinner et al (45) suggested the term KID syndrome as an acronym to refer to *K*eratitis, *I*chthyosis and *D*eafness.

Caceres-Rios et al (7) reviewed sixty-one patients from the literature. All had cutaneous and auditory abnormalities, and 95% also had ophthalmologic defects. The frequencies of clinical features were as follows: neurosensory deafness in 90%, erythrokeratoderma in 89%, vascularizing keratitis in 79%, alopecia in 79%, and reticulated hyperkeratosis of the palms and soles in 41%. Caceres-Rios et al (7) considered that the KID acronym does not accurately define this condition, since the disorder is



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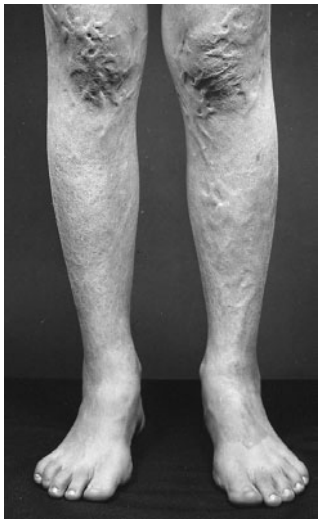

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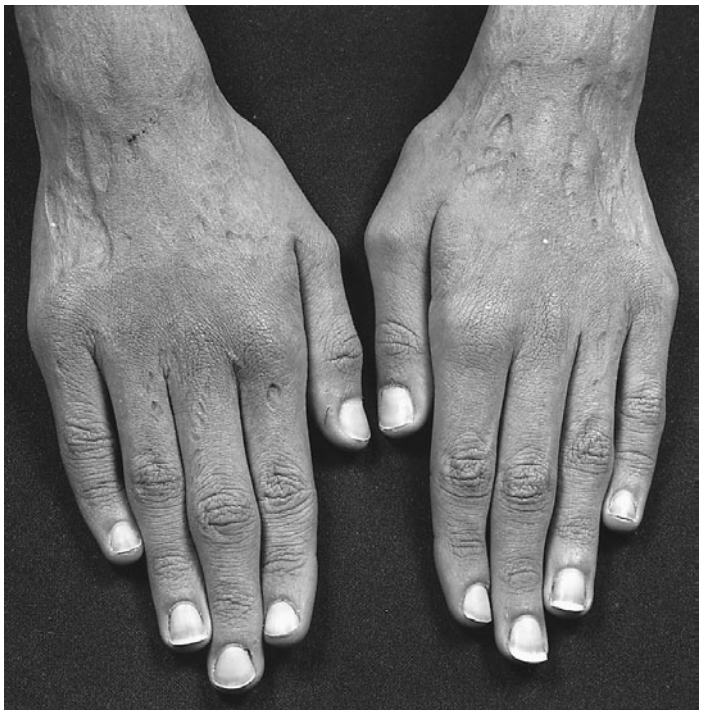

B

Fig. 13–146. *Tongue atrophy, linear skin atrophy, scarring alopecia, and anonychia*. (A) Note sparcity of hair and skin lesions over scalp and forehead. (B) Linear/reticular array of shiny, wrinkled, and pitted skin of forearm and dorsa of hands. (C) Similar lesions of lower legs. (A–C from J Sequeiros and GH Sack Jr, Am J Med Genet 21:669, 1985.)

not an ichthyosis (scaling is not the main cutaneous feature) and keratitis is not present in all patients early in the course of the disorder.

Extensive cutaneous mycoses have been described in these patients (17,43).

Postnatal growth deficiency has been evident in about 50% of the cases.

Skin. Congenital erythrokeratoderma principally involves the cheeks, nose, chin, ears, and limbs, especially the extensor and flexor surfaces of the elbows and joint areas of the knees, hands, and feet, and on the buttocks. Eyebrows, lashes, and scalp hair are scant. In some cases, scalp involvement results in partial or complete alopecia (Fig. 13–147A–C). The nails are frequently thickened and dystrophic. There is palmar and plantar hyperkeratosis characterized by a stippled or dotted pattern (26,40) (Fig. 13–147D). Microscopically, the skin changes most clearly resemble lamellar ichthyosis, the keratin layer having a basket weave pattern. A prominent granular layer is present. Recurrent bacterial and mycotic (especially candidal) infections of the skin are found in 40%. Cutaneous squamous cell carcinoma has been noted (13,25,42).

Ears. Hearing loss, found in nearly all patients, is sensorineural, usually bilateral, congenital, and often severe. The patient of Cram et al (8) had only mild hearing loss while one patient (28) had more severe conductive deafness.

Eyes. Severe bilateral vascularized keratitis, preceded by photophobia, appears in early childhood and not uncommonly is complicated by corneal ulceration, which leads eventually to at least partial blindness (Fig. 13–147E).

Nervous system. Intelligence is normal. Reflexes appear to be decreased, and often there are motor disturbances, especially fine motor. Tight heel cords, pes cavus, and contractures of the knees and elbows are seen in about half the patients (8,32,34,41,44). Wilson et al (50) presented evidence for a recessive form associated with progressive cirrhosis and mental retardation. Cerebellar hypoplasia has been documented (18,19).

Oral manifestations. Occasionally the oral mucosa is the site of generalized or linear leukokeratosis or, occasionally, furrowing. Squamous cell carcinoma of the tongue (1,22) and oral leukoplakia (13,26) have been reported. Perhaps proclivity to oral cancer reflects a complication of mucocutaneous candidosis (27).

Inheritance and genetics. Both dominant and recessive forms have been described (10,13,42,50). Langer et al (23) suggested spontaneous new mutation as the basis of the disorder. Kone-Paut et al (21) reported KID syndrome in two half siblings born to the same unaffected mother.

Differential diagnosis. Cases with overlap, but far less certain diagnosis, are those of Ruzicka et al (37) in which the patient had brachydactyly, clinodactyly, accessory cervical ribs, and carcinoma of the thyroid.

The patient with ichthyosis vulgaris, sensorineural hearing loss, pili torti, and tooth anomalies reported by Braun-Falco and Landthaler (4) must represent another entity. It may well be that the deafness is fortuitous. A syndrome of severe ichthyosis hystrix and sensorineural hearing loss reported by Gülzow and Anton-Lamprecht (14) may be related to the disorder reported by Morris et al (29) and Myers et al (30). Possibly, the patient reported by Freire-Maia et al (12) also belongs in this category. There is some overlap with *endocrine candidosis*.

The kindred described by Desmons et al (10) must have a different condition. They reported three sibs with congenital ichthyosiform erythrokeratoderma and profound congenital sensorineural hearing loss, but all had hepatomegaly. Autosomal recessive inheritance is likely in the kindred of Desmons et al (10).

Laboratory findings. Hyperimmunoglobulin E has been found by a few investigators (15,34). Absence of lymphocyte stimulation by Candida has been described (5,15).

References [Keratitis-ichthyosis-deafness syndrome (KID syndrome)]

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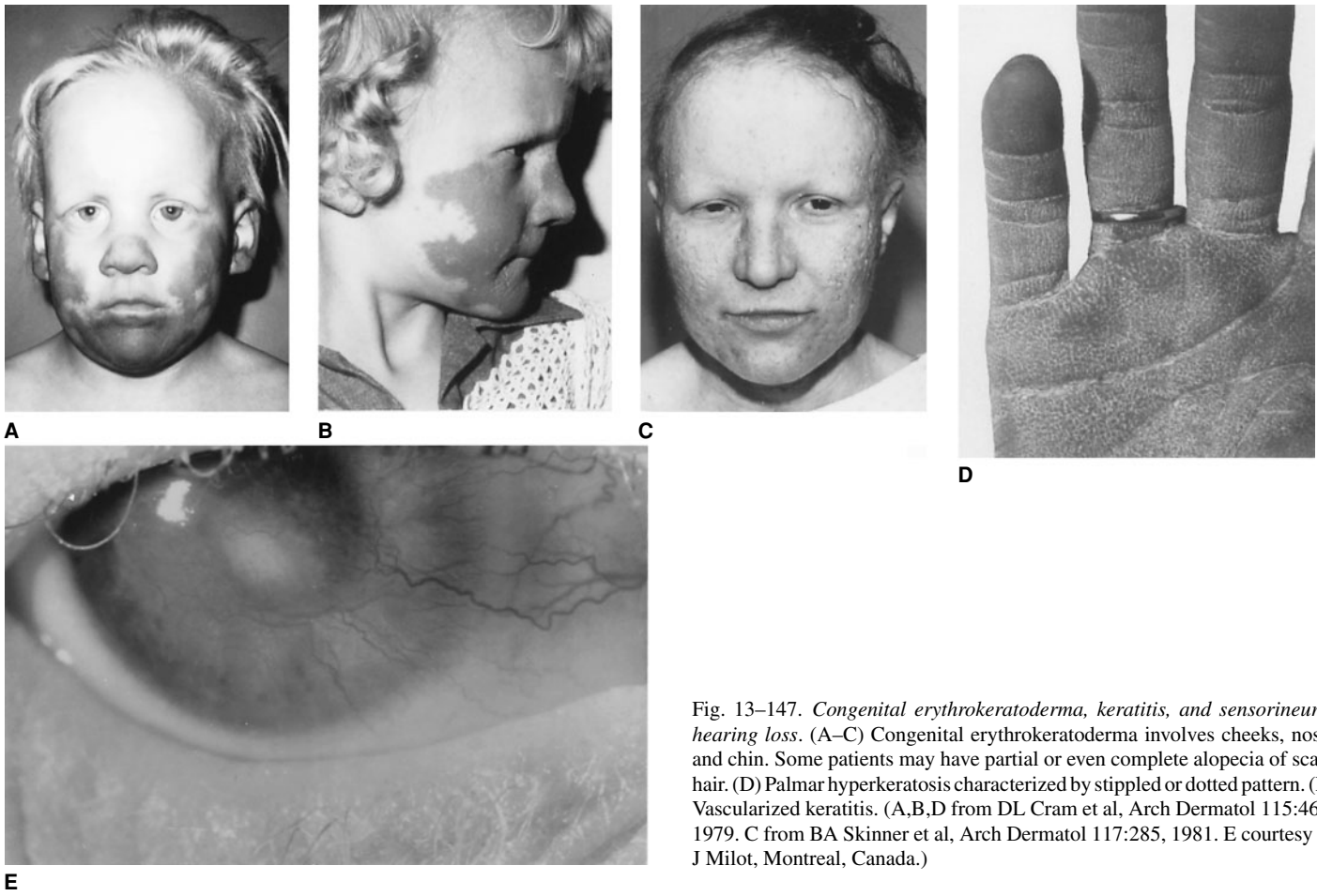

Fig. 13–147. *Congenital erythrokeratoderma, keratitis, and sensorineural hearing loss*. (A–C) Congenital erythrokeratoderma involves cheeks, nose, and chin. Some patients may have partial or even complete alopecia of scalp hair. (D) Palmar hyperkeratosis characterized by stippled or dotted pattern. (E) Vascularized keratitis. (A,B,D from DL Cram et al, Arch Dermatol 115:465, 1979. C from BA Skinner et al, Arch Dermatol 117:285, 1981. E courtesy of J Milot, Montreal, Canada.)

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Acrodermatitis enteropathica

This condition was first described in 1943 by Danbolt and Closs (1). It is characterized by cutaneous lesions of irregular plaques of vesicles and bullae, on an erythematous base. There may be satellite vesicles, bullae and pustules on the skin around the plaques. Typically, the lesions are at the mucocutaneous orifices and on the distal parts of the extremities (mouth, eyelids, knees, nails, anogenital areas) (Figs. 13–148 and 13–149). The nails usually have paronychia and dystrophic changes. Hair loss occurs early in the disease and involves the eyebrows, eyelashes, and scalp, resulting in alopecia totalis. Intractable diarrhea accompanies the skin changes (1,2,4). The inheritance is autosomal recessive.

Histologic examination of a bullous lesion shows acanthosis with large intraepidermal vesicles containing single and clumped acantholytic cells, neutrophils, and eosinophils (5).

Moynahan (6), in 1974, reported successful treatment with the oral administration of zinc sulfate. Since then, other reports (2,7) have confirmed the excellent results of continuous zinc sulfate therapy with resolution of the skin lesions, regrowth of hair, and arrest of the diarrhea.

Although the basic pathophysiology of the disease is still unclear, there is sufficient evidence to suspect that the defect is in zinc metabolism or absorption. In 1976, Evans and Johnson (3) suggested the absence of a low-molecular-weight zinc-binding factor as the possible cause of deficient zinc absorption. This factor is produced by the pancreas, binds dietary zinc, and transports it into the epithelial cells.

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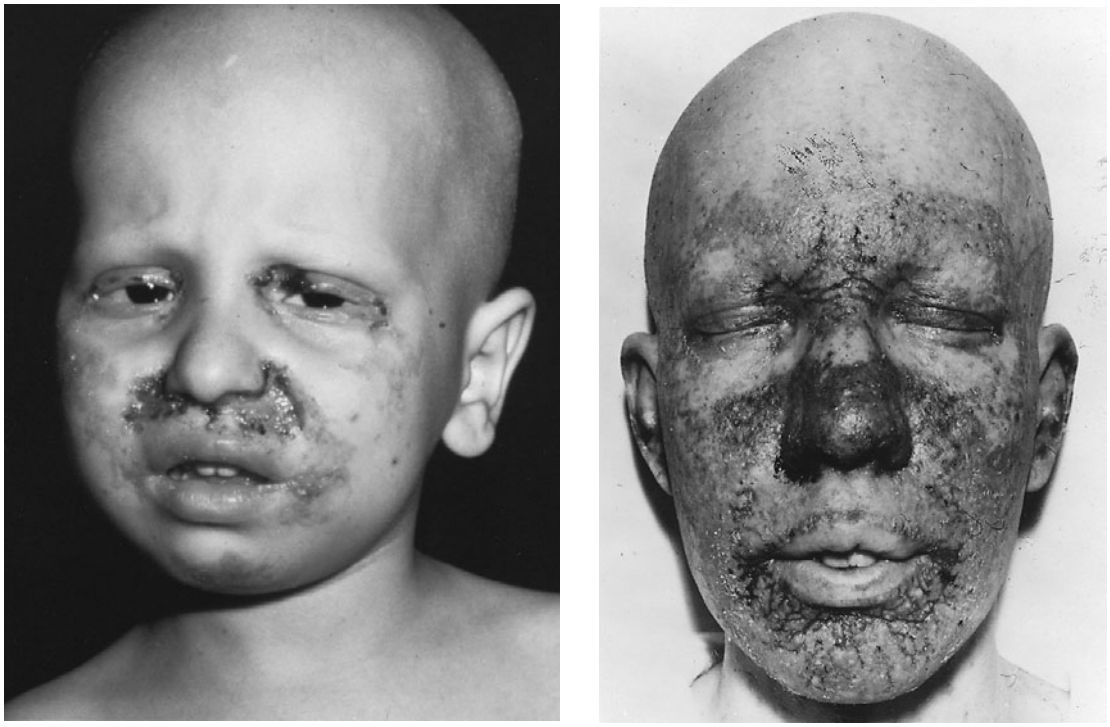
Fig. 13–148. *Acrodermatitis enteropathica*. (A) Note alopecia totalis and lesion in the paranasal and perioral region. (B) Older patient.



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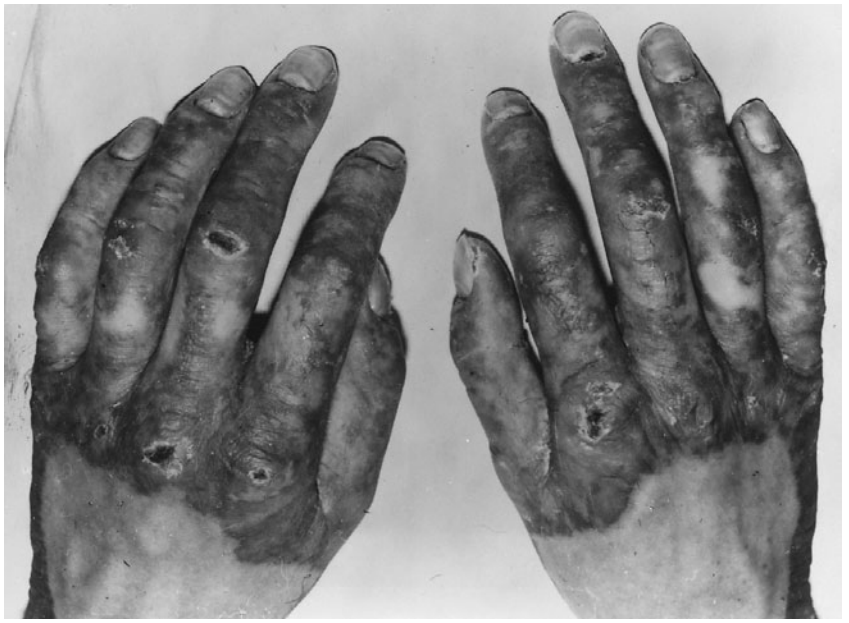

Fig. 13–149. *Acrodermatitis enteropathica*. Involvement of hands.

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Atrichia, somatic and mental retardation, and skeletal anomalies

Schinzel (9) described a female patient with severe somatic and mental retardation, almost complete absence of body hair, ichthyosiform hyperkeratosis of the skin of the lower legs, nail dysplasia, small hands and feet with short fifth fingers and toes, and complete cutaneous syndactyly of toes 4 and 5 (Figs. 13–150 and 13–151).

Radiographic studies revealed fusion of several vertebral bodies, humeroradial ankylosis, fusion between talus and navicular, lunate and triquetral, proximal metacarpals 4 and 5, and hip dislocation (Fig. 13–152).

Pfeiffer and Volklein (6) and Mosavy (5) reported sibs with absence of body hair, short stature, microcephaly, and mental retardation. Del Castillo et al (2) described sibs with atrichia, mental retardation, and papular lesions (follicular cysts) of the skin. Similarly affected sibs were documented by Damste and Prakken (1) and Lowenthal and Praaken (4).

Atrichia, mental retardation, seizures, and hypergonadotrophic hypogonadism were reported in sibs by Richieri-Costa and Frota-Pessoa (8), Wessel et al (10), Pridmore et al (7), and Devriendt et al (3).

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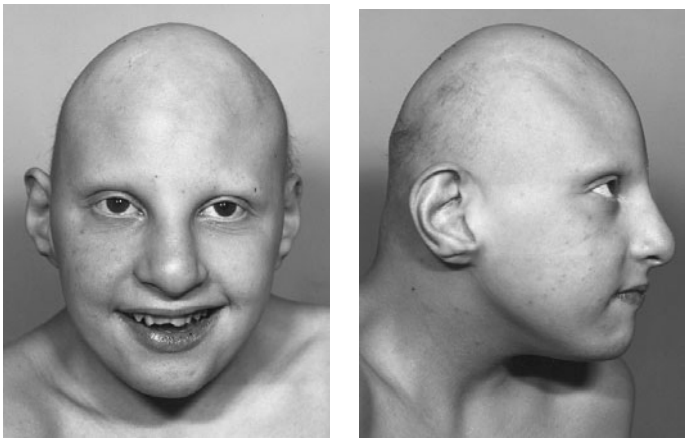
Barraquer-Simons partial lipodystrophy syndrome

The Barraquer-Simons lipodystrophy syndrome is a subtype of the partial lipodystrophies, the so-called cephalothoracic type (2,3,11). The patients gradually lose their subcutaneous fat in clearly demarcated, generally symmetric areas of the body over several years. Usually the face is affected first, with loss of retroorbital and periorbital tissue, resulting in the sinking of the eyes deeply into the sockets (Fig. 13–153). The buccal fat pads disappear. Loss of fat spreads caudally and stops mostly above or at

Fig. 13–150. *Atrichia, somatic and mental retardation, and skeletal anomalies*. (A,B) Microbrachycephaly, baldness, absence of eyebrows and lashes, large prominent nose, short philtrum, relatively large dysmorphic pinnae. (From A Schinzel, Helv Paediatr Acta 35:243, 1980.)



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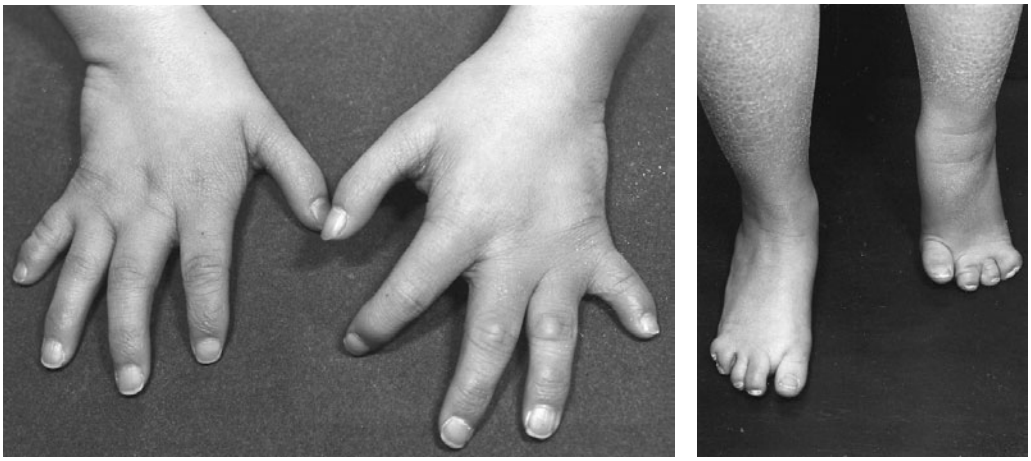

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Fig. 13–151. *Atrichia, somatic and mental retardation, and skeletal anomalies*. (A) Short index and little fingers. (B) Hyperkeratosis, left hammertoe, wide space between hallux and rest of toes, 4–5 cutaneous syndactyly. (From A Schinzel, Helv Paediatr Acta 35:243, 1980.)

the middle of the thighs. This results in a relatively obese appearance of the unaffected parts of the body. Patients develop a progeroid appearance (5,10). Onset is usually prepubertal.

The histological examination of the lipodystrophic skin shows not only an absence of fatty tissue, but also abnormalities of the dermo-epidermal junction with hyaline bodies. Leukocytoclastic vasculitis of the dermal vessels has been noted (8).

In addition to the loss of fat and the clinical manifestations affecting the skin, abnormalities of other systems, in particular the renal and nervous systems, have been described (4,6,7,11). In a review of 25 patients (11), 14 had renal disorders and 10 had abnormalities of the central nervous system. Seven were mentally retarded, 1 had epilepsy, 2 showed an abnormal pneumoencephalogram, and 2 other cases had nerve deafness.

The disorder is rare and of unknown cause. Approximately 80% are females. While most cases were sporadic (1) and, in fact, discordant in identical twins, similarly affected relatives were reported in the families of four patients, suggesting autosomal dominant inheritance (9,11). Lipoatrophy of the face resembles the appearance in a variety of disorders such as *Cockayne syndrome, SHORT syndrome*, and *Berardinelli-Seip syndrome*.

There is decreased serum complement C3 being diminished in 70%. Decreased synthesis and increased catabolism have been alleged. The presence of C3 nephritic factor, an immunoglobulin that activates complement, has been found (4,12).

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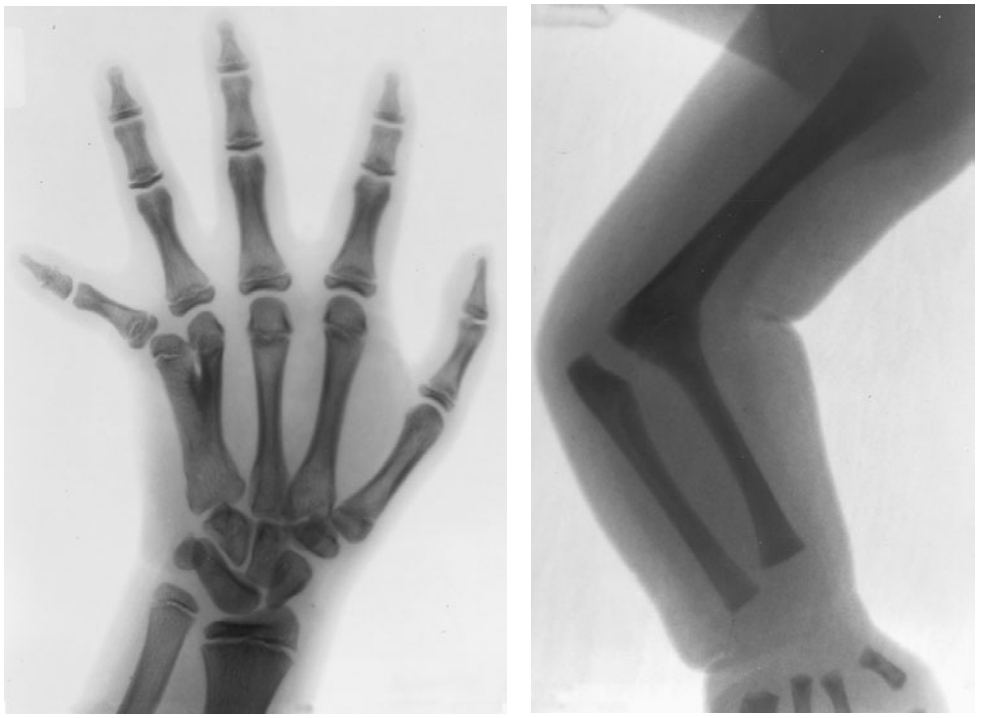

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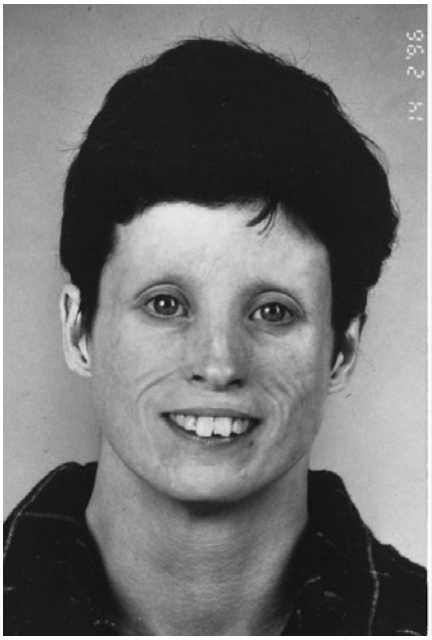
Fig. 13–152. *Atrichia, somatic and mental retardation, and skeletal anomalies*. (A) Lunatetriquetral fusion, proximal Y-shaped synostosis of metacarpals 4–5, short middle phalanges, especially of fingers 2 and 5. (B) Radiohumeral synostosis. (From A Schinzel, Helv Paediatr Acta 35:243, 1980.)



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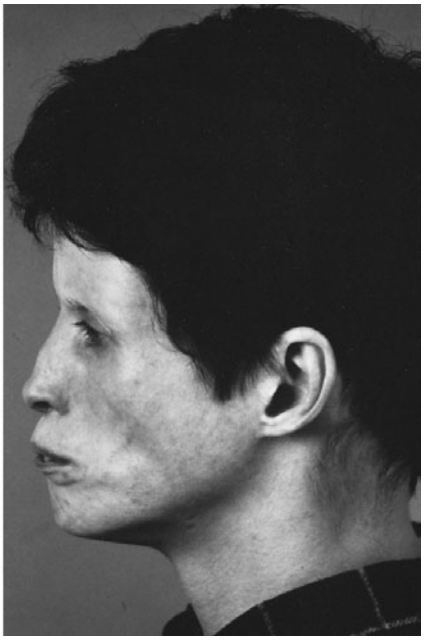

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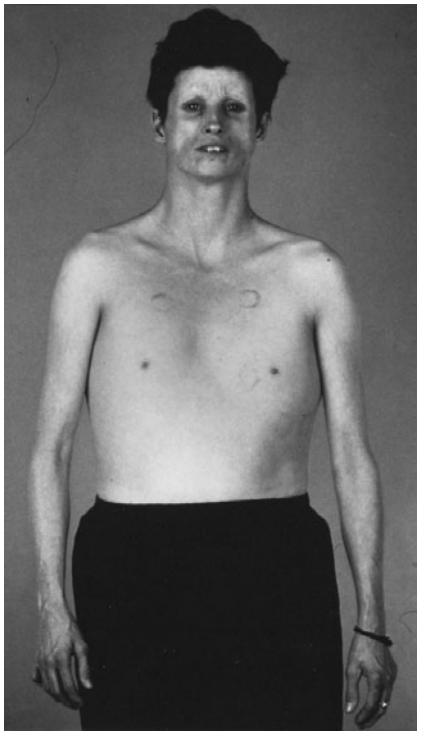

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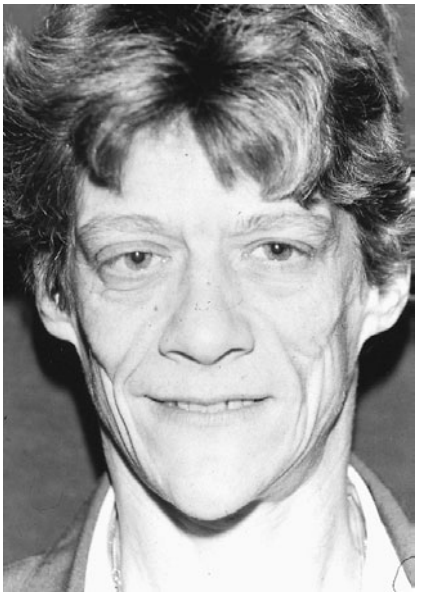

D

Fig. 13–153. *Barraquer-Simons syndrome*. (A,B) Face of 27-year-old. Note hollowed cheeks and deeply sunken eyes. (C) Note diminished fat of the upper body, including breasts. (D) Compare facies with patient seen in A–C. (A courtesy of S Spranger. B,C from S Spranger et al, Am J Med Genet 71:397, 1997. C from PJ Guelinckx and NK Sinsel, Plast Reconstr Surg 105:1730, 2000.)

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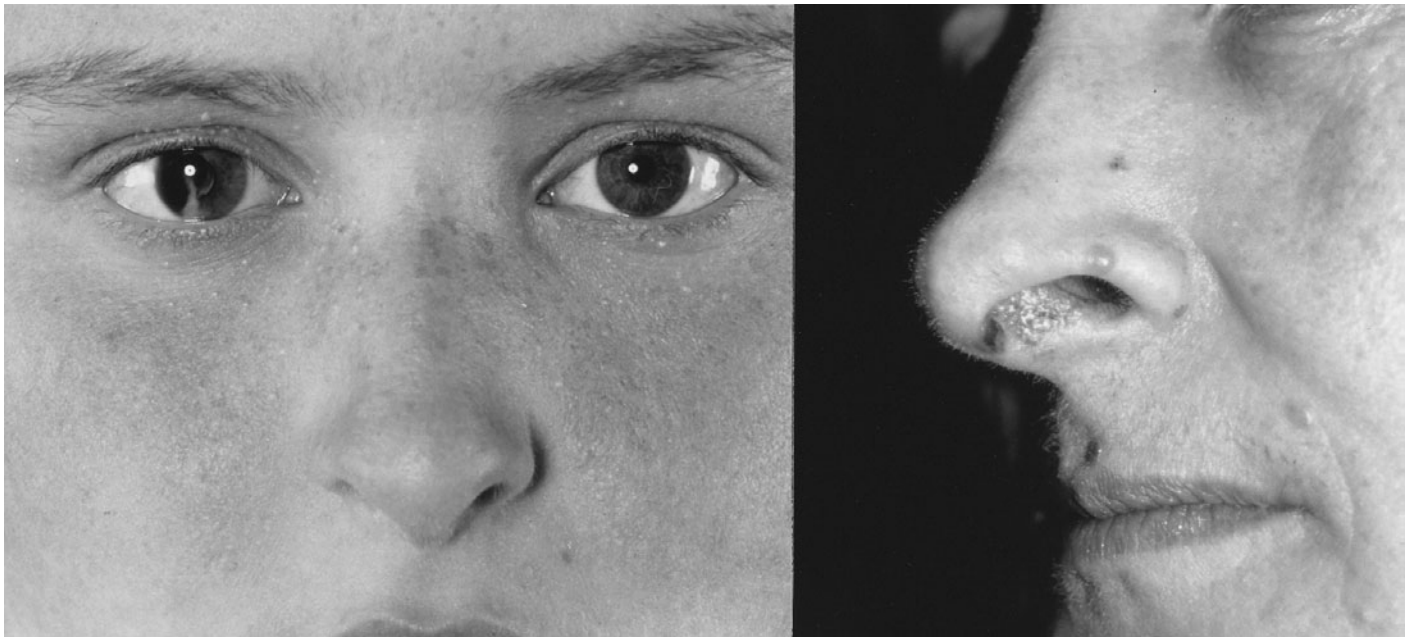

A B

Fig. 13–154. *Bazex-Dupré-Christol syndrome*. (A) Periorbital milia and characteristic nose (appearance of right eye is the result of injury. (B) Multiple basal cell carcinomas and prominent columella. (From A Kidd et al, J Med Genet 33:493, 1996.)

Bazex-Dupré-Christol syndrome

In 1964 and 1966, Bazex et al (1,2) described a complex genodermatosis with hypotrichosis and a generalized state of "atrophoderma." Patients develop basal cell carcinomas on the face between the ages of 15 and 25 years. "Pinched" nose with hypoplastic alae and a prominent columella may be another characteristic manifestation of the disorder (Fig. 13–154). Affected persons have lesions resembling "multiple ice-pick marks" on the dorsa of hands and elbows dating from early infancy (Fig. 13–155). These lesions are fairly specific to this syndrome because they are seen in only one other inherited condition, X-linked dominant chondrodysplasia punctata. However, the term "atrophoderma" is not appropriate, since histologic studies do not show atrophy (8).

On scanning electron microscopy, hairs have a twisted and flattened or smooth appearance (3) (Fig. 13–156).

Several reports of pedigrees describing the condition in many generations are suggestive of X-linked dominant inheritance (3–7,9–12).

Using microsatellite markers of the X chromosome in three families with Bazex-Dupré-Christol syndrome, Vabres et al (11) found evidence for assignment of the gene to the Xq24–q27 region.

Diagnosis of this syndrome is sometimes difficult. Multiple basal cell carcinomas also occur in *nevoid basal cell carcinoma syndrome*. However, pits of the palms and soles, as well as skeletal anomalies, are absent in the Bazex-Dupré-Christol syndrome.

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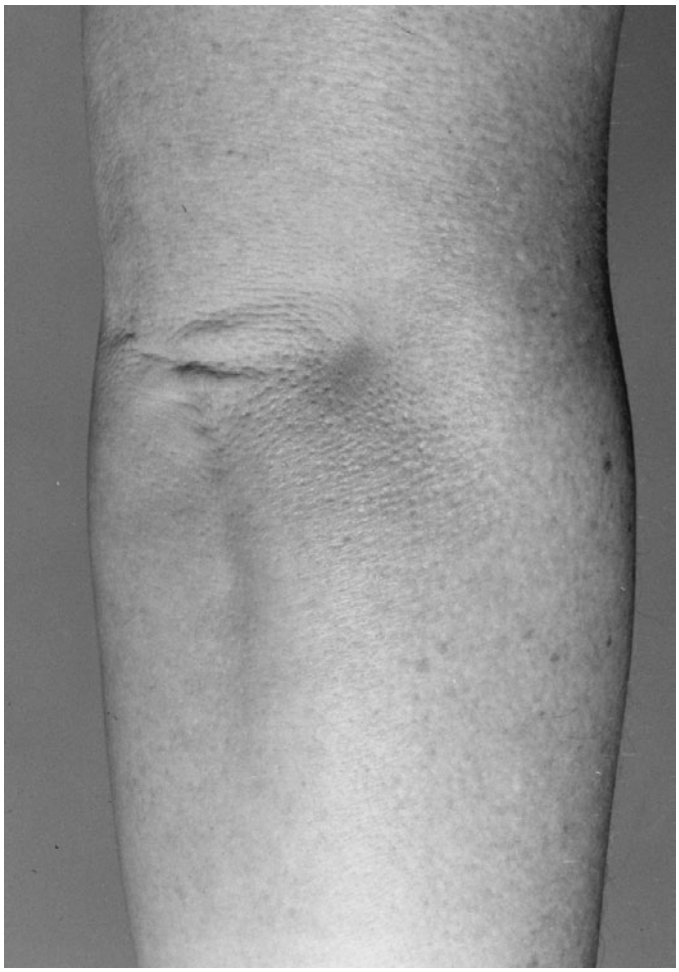
Costello syndrome

Costello, in 1971 (7) and in 1977 (8), reported two unrelated children with mental retardation, short stature, curly hair, coarse facies, loose skin of the hands and feet, and nasal papillomata. These papers were essentially unrecognized until 1991, when Der Kaloustian et al (12) and Martin and Jones (29) reported additional patients and named the condition Costello syndrome. Since then, around 40 cases have been described (2,3,6–10,13–19,21,24,28,32,35–38,40,44,46–53). A debate still rages whether the facio-cutaneous-skeletal (FCS) syndrome is the same as Costello syndrome (3,4,11,12,29,35,45,53). Although affected sibs were reported (2,22,53), all other examples have been isolated (3,6–10,13–19,21,24,28,32,35,37,40,46–52). Consanguinity was found by Borochowitz (3) and Franceschini et al (16). We agree with Lurie (27), that Costello syndrome appears to have sporadic autosomal dominant mutations, the sib pairs representing gonadal mosaicism. Advanced paternal age has been demonstrated (22,27). A chromosomal translocation [46,XX,t(1;22)(q25;q11)] associated with this condition has been reported (10). Cultured fibroblasts from Costello syndrome patients do not assemble elastic fibers, a fundamental deficiency of elastin-binding protein (20a).



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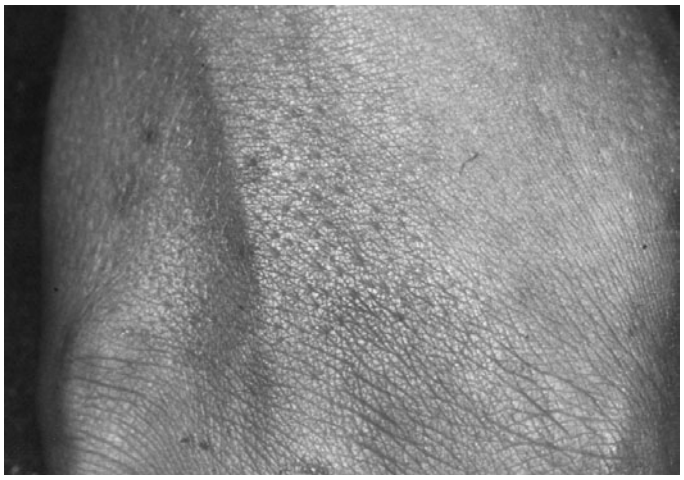
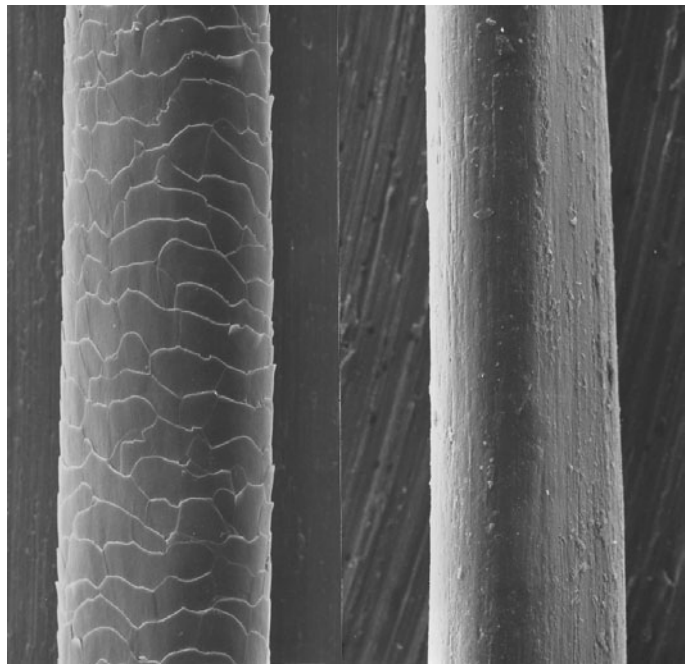


B

Fig. 13–155. *Bazex-Dupré-Christol syndrome*. (A,B) Note patch of follicular atrophoderma (ice pick marks) over lateral elbow. (From A Kidd et al, J Med Genet 33:493, 1996.)

Polyhydramnios is noted in 50% (18,22). Almost 90% are large for dates. Poor suck and poor growth postnatally are noted in 100% (24,28,46,48). Delivery by C-section is frequent.

Facies. There is relative macrocephaly in 100% with a somewhat hirsute forehead (Fig. 13–157). The hair is curly in 75% and the eyebrows are thick in 75%. The pinnae are usually low-set (65%) and posteriorly angulated, with large lobes in 45%. Depressed nasal bridge (75%), bulbous nose, epicanthic folds, thick lips (80%), and strabismus (65%) are common and combine to give a coarse facies in 100%. The mouth appears wide in 90%. The tongue is large in 80%. Papillomata appear progressively from 2 to 15 years in the nostrils, on the face, and around the mouth (17) and are usually not present in the newborn (52). The voice may be hoarse in some cases due to papillomata of the vocal cords (40,47,53). The neck appears short in at least 60%. Fryns et al noted blue sclerae (17) (Fig. 13–157A).



A B

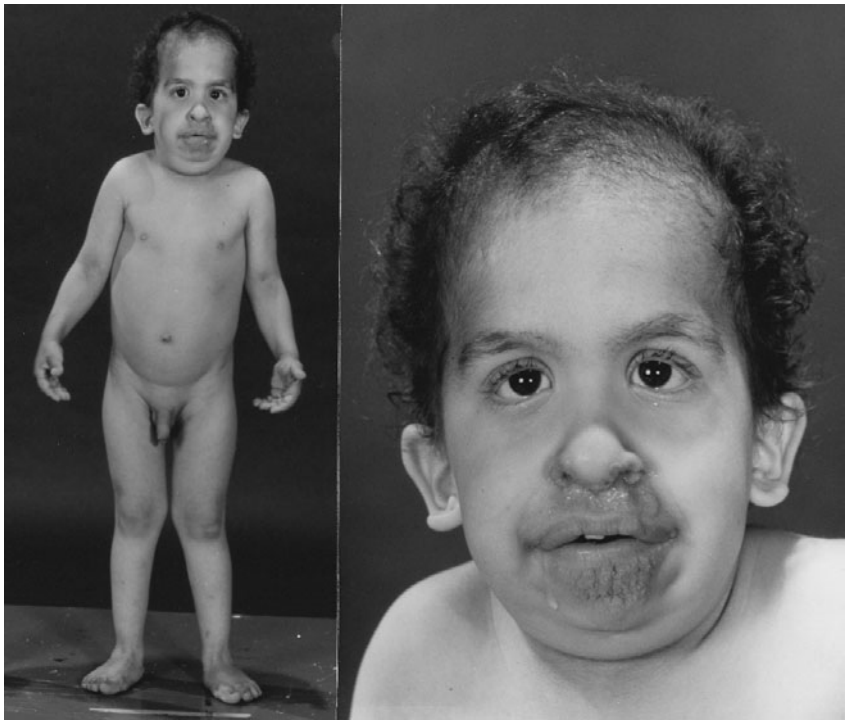
Fig. 13–156. *Bazex-Dupré-Christol syndrome*. (A,B) Scanning electron micrograph of (A) normal hair and (B) hair from a patient showing complete absence of cuticular scales. (From A Kidd et al, J Med Genet 33:493, 1996.)

Skin and appendages. The skin, especially of the neck, hands, and feet, is thickened, loose, and velvety in feel in 100% (Fig. 13–158). The skin color is darker than normal in 20% and acanthosis nigricans is seen in about 30% (12,14,16,22,29,32,46,47). Deep creases become evident on the palms and soles in at least 60%. Pigmented nevi may present on the soles (45). Mori et al (30) described elastic fiber degeneration. The skin over the digital pulps is loose, like that of one whose hands have been in water overly long, in 100% of the patients. With age, palmar and plantar hyperkeratoses are noted. The nails are thin, deeply set (25), and hyperconvex in 40% (28). The nails are dysplastic in 60%.

Papillomata are found, with age, not only in the nose but over the joints, extremities, periorally, or perianally (13). Pigmented nevi appear to be increased (11).

Intelligence. IQs have ranged from 50 to 80. Most patients have a pleasant, happy outgoing nature (28,46).

Musculoskeletal. Increased A-P diameter of chest (55%), tight Achilles tendons (55%), inguinal hernias (60%), and hyperextensible metacarpophalangeal and interphalangeal joints (80%) with ulnar deviation, wide phalanges, talipes, increased carrying angle with decreased range of motion at the elbow (9), kyphoscoliosis, large or late-closing anterior fontanel (35%), and osteoporotic long bones have been found. Bone age is delayed.



A B

Fig. 13–157. *Costello syndrome*. (A) General view of the body. (B) Note coarse appearance of face and perioral papillomata. (From VM Der Kaloustian et al, Am J Med Genet 41:69, 1991.)

Cardiovascular. Hypertrophic cardiomyopathy (2,11,19,22,35,53), mitral value prolapse (28), VSD, ASD, and pulmonic stenosis have been described in over 50% (3,4). Arrhythmias such as atrial ectopic tachycardia, supraventricular tachycardia, and atrial fibrillation have been reported in about 60% (41,50).

Urogenital. Cryptorchidism has been noted in 10% (16).

Miscellaneous. Ganglioneuroblastoma, acoustic neuroma, epitheliomata, bladder carcinoma, and embryonal rhabdomyosarcoma have been found (2a,15,16,19a,23,29,30a,35,40a,53). Hypothyroidism, late puberty, and growth hormone deficiency have been documented.

Laboratory findings. Sialuria has been reported in two unrelated patients (14). C Anichini (personal communication, 1997) also found sialuria. Moreover, high IgM level was detected during the early infantile period of another patient (32).

In a Japanese patient who died of rhabdomyolysis at the age of 6 months, the major pathological findings were fine, disrupted, and loosely constructed elastic fibers in the skin, tongue, pharynx, larynx, and upper esophagus, but not in the bronchi, alveoli, aorta, or coronary arteries (30). The degeneration of elastic fibers was confirmed in a second patient with Costello syndrome. Expression of elastin mRNA in the patient's fibroblasts was normal. Since elastic fiber degeneration was observed, it is speculated that a defect in elastin microfibrils might be responsible for the pathogenesis of Costello syndrome (30). Loss of anastomosing points in elastic tissue has been demonstrated (50). Hyperplasia of collagen fibers in the skin, hyperplasia of the mucous glands in the bronchus, narrowing of the pulmonary artery, degeneration of the atrial conduction system, calcification and ballooning of skeletal muscle fibers with infiltration of macrophages, and myoglobin deposition in the collecting ducts of the kidney were also observed (30).

Differential diagnosis. Various congenital *cutis laxa syndromes, Noonan syndrome*, and *cardio-facio-cutaneous syndrome* share some findings (5,9,13,20,26,31,33,34,42,43), as do *Weaver syndrome* and *Donohue syndrome (leprechaunism). SCARF syndrome (skeletal abnormalities, cutis laxa, craniosynostosis, psychomotor retardation, and facial abnormalities)* (25) needs to be considered. All patients with cutis laxa–macrocephaly–short stature–delayed psychomotor development should also be investigated (1,39).

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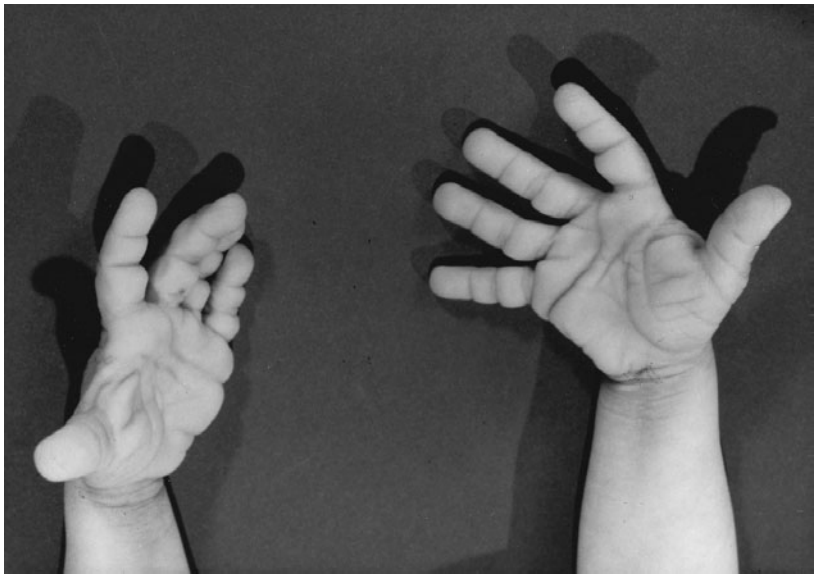

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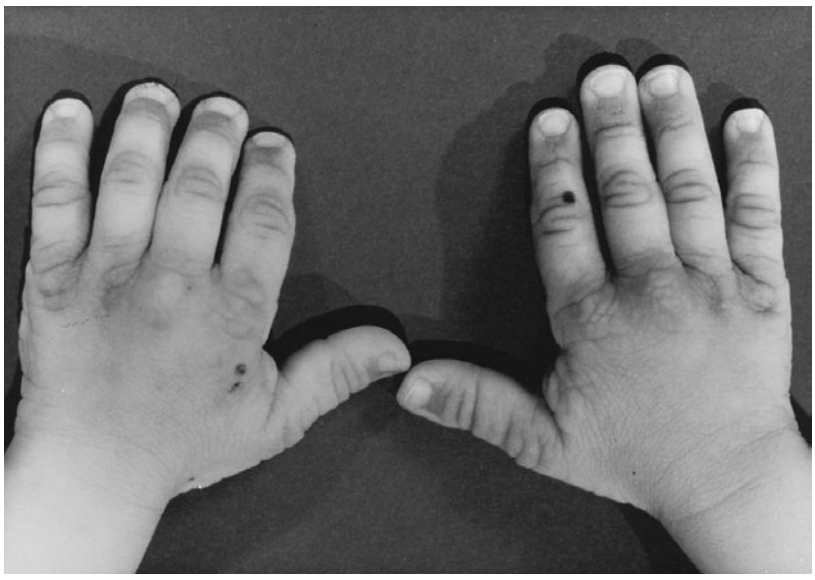

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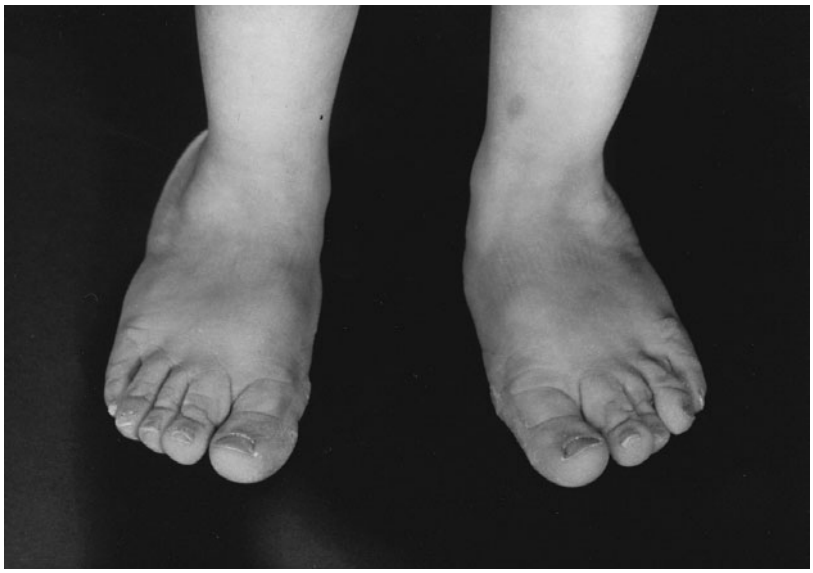

C

Fig. 13–158. *Costello syndrome*. (A) Note redundant, loose skin of palms. (B) Dorsal view of hands. (C) Redundant, loose skin of feet. (From VM Der Kaloustian et al, Am J Med Genet 41:69, 1991.)

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Macrocephaly, cutis marmorata telangiectatica congenita, and syndactyly (Van Lohuizen syndrome)

Although the term "cutis marmorata telangiectatica congenita" was coined by Van Lohuizen (32), the condition has been known by a plethora of names (12). In 1974, Way et al (34) reviewed 41 examples of congenital telangiectatic cutis marmorata and Pehr and Moroz (22), in 1993, described 126 affected. The former noted 50% to have associated anomalies, the latter 68%. Moore et al (18), in 1997, reporting 13 unrelated children, formally defined the syndrome of abnormalities of somatic growth, abnormal facies, abnormalities of the brain, and congenitally mottled skin. Clayton-Smith et al (3), in 1997, presented 9 affected children. Many additional examples have been described (1,2,4,5,7b,11–33). All cases have been sporadic (12).

The infants are large at birth, mean weight being +2 SD. However, with age, the weight and height centiles decrease, in some cases falling below the 3rd centile by age 4 years (29). Fetal hydrops has been noted in a few cases (3).

Craniofacial anomalies. Macrocephaly (+4 SD, at birth and increasing with age even with shunting), squared frontal bossing, increasing dolichocephaly, high forehead, deep-set eyes, full cheeks and facial and/or cranial asymmetry (including cerebral ventricles), and philtral/nasal/upper labial nevus flammeus are common features (3,25) (Fig. 13–159). Cleft palate has also been described (13).

Eyes. There have been reports of glaucoma, usually associated with nevus flammeus (15,22,24). Retinal detachment (23) has also been noted.

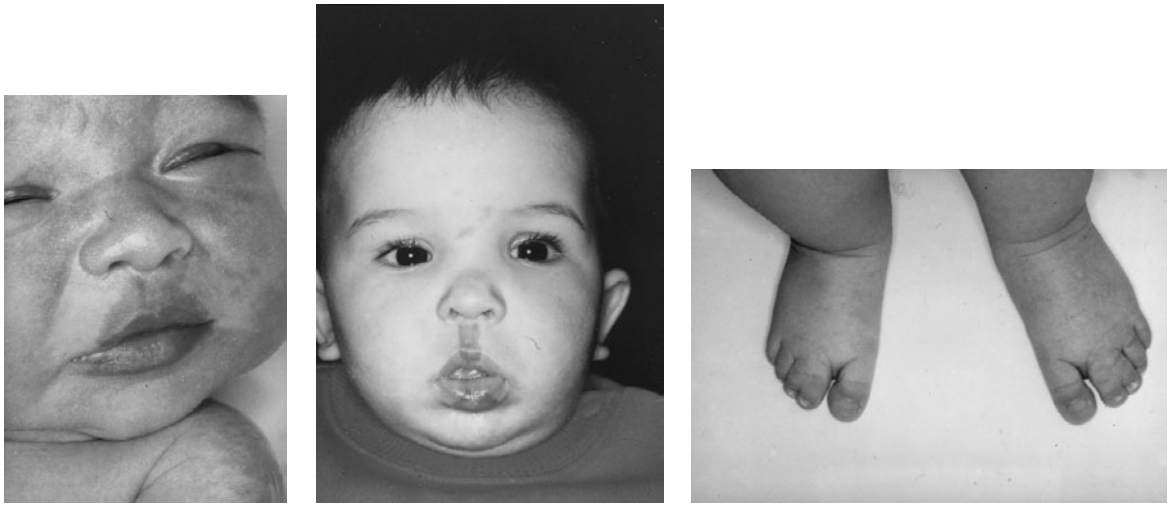
Skin. Congenitally mottled skin is due to prominent capillaries and veins. Intermixed are telangiectasias, capillary and cavernous hemangiomas, nevus flammeus, and varicose veins (4) (Fig. 13–160). It may, however, be absent (7a). Nevus flammeus of the nose and/or philtrum and upper lip is frequent (Fig. 13–159A,B). The cutis marmorata may fade with age, but it may persist (25). It is exaggerated with crying. Dilated veins of the head, neck, and trunk, even to the degree of venous aneurysms, are seen (25). After 1 year of age, capillary angiomas of the scalp may be noted.

The skin is loose, stretchable, and velvety to the feel. Less often, the joints are hyperextensible, and hernias are more common than normal. Doughy subcutaneous tissues are a constant feature. Aplasia cutis congenita associated with Adams-Oliver syndrome has also been described (7,30).

Extremities. The shoulder girdle is narrow due to poor musculature. An almost constant feature is mild body or limb asymmetry, especially of the lower limbs. Girth differences are more marked than differences of length (6,11)

Terminal transverse limb defects as part of Adams-Oliver syndrome, as noted above, have been reported in association with cutis marmorata telangiectatica congenita (7,30). Variable syndactyly of toes 2–4 is an almost constant feature (3,10) (Fig. 13–159C). Toes 1–2 are widely spaced. The fingers, less often than toes, may exhibit 3–4 syndactyly. Postaxial polydactyly has been noted in perhaps 30% (3).

Central nervous system. Congenital hypotonia (76%), which normally resolves within 12 months, megalencephaly, and hydrocephalus (85%) are described. Developmental delay has been noted in probably

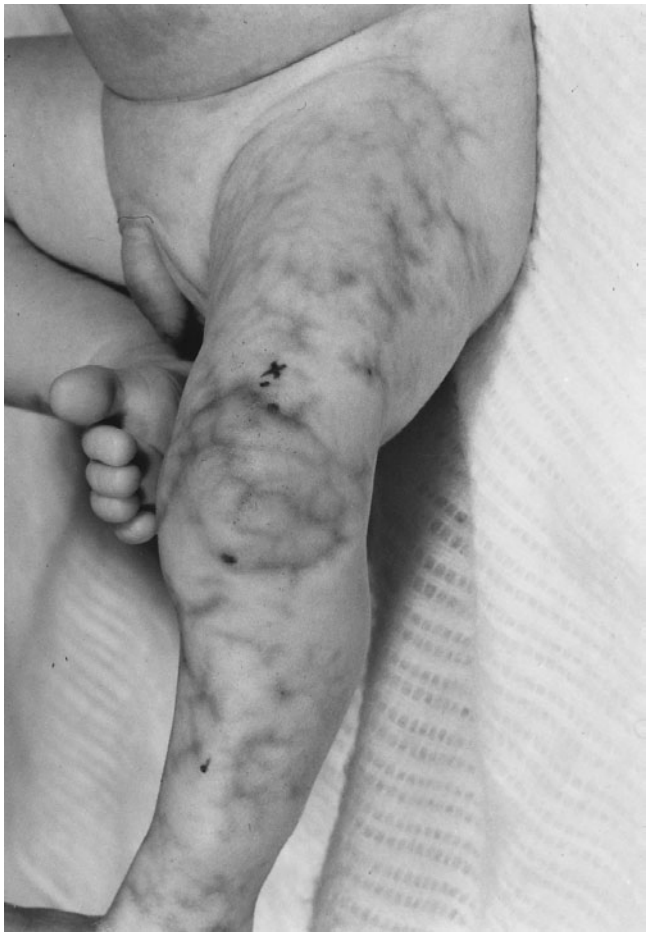


A B C

Fig. 13–159. *Macrocephaly, cutis marmorata, telangiectatica congenita, and syndactyly* (*Van Lohuizen syndrome*). (A,B) Note philtral superficial angioma. (C) Syndactyly 2–3 of toes. (From J Clayton-Smith et al, Clin Dysmorphol 6:291, 1997.)

90% (3,18,29,31). The megalencephaly is accompanied by MRI findings of CNS dysgenesis with protrusion of the cerebellar tonsils through the foramen magnum (Chiari I), lumbar syrinx, and hydrops of optic nerves (1a).

Fig. 13–160. *Macrocephaly, cutis marmorata, telangiectatica congenita, and syndactyly* (*Van Lohuizen syndrome*). Note severe cutis marmorata. (Courtesy of B Moroz, Montreal, Canada.)



Other findings. Vascular anomalies with hypoplasia of the right iliac and femoral veins (19), as well as double aortic arch (21) have also been described in this condition. One patient was reported with congenital hypothyroidism (22).

Diagnosis. One must exclude a plethora of macrocephalic conditions (8). Several patients with congenital hemihyperplasia clearly have the syndrome (26,27,33). Halal and Silver (10) reported a father and son with cutis marmorata telangiectatica congenita, joint hypermobility, and hemangiolipomas. Perhaps this was an example of *Ruvalcaba-Myhre-Smith syndrome*. *Klippel-Trenaunay-Weber syndrome* and *Sturge-Weber syndrome* must also be excluded. Excellent discussions of differential diagnosis are those of Cohen and Zalar (4) and Powell and Su (25). The patient reported by Meyer (17) merely has a variant of Van Lohuizen syndrome.

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Cutis verticis gyrata

Cutis verticis gyrata, described by McDowell (20) in 1893, is characterized by folds or furrows in the scalp that resemble the convolutions of the cerebrum (34). Unna (35) coined the term in 1907. There is no underlying skull defect. Associated findings include microcephaly, chronic seizures, mental retardation and spastic tetraplegia (9,26,28). The syndrome is seen in about 1 in 100,000 males and 2.6 in 10,000,000 females (2,3). In institutionalized males, the prevalence is about 0.2%–4% (2,32). Etiology is diverse (3) (vide infra). An excellent review of the early literature is that of Polan and Butterworth (29).

The folds may be present at birth (primary) or appear later in life (secondary) (Fig. 13–161). Among numerous reports, about 50% are concerned with each type. Those with mental retardation and/or other central nervous system anomalies generally appear to develop the skin folds after puberty (4,19).

The furrows are usually longitudinal, but a few may be transverse. They are usually at the vertex but may be located at other sites on the scalp (14). Cortical and subcortical atrophy with ventricular dilatation has been reported (21), with polymicrogyria in others (34). There is also an increased frequency of eye abnormalities: strabismus, nystagmus, cataract, keratoconus (2).

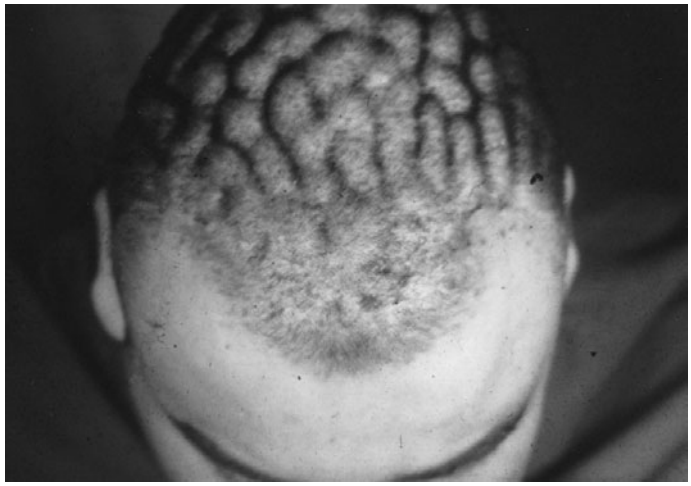

Fig. 13–161. *Cutis verticis gyrata*. Extreme example.

Endocrinological disorders have included hypergonadotrophic hypogonadism, but other studies have not shown significant changes (25).

Fragile sites have been reported by some authors (21,32) and denied by others (7). We suspect that they are aleatory.

The cutaneous anomaly may be an isolated finding (primary essential) (8,11,22) or secondary to chronic skin disorders or infiltration of the skin with tumor or leukemic cells, amyloid, nevi, fibromas, or neurofibromas (5,6,10,12,13,18,24,27). Melanoma has been reported to occur in those with nevus cell nevi (12). The skin lesions may also be seen in *pachydermoperiostosis*. Other conditions having cutis verticis gyrata are acromegaloid changes and corneal leukoma inherited as a dominant disorder (31) and thyroid aplasia and mental retardation with possible X-linked inheritance (1). It may also be seen in acromegaly (10,23), with *Turner syndrome* (17,30), and with *Noonan syndrome* (16), presumably resulting from lymphangiectasia in the latter two conditions. Cerebriform intradermal nevus must be excluded (15). A recessive syndrome involving retinitis pigmentosa, cataracts, and deafness has been reported (20a).

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Facial hemangiomas, sternal nonunion, supraumbilical midline raphé, vascular anomalies, and Dandy-Walker malformation (PHACES)

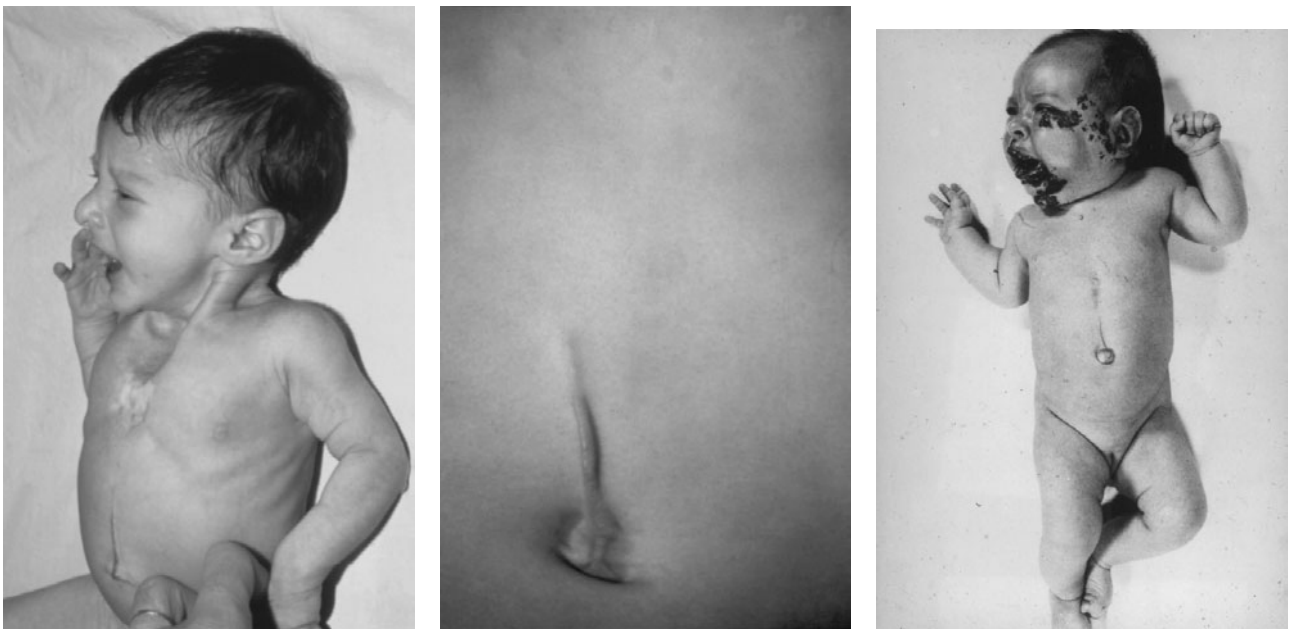
Leiber (18) and a host of earlier investigators noted the syndrome in binary, tertiary, or quaternary form in various combinations. These have been documented by Gorlin et al (11). Frieden et al (7) suggested use of the term PHACES syndrome for *P*osterior fossa CNS anomalies, *H*emangioma, *A*rterial anomalies, *C*oarctation of the aorta and *C*ardiac anomalies, *E*ye anomalies, and *S*ternal defects.

There is no reason to believe that the syndrome has a genetic basis. Haque (13) noted facial hemangioma and nonunion of the sternum in a male born to consanguineous parents. A sister had only non-union of the sternum. We have seen sisters with nonunion of the sternum and teardrop-shaped umbilicus in the first and facial hemangiomas in the second.

The marked female predilection demonstrated by Gorlin et al (11) for the *triad* of facial hemangiomas with non-union of the sternum and supraumbilical raphé (20F:1M) contrasts sharply with the 1:1 sex ratio for the *binary* combination of sternal non-union and supraumbilical raphé. However, the skewed sex ratio appears not to hold if other vascular anomalies are added (Fig. 13–162).

Sternal non-union. Sternal defects (cleft sternum, bifid sternum) is classified as superior, inferior, or complete and really represents embryonal non-union. Inferior sternal clefts are very rare and usually associated with other abnormalities of midline fusion (pentalogy of Cantrell). In this syndrome, the anomaly ranges from a notch in the upper manubrium to complete separation of the sternal bars, resulting in what appears clinically to be sternal agenesis (Fig. 13–162A). Depending on the degree of nonunion of the sternal bands, during respiration and crying, there is sinking and bellowing of the upper chest into and out of the concavity. The pulsations of the heart and aorta are evident in the same space. The clavicles and nipples are widely separated.

Fig. 13–162. *Facial hemangiomas, sternal nonunion, supraumbilical midline raphé, vascular anomalies, and Dandy-Walker malformation* (*PHACES*). (A) Note suprasternal repaired defect and supraumbilical raphé. (B) Supraumbilical raphé. (C) Facial angiomata and supraumbilical raphé.



A B C

Supraumbilical raphé. The cutaneous raphé, often resembling a well-healed scar, extends upward from the umbilicus by several centimeters, but fails to reach the sternal defect (Fig. 13–162B). Embryologically, supraumbilical midline fusion occurs later than infraumbilical midline fusion (2). During the 8th week in utero, the mesoderm reaches and fuses in the midline, supporting the overlying ectodermal epithelium. Absence of this supporting mesoderm results in necrosis of the overlying epithelium (21). We have seen a few patients with aplasia of skin of the upper sternal area. Zullino (34) has also noted this finding.

Hemangiomas. Hemangiomas may be present at birth, but far more often appear during the first few weeks or months of life (Fig. 13–162C). They usually are small tumors, most commonly located on the face (forehead, cheeks, lips, chin, ear, and preauricular area), only rarely manifesting below the shoulder. Occasionally, hemangiomata have been reported to involve the larynx and trachea. Subglottic, lingual, and gingival lesions have been noted (3). These have been extensively cited by Gorlin et al (11). Hersh et al (14) described small bowel and pancreatic involvement.

Vascular anomalies. Right aortic arch arises from persistence of the right dorsal aorta, a remnant of the six pairs of aortic arches that are formed during the late 4th and 5th weeks of fetal life. If there is no double arch, then there has to be involution of part of the left dorsal aorta. With mirror-image branching, the segment of the left dorsal aorta distal to the left 7th intersegmental artery involutes, but when the left subclavian artery arises aberrantly, the left 4th arch has involuted and the left distal dorsal aorta persists. Pascual-Castroviejo (22,23), utilizing carotid angiography to examine the vertebral basilar system of children with facio-cutanous vascular lesions, proposed two groups of patients. The first group had unilateral facial hemangioma; various intracranial and extracranial arterial anomalies, the most striking being the absence of the ipsilateral carotid arteries and persistence of intracranial or extracranial embryonal arteries; anomalies of the aortic arch; and hypoplasia of the cerebellum, ranging from unilateral partial deficit to severe hypogenesis associated with Dandy-Walker malformation. Pascual-Castroviejo further suggested that the more marked the severity and extent of the hemangioma, the more extensive the intracranial vascular anomalies. Three of 7 patients he described had congenital heart malformations. The second group had unilateral facial hemangioma extending to involve the parotid, orbital, lingual, and maxillonasal areas, the blood flow being across several branches of the external carotid artery. The internal carotid artery exhibits dilatation from its origin to at least the zone of the carotid siphon. In some cases, the aneurysmal dilatation extends from its origin to its terminus, producing a mega-arterial system ipsilateral to the facial hemangioma (22,26,28). Bilateral facial hemangioma is paralleled by intracranial vascular involvement, more often in the zone of the carotid siphon and the Circle of Willis. A female predilection was found in both groups of anomalies. Gorlin et al (11), however, did not support the separation into the two divisions proposed by Pascual-Castroviejo (22,23) because there was overlap of the two groups mentioned above with the syndrome of defective sternal union, supraumbilical raphé and facial hemangioma. Rizzo et al (28) described a boy with supraumbilical raphé, hypoplasia of the right shoulder girdle, short right humerus, radius, and ulna; right camptodactyly; and short sternum. The right subclavian artery terminated just distal to the origin of the internal mammary artery. Geller et al (8) reported a male with supraumbilical raphé and sternal non-union. Hemangiomas involved not only the face but the limbs, groin, trunk, and soles. There was also macrocephaly, unilateral microphthalmia, absent corpus callosum, hydrocephalus, and various cardiac anomalies (hypoplastic right ventricle, pulmonary stenosis, ventricular septal defect, patent ductus arteriosus, and right aortic arch). The female patient (Case 8) of Reese et al (27) exhibited sternal non-union, midline abdominal raphé, facial and ipsilateral hemangioma of upper limb and trunk, contralateral optic nerve hypoplasia, aortic arch dilatation, coarctation of descending aorta, aberrant subclavian artery, and hypoplastic contralateral ear. They further described seven female patients with facial hemangiomas (some involving the upper trunk), some with ipsilateral microphthalmus, and most with Dandy-Walker or other posterior fossa abnormalities. Pasic (24) described a female with hemangiomas of the brain, face, and neck associated with sternal non-union, supraumbilical raphé, aneurysm of the aortic arch involving the innominate artery and left carotid artery, anomalous origin of the coronary arteries, left superior vena cava, micrognathia, and cervical cyst. Gorlin (personal communication, 1994) saw a child with extensive hemangioma of the face, neck, and back with a double aortic arch, double aortic coarctation, single carotid artery, and stridor due to unknown cause. Schneeweiss et al (31) described two male and two female patients with facial hemangioma and coarctation of the aorta. Three had congenital aneurysm of a subclavian or innominate artery; the other had mitral insufficiency. Valvular aortic stenosis was present. Schieken et al (30) described the association of facial hemangiomas, aneurysm of the ascending aorta, and occlusion of the right innominate artery and tricuspid aortic valve in a female with superior sternal cleft. Góh and Lo (9) reported 2 female patients with facial hemangioma, cerebellar hypoplasia, and coarctation of the aortic arch. Mizuno et al (20) noted a 5-year-old girl with facial hemangioma, ipsilateral optic atrophy, ipsilateral cerebellar hypoplasia, internal carotid arterial stenosis, basilar artery occlusion, and saccular aneurysm of the left carotid siphon. No mention was made of sternal abnormalities or of supraumbilical raphé.

Vaillant et al (33) reported a male infant with facial, lingual, shoulder, and laryngeal angiomas. Right aortic arch with coarctation was found. The left and right common carotid arteries and left subclavian artery arose successfully from the aortic arch. Honey et al (16) reported a male infant with multiple hemangiomas of the face, right aortic arch, coarctation of aorta, and ventricular septal defect.

Kishnani et al (17) reported a female infant with hemangioma, supraumbilical midline raphé, and coarctation of aorta with a right aortic arch. The hemangiomas involved the gingiva and tongue as well as the face. Similar examples are noted by Crisponi et al (5a).

Enroljas and Gelbert (6), in their survey of 175 cases of superficial hemangiomas, noted (a) aortic arch interruption and laryngeal hemangioma, (b) coarctation of the aorta, (c) intracranial arterial anomalies, (d) imperforate anus, (e) microphthalmia, and (f) Dandy-Walker anomaly and/or cerebellar hypoplasia. All were female infants.

Dandy-Walker malformation. Dandy-Walker malformation has been seen in combination with facial hemangiomas and mental retardation by a number of authors (6,9,12,14,15,28,29,31). Hall and Gilmore (12) described female twins of unknown zygosity born to consanguineous parents. One twin had Dandy-Walker malformation at autopsy at 5 1/2 months. The other twin had facial hemangioma and Dandy-Walker malformation, seizures, and mental retardation.

Patel and Gupta (25) described an infant female with facial hemangiomas, Dandy-Walker malformation, and retroorbital and parasagittal venous malformations. Matsue et al (19) reported cerebellar hypoplasia and vascular abnormalities.

Sacral hemangiomas have been associated with imperforate anus and bony abnormalities of the sacrum as well as lipomeningomyelocele and skin tags (10).

Diagnosis. About 10%–12% of children develop hemangiomas and 70%–90% of these are noted by age 1 month. Classical hemangiomas have a significant 3–7F:1M predilection (6). Hemangiomas and vascular malformations are discussed extensively on pp. 577–578 and by Burns et al (4). Hemangiomas of the overlying skin may be seen with underlying spinal dysraphism, lipomeningocele, and tethered cord syndrome (21).

References [Facial hemangiomas, sternal non-union, supraumbilical midline raphé, vascular anomalies, and Dandy-Walker malformation (PHACES)]

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Hyperkeratosis palmoplantaris striata, pili torti, hypohidrosis, oligodontia, and sensorineural hearing loss

Egelund and Frentz (2), in 1982, reported 14-year-old female with lusterless coarse terminal scalp hair, sparse eyebrows and lashes, hyperkeratosis of palms and soles, generalized hypohidrosis (except for palms) oligodontia, and moderate nonprogressive midfrequency sensorineural hearing loss.

Braun-Falco and Landthaler (1) described an 18-year-old female with ichthyosis vulgaris, pili torti, hypodontia, and sensorineural hearing loss. Both parents had hearing loss but none of the other stigmata.

Pili torti, usually occurring as an isolated finding, has been described in an autosomal dominant pattern with absence of lower premolar teeth (3). In looking at the pedigree, we cannot say whether the two traits were independently inherited.

References (Hyperkeratosis palmoplantaris striata, pili torti, hypohidrosis, oligodontia, and sensorineural hearing loss)

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Palmoplantar hypokeratosis, hypotrichosis, hypodontia, enamel and dentin dysplasia, cleft palate, strabismus, and cryptorchidism

Šalamon et al (1) described an apparently unique young male with desquamative, erosive lesions of the palms and soles that appeared at age 5. Sweating was reduced. The teeth had defective enamel and dentin, and there was a deficient number of teeth. In addition to cleft palate, strabismus and cryptorchidism were found.

Reference (Palmoplantar hypokeratosis, hypotrichosis, hypodontia, enamel and dentin dysplasia, cleft palate, strabismus, and cryptorchidism)

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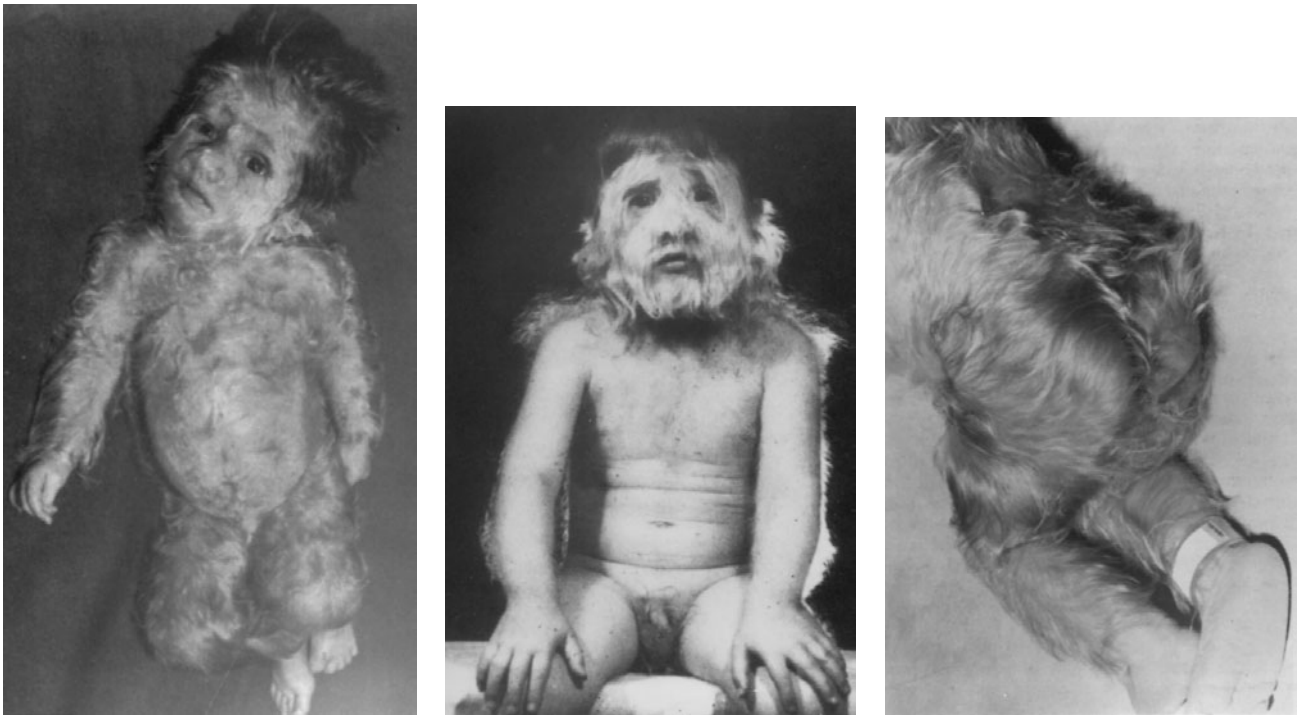
Congenital hypertrichosis universalis (Ambras syndrome)

Congenital hypertrichosis universalis with unusually excessive deposits of hair on the face, ears, and shoulders has been reported since the Middle Ages. Over 150 affected individuals have been described, variously characterized as "hair man," "dog men," and "human werewolves" (4–6,14,15). It has been called "Ambras syndrome" (2).

Approximately 10 cases have been reported in the literature. The entire body is covered with fine, long hair except in areas where no hair normally grows: palms, soles, dorsal terminal phalanges, and mucosa. The forehead, eyelids, nose, cheeks, and preauricular region are uniformly covered with hair, which often reaches an enormous length if not shaved. The hair is light-colored, silky or golden. Only the scalp hair, eyebrows, eyelashes, and axillary hair are darker. Long curls protrude from the external auditory canal, and often the eyelashes are long. The generalized hypertrichosis is usually present at birth (3,10,12) (Fig. 13–163).

The face is triangular and coarse with marked intercanthal distances. Broad palpebral fissures, long prominent nasal bridge with a rounded



A B C

Fig. 13–163. *Congenital hypertrichosis universalis* (*Ambras syndrome*). (A) Three-week-old with extensive hirsutism. Notice that hands and feet are not involved. (B) Three-year-old. (C) Four-day-old with similar involvement. (From FAM Baumeister et al, Clin Genet 44:121, 1993.)

tip, broad interalar distance, anteverted nares, short lower lip, and a flat sulcus mentolabialis (3,10). Both dentitions are retarded in eruption. The upper molars and premolars are very often absent (3,12).

In Ambras syndrome, the follicles of the body hair extend into the subcutis. The hair is pigmented and medullary (1), being of the vellus type.

The Ambras syndrome differs from other congenital hypertrichoses in the pattern of hair distribution and associated anomalies. In the other syndromes, the facial hair is accentuated in the frontal, temporal, and preauricular regions. The eyebrows are bushy and sometimes confluent. The external ears are seldom hairy and never to such an extent as in the Ambras syndrome. On the back, the hair streams from the sides, converges at the midline, and often forms a whorl over the spine, resembling that found in familial or racial hypertrichosis. Congenital hypertrichosis lanuginosa has a different hair growth pattern at birth. The entire body is covered homogeneously with fine blond hair except for the hands and feet (8,9,13). During the first year of life, hair shedding begins over the trunk, progressing to the arms and legs. The face is glabrous. An incisor has been present at birth, and there have been supernumerary teeth (13). Glaucoma has been noted in another child (9).

Autosomal dominant inheritance has been demonstrated (10). X-linked dominant inheritance was also suggested (10), and the gene has been mapped to Xq24–q27.1 (7). There has been an association with pericentric inversion (8)(p11.2;q22) (1,2).

References [Congenital hypertrichosis universalis (Ambras syndrome)]

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Congenital ichthyosis, follicular atrophoderma, hypotrichosis, and hypohidrosis

In 1998, Lestringant et al (2) reported on five Bedouin sibs (three girls and two boys) with diffuse congenital ichthyosis, patchy follicular atrophoderma, generalized and diffuse nonscarring hypotrichosis, and marked hypohidrosis. The parents were first cousins.

In the five patients studied, ichthyosis was congenital, non-erythrodermic, involved the great flexures, and family history was typical of autosomal recessive inheritance (2).

Electron microscopic studies failed to demonstrate the typical structures of classical autosomal recessive lamellar ichthyosis, such as lipid vacuoles, elongated membrane structures, and abnormal vesicular keratosomes. Steroid sulfatase activity was normal.

The patients were reminiscent of *Bazex syndrome* (1,3,4). However, ichthyosis is not a component of that disorder (2).

References (Congenital ichthyosis, follicular atrophoderma, hypotrichosis, and hypohidrosis)

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Ichthyosis follicularis, atrichia, and photophobia (IFAP) syndrome

The syndrome of ichthyosis follicularis, alopecia, and photophobia (IFAP) was first recognized by MacLeod (6) in 1909 in three brothers (11). Since then, only 11 male patients have been reported from 9 families (1–3,5–7,13). In one family, two maternal uncles were probably also affected (7).

The skin shows ichthyosiform hyperkeratosis, ichthyosis follicularis, and lack of sebaceous glands. Alopecia is noted in all the patients. Dystrophic nails may be present in some.

The ears may be large and dysplastic. Enamel hypoplasia may be present. Photophobia may also be observed.

Findings that are often present include growth and psychomotor retardation, chill-like seizures accompanied by fever, a tendency to infection, and skeletal abnormalities (5).

In one patient, olivocerebellar atrophy, a peculiar malformation of the temporal lobes, and mild inner cerebral atrophy were noted (5). These findings may, in part, explain the neurological symptoms of IFAP syndrome patients.

Although the genetic basis of IFAP syndrome is unclear, X-linked inheritance is probable because all reported patients are males. An association between X-linked ichthyosis and microdeletions or a contiguous gene defect in the chromosome regions Xp22.3–p22.2 and Xq28 has been suggested (4,8,11).

In differential diagnosis, a very similar syndrome must be taken into account. It was reported in two daughters of a man who presented with alopecia and follicular keratosis from early childhood, thus suggesting autosomal dominant inheritance (9). This disease shares, with IFAP syndrome, keratosis follicularis including the scalp, trunk and extensor aspects of the arms and legs, and noncicatricial alopecia. Other defects such as scaling between the hair follicles, and true ichthyosis are absent. Two other cases reported by van Gelderen (12) and Schinzel (10) also share abnormalities with IFAP syndrome but can be distinguished by the absence of ichthyosis follicularis (12) and photophobia (10,12).

References [Ichthyosis follicularis, atrichia, and photophobia (IFAP) syndrome]

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Johnson-McMillan syndrome

Johnson et al (2), in 1983, reported a large family with autosomal dominant alopecia, hyposmia or anosmia, conductive hearing loss, microtia, and hypogonadism (Fig. 13–164). Another case was added by Johnston et al (3) in 1987. Still another example in a mother and son was described by Hennekam and Holtus (1). Both mother and son exhibited facial nerve palsy, multiple truncal café-au-lait spots, and mild developmental delay. The mother also had hyposmia and growth retardation, while the son exhibited hypotrichosis, conductive hearing loss, and microtia.

References (Johnson-McMillan syndrome)

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Laryngo-onycho-cutaneous syndrome (LOGIC syndrome)

In 1986, Shabbir et al (5) reported 22 patients they designated *laryngo-onychocutaneous syndrome*. Ainsworth et al (1,2), and Phillips et al (4), and Bedlow et al (3) added examples. Ainsworth et al (1,2) suggested the acronym *LOGIC* to indicate the following salient features: *L*aryngeal and *O*cular *G*ranulomatosis *I*n *C*hildren from the Indian subcontinent.

In most cases, death occurs during childhood.

Dermal and submucosal granulomas produce skin lumps and weak hoarse cry and voice due to laryngeal involvement. The submucosal tissues are massively inflamed, and the philtrum breaks down. The conjunctival, oral, tracheal, and esophageal mucosae are also involved. Within the first few months of life, skin ulceration, conjunctival scarring with symblepharon at the lateral fornix, and loss of nails due to nail bed granulomas are seen. The skin lesions break down, bleed, and become crusted. The esophagus becomes constricted.

Amelogenesis imperfecta of both dentition has been described in some patients (1–5).

Phillips et al (4) and Bedlow et al (3) found abnormal hemidesmosomes and consigned this to the group of junctional *epidermolysis bullosa* or cicatricial pemphigoid.

To date all affected have been Muslim families of Punjabi origin. Nearly all families have been consanguineous. Inheritance is autosomal recessive (1–5).

References [Laryngo-onycho-cutaneous syndrome (LOGIC syndrome)]

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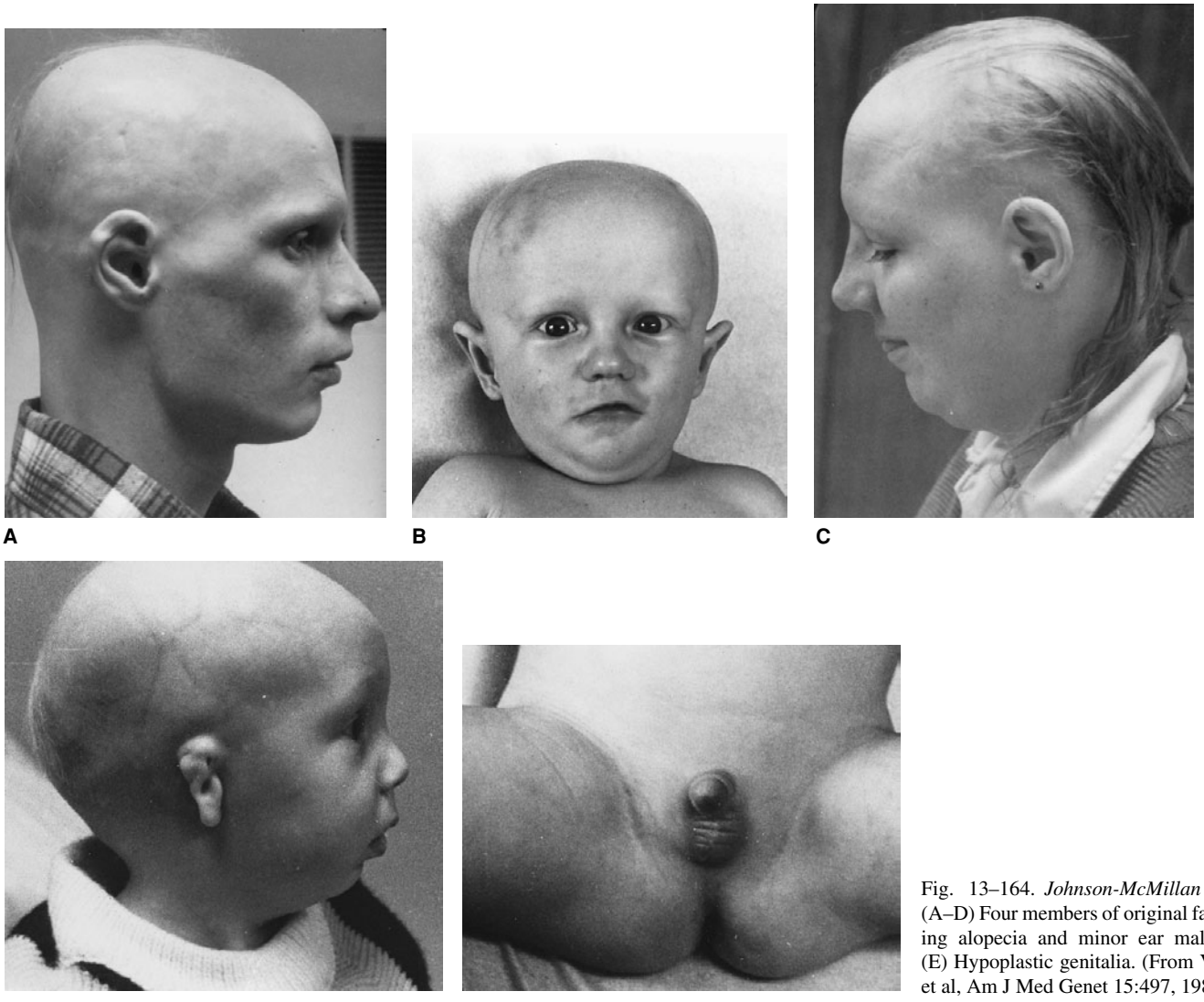

Fig. 13–164. *Johnson-McMillan syndrome*. (A–D) Four members of original family showing alopecia and minor ear malformations. (E) Hypoplastic genitalia. (From VP Johnson et al, Am J Med Genet 15:497, 1983.)

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Kindler and Weary syndromes

Kindler (11), in 1954, described a syndrome of neonatal bullae, photosensitivity, and atrophy of the skin of the hands and ears. Weary et al (19), in 1971, reported a similar condition. There has been disagreement as to whether these reports illustrate the same disorder. Approximately 70 cases have subsequently been described.

Inheritance was thought to be autosomal recessive because of parental consanguinity (8–10,14,17). However, the vast majority of examples have been sporadic, and it has been suggested that there is genetic heterogeneity (7), Kindler syndrome having autosomal recessive inheritance while Weary syndrome has autosomal dominant transmission.

Skin. Acral cutaneous bullae are congenital or appear during the first few days of infancy. They appear to follow trauma or sun exposure. There is spontaneous regression of bullae formation in late childhood. This is followed by the appearance of reticular skin pigmentation (4).

Photosensitivity ranges from relatively mild sunburn (9,11,17) to severe blister formation (8). It is manifested as facial erythema following minimal sun exposure. Poikiloderma, beginning with erythema and red patches, appears around 3–5 years and involves the face, spreading to the chest, upper back, abdomen, groin, and arms and legs. It is manifest by speckled pigmentation, atrophic areas, and wrinkled skin. The poikiloderma persists throughout adult life. The dorsa of the hands are especially marked by cutaneous atrophy, less often the abdomen, thighs, knees and elbows. Hyperkeratosis of the palms and soles has also been noted (11,17). The fingers and/or toes may rarely be proximally webbed (7).

Histologically, the poikilodermic skin changes are characterized by epidermal atrophy with decreased thickness of the stratum spinosum and orthohyperkeratosis. There is focal vacuolization of the basal layer, vascular ectasia, and melanophages in the upper dermis. The bullous lesions show intraepidermal cleft formation or dermatoepidermal clefts under an intact basal layer (2,11,14,17).

Oral manifestations. Few case reports comment on the oral findings: white mucosal patches (8,17), gingival swelling and bleeding (1,8,9,11), atrophy of oral mucosa (9), erosions (10,12,13), and pigmentation of the lips (10). Restricted mouth opening has also been noted (5,8,15). Squamous carcinoma of the lower lip was noted (1).

Other mucosal involvement. Dysphagia, which has been reported in several cases, may result from esophageal strictures (1). Urethral

meatal stenosis as well as anal fissuring and stenosis have been noted (1,2,17). Ectropion of the lower eyelid has also been described (1,8,17).

Diagnosis. Some investigators have proposed that Kindler syndrome has congenital bullae, frequent photosensitivity, poikilodermia with onset after 1 year, mucosal involvement, and autosomal recessive inheritance. Weary syndrome, in contrast, has cutaneous bullae that are not congenital, no photosensitivity, acral keratotic papules, no mucosal involvement, and autosomal dominant inheritance. The position of the blister cleavage level is variable in Kindler syndrome and intraepidermal in Weary syndrome.

Because of infantile cutaneous bullae, one must exclude *epidermolysis bullosa*. Weary syndrome should be excluded on the basis of different inheritance pattern, absence of photosensitivity, and onset of poikiloderma within the first year of life. Various examples of Weary syndrome have been cited (3,6,7,16,18,19). *Rothmund-Thomson syndrome, xeroderma pigmentosa*, and *dyskeratosis congenita* must also be excluded.

References (Kindler and Weary syndromes)

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Infantile systemic hyalinosis

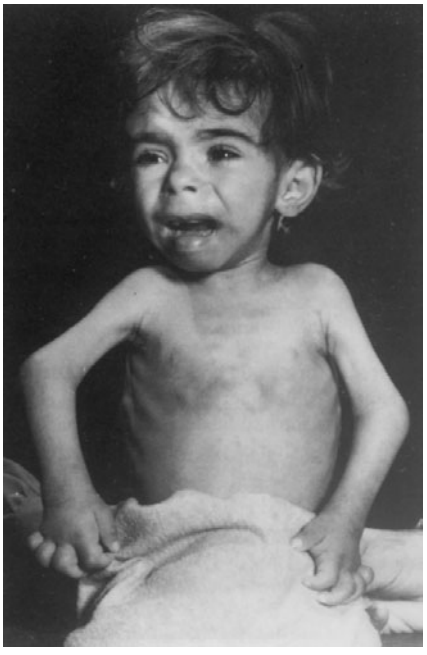
Nezelof et al (7), in 1978, and Landing and Nadorra (5), in 1986, defined a disorder of collagen characterized by thickening and nodularity of the skin, joint contractures, osteoporosis, and gingival enlargement. Other cases have been added (1–4,6,8,9), some having been erroneously labeled as examples of Winchester syndrome (2,6).

Failure to thrive dates from the neonatal period with death usually occurring before the third year of life, most before the second. There is associated severe diarrhea and wasting and recurrent severe infections.

Facial changes include frontal bossing, deep-set eyes, downslanting palpebral fissures, low-set large pinnae, small mouth, and short neck (Fig. 13–165).

Pearly papular nodules appear about the face, especially around the nose, mouth, chin, and lower abdomen (Fig. 13–165B,C). The skin is diffusely firm. Fleshy nodes are evident around the anal margin (Fig. 13–166A). The skin over the metacarpophalangeal joints and malleoli is nodular and hyperpigmented (Fig. 13–166B).

Fig. 13–165. *Infantile systemic hyalinosis*. (A) Pain and restriction of joints, especially those of hands and feet. Note swollen lower lip. (B) Numerous pearly papules of face and ears as well as nodules of lips and gingival hyperplasia. Observe velvety perioral pigmentation. (C) Compare with patients seen in A and B. Note numerous pearly papules of nose, brows, perioral and skin area. (A from DB Dunger et al, Eur J Pediatr 146:615, 1987. B from EE Sahn et al, Pediatr Dermatol 11:52, 1994. C from MT Glover et al, Pediatr Dermatol 9:255, 1991.)



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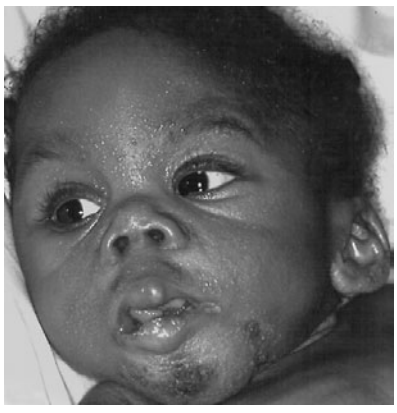

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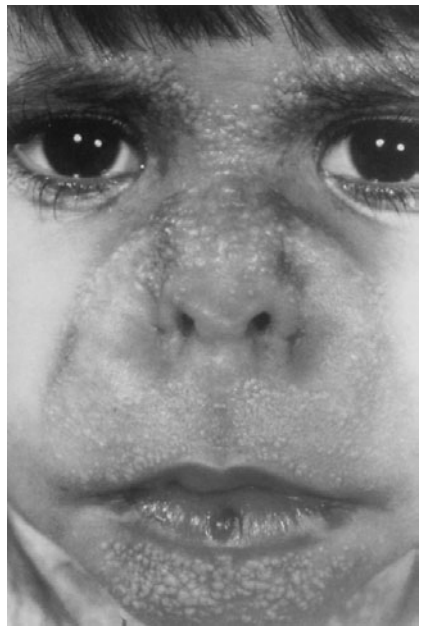

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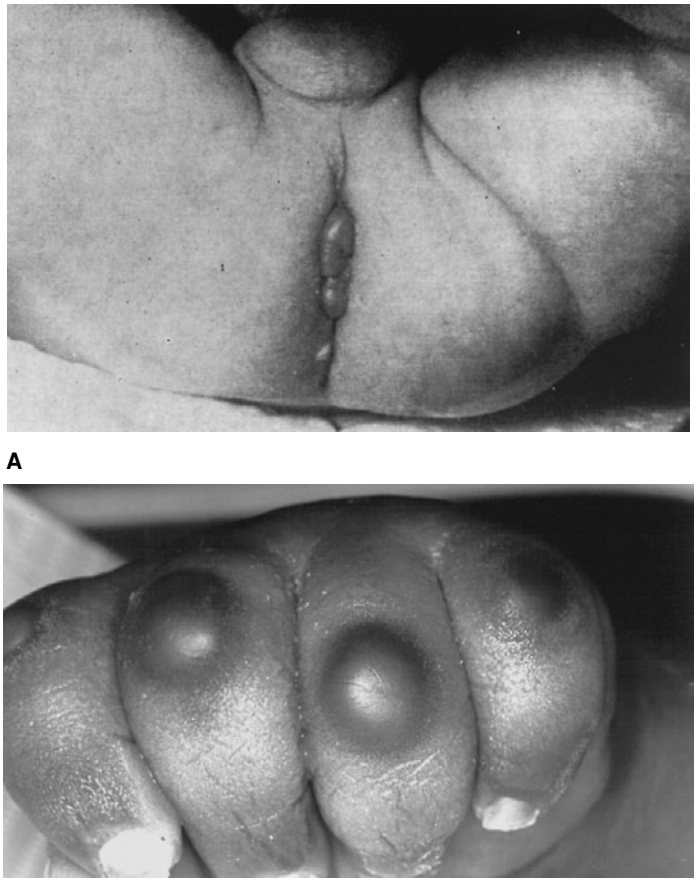

Fig. 13–166. *Infantile systemic hyalinosis*. (A) Perianal nodules at 16 months. (B) Hyperpigmented nodular plaques over proximal interphalangeal joints of hands. (A from C Nezelof et al, Arch Franc Pediatr 35:1063, 1978. B from EE Sahn et al, Pediatr Dermatol 11:52, 1994.)

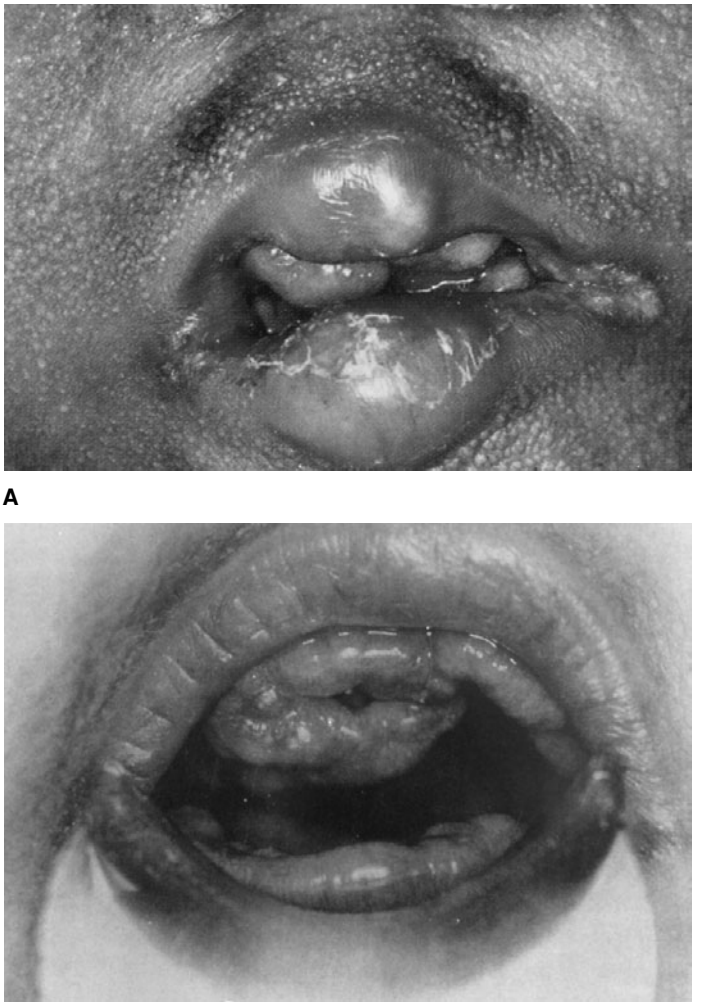

Fig. 13–167. *Infantile systemic hyalinosis*. (A) Lip nodules and perioral papules. (B) Gingival enlargement. (A from EE Sahn et al, Pediatr Dermatol 11:52, 1994. B from MT Glover et al, Pediatrics 87:228, 1991.)

There is gross soft flabby enlargement of gingival tissue which becomes evident about the time of initial tooth eruption. The teeth may become entirely covered (Fig. 13–167).

Microscopic examination reveals widespread deposits of hyaline material in skin, endocrine glands, muscle, and gastrointestinal tract shown to be type VI collagen. The collagen can be identified by use of fluorescent antibodies to type VI collagen (1).

Hypoproteinemia may result in generalized edema. Intestinal lymphangiectasia and hyaline deposits are evident on jejunal biopsy. This is associated with protein-losing enteropathy. Hypoproteinuria may result in generalized edema. Serum protein, but especially serum albumin, is low. Bloody diarrhea may be noted.

Painful joint contractures (arthrogryposis) are evident within the first few months of life. The patient often lies supine in a frogleg position with little spontaneous movement. Generalized bone demineralization is a constant feature (Fig. 13–168). The fingers are thickened and spindled, held in extension at the metacarpophalangeal joints and flexed at the interphalangeal joints.

Normal parents with multiple affected sibs suggest autosomal recessive inheritance (5). Consanguinity has also been noted (1,3,4,5).

One must exclude *juvenile systemic hyalinosis* (*Murray-Puretiç-Drescher syndrome*) and *Winchester syndrome*.

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Linear skin defects and microphthalmia (MIDAS syndrome)

The syndrome of linear skin defects and microphthalmia was first described by Ropers et al (18) in 1982, but was defined and expanded by Al-Gazali et al (1,2) in 1988–90 and many others (3–16,20,21). Happle

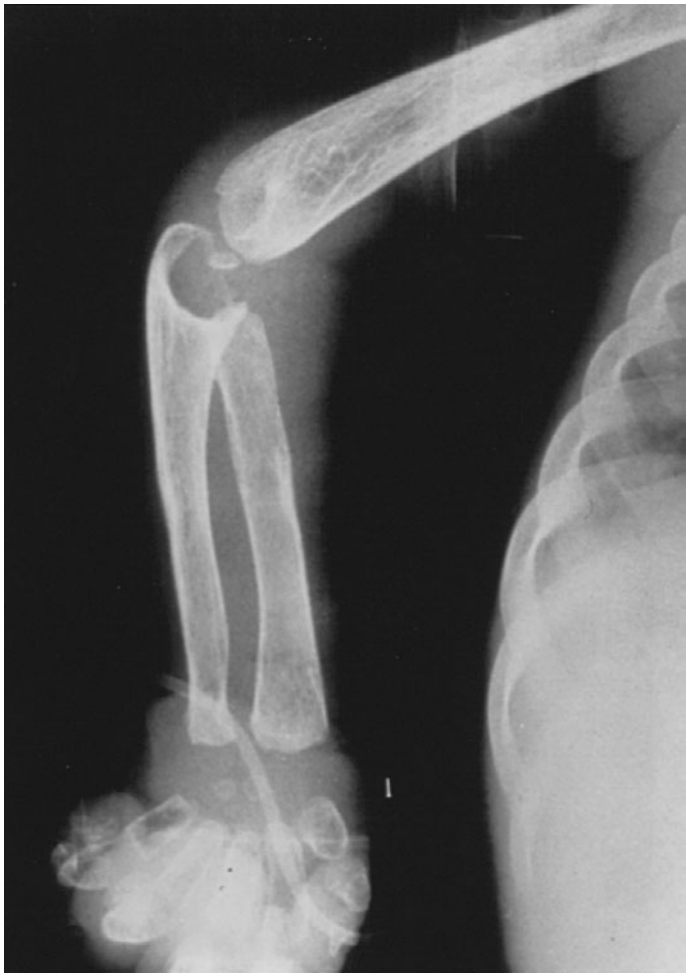

Fig. 13–168. *Infantile systemic hyalinosis*. Well-circumscribed defect in ulna with generalized bone demineralization. (From EE Sahn, Pediatr Dermatol 11:52, 1994.)

et al (10) termed the condition the MIDAS syndrome (*MI*crophthalmia, *D*ermal *A*plasia, *S*clerocornea) (Fig. 13–169).

Overlapping both Aicardi syndrome and Goltz (focal dermal hypoplasia) syndrome, the syndrome reflects deletions and translocations involving the distal short arm (Xp22.3) of the X chromosome (6,11,21). It requires a mosaic state for survival. In XY patients, this results in nullisomy for Xp which is lethal (2,4). In XX patients (even XX males), deletion and unbalanced translocations of the region cause short stature and cutaneous and ocular defects (13). An X/Y translocation has been documented on several occasions (14,18,19). Approximately 20 cases have been described, all but a few in females. It has been seen in a mother and daughter (14). An affected mother has given birth to an anencephalic fetus (13).

Lindsay et al (13) suggested that *Aicardi syndrome* and *Goltz syndrome* are due to involvement of the same gene or genes, the *different patterns* of clinical expression being due to *different patterns* of X-inactivation. However, Mücke et al (15) suggested that they represent different entities, due to mother–daughter involvement.

Short stature (3rd–10th centiles) has been attributed to deletion of a pseudoautosomal gene for height (1,2,12).

Skin. The hypoplastic skin defects are asymmetric, linear, less often stellate or reticular, erythematous, and essentially limited to the anterior face and neck, rarely the upper torso (Fig. 13–169A,B). Later, the scars become hyperpigmented. Nail dystrophy has been described (8,16). In one biopsied example, the hypoplastic area showed smooth muscle hamartoma (16).

Eyes. Severe microphthalmia (1–3,7,9,10,12,13,16,17,20), sclerocornea (1–3,7,12–15), cataracts, orbital cysts, chorioretinal abnormalities, microcornea (13), and glaucoma (14,15) have been reported (Fig. 13–169C).

Ears. Several authors have described malformed pinnae (3,7,16).

Central nervous system. Hydrocephalus, mental retardation (13), normal intelligence (3,13), infantile seizures, and agenesis of the corpus callosum (3,8,16,17) have been documented. Profound hearing loss has been demonstrated (17).

Heart. Oncocytic cardiomyopathy (which has its own ample literature) is probably more common than has been reported. This results in refractory arrhythmias, AV block, and cardiac arrest (5,10,12,16). ASD and VSD have also been noted (12,17).

Genital anomalies. A variety of anomalies has been reported: hypertrophic clitoris, hypoplastic uterus, dysgenetic testis, small phallus, hypospadias, and ovotestis (14,15,17).

Miscellaneous findings. These include hyperextensible joints (13), diaphragmatic hernia (3), nasal cyst (13), anterior placed anus (7), and imperforate anus (17).

Diagnosis. The syndrome is distinct from both Aicardi syndrome (agenesis of corpus callosum, infantile seizures, chorioretinal lacunae, developmental delay) and *focal dermal hypoplasia*. The skin lesions in the latter are far more extensive in location and in nature (10).

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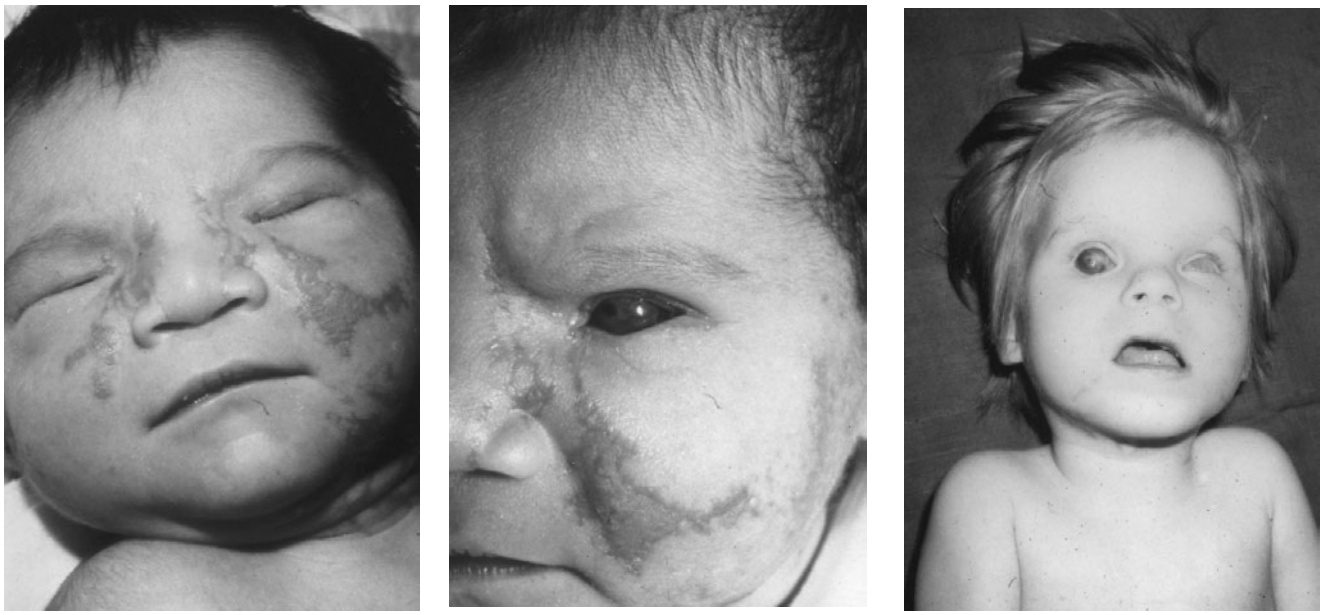

A B C

Fig. 13–169. *Linear skin defects and microphthalmia* (*MIDAS syndrome*). (A) Characteristic linear skin lesions of cheeks. (B) Also note microphthalmia and corneal opacity. (C) Microphthalmia, corneal opacities, aplasia of skin on chin. Child also had agenesis of corpus callosum, atrophy of foreskin, and true hermaphroditism. (A,B from BR Paulger et al, Pediatr Dermatol 14:26, 1997. C from J Mücke et al, Am J Med Genet 57:117, 1995.)

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Melanoleukoderma, hypodontia, hypotrichosis, somatic and mental retardation, and infantilism

Berlin (1), in 1961, reported four sibs, two male and two female, the products of a consanguineous union, with somatic and mental retardation, hypotrichosis, hypodontia, and melanoleukoderma.

The sibs, of Iranian descent, had mottled skin exhibiting various nuances of brown, gray, yellow, and white. Most of the skin was affected, including that of the face. The hair became gray early. Telangiectases were noted on the lips. Palms and soles were hyperkeratotic.

Adult height was about 150 cm. Mild mental retardation was evident in all three sibs. Build was slender. There was some hypermobility of the fingers.

The facies was somewhat unusual with sparse eyebrows, flat saddle-shaped nose, full lips, and deep furrows around the eyes and mouth.

Hypospadias, micropenis, and small testes were noted in the males. Puberty was delayed, and there was impotence. Females matured normally.

Reference (Melanoleukoderma, hypodontia, hypotrichosis, somatic and mental retardation, and infantilism)

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Trichothiodystrophy (Tay syndrome, IBIDS syndrome)

The trichothiodystrophies (TTDs) are a heterogeneous group of disorders. After proposing a tentative classification of 7 groups based on clinical classifications, we will concentrate on the group associated with defects in DNA repair mechanisms.

The finding common to all types of trichothiodystrophies is fragile and poorly growing hair which, on polarization, shows a pattern of bright and dark bands. There is involvement of the scalp hair, eyebrows, and eyelashes (Fig. 13–170) (20). Body, axillary, and pubic hairs may also be affected. The nails, in certain cases, may be friable, thinned, demonstrating horizontal splitting, longitudinal ridging, and koilonychia with erythroderma or photosensitivity.

Pending identification of specific mutations in the different categories, Sybert (27) has proposed the following classification:

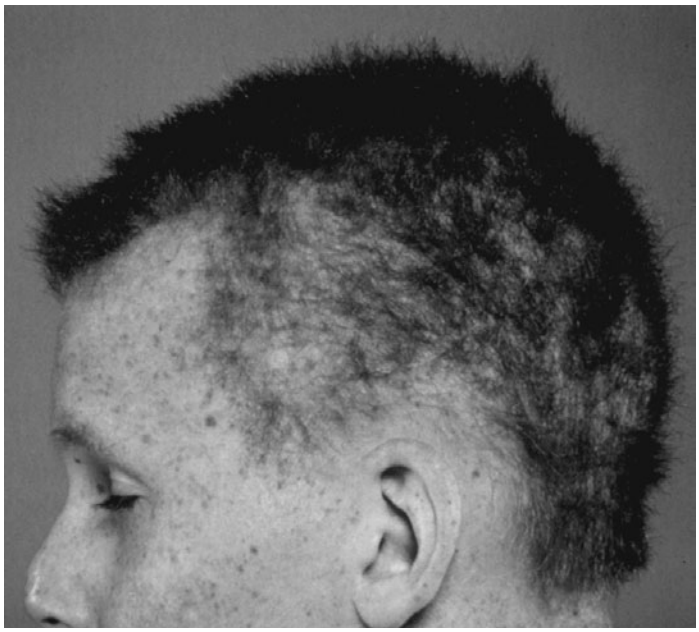
Type A: The hair is abnormal. The nails may or may not be affected (27).

Type B: (Sabinas syndrome). The hair is affected; the nails may or may not be abnormal. Mental retardation is present (27).

Type C: (Pollitt syndrome). The hair is affected; the nails may or may not be abnormal. The teeth may be carious. Mental retardation, retarded bone age, and folliculitis are present (27).

Type D: (*b*rittle hair, *i*nfertility, *d*evelopmental delay, *s*hort *s*tature; BIDS; hair-brain syndrome). The hair is affected; the nails may or may not be abnormal. Mental retardation and short stature are present. Gonadal dysfunction may be noted in some cases (27).

Type E: (*i*chthyosis with BIDS, or IBIDS; Tay syndrome). The hair is affected, but the nails may or may not be. Mental retardation and short stature are present. The following manifestations may be noted in certain cases: decreased gonadal function, lenticular opacities or cataracts, failure to thrive, "progeria" with loss of subcutaneous tissue, microcephaly,



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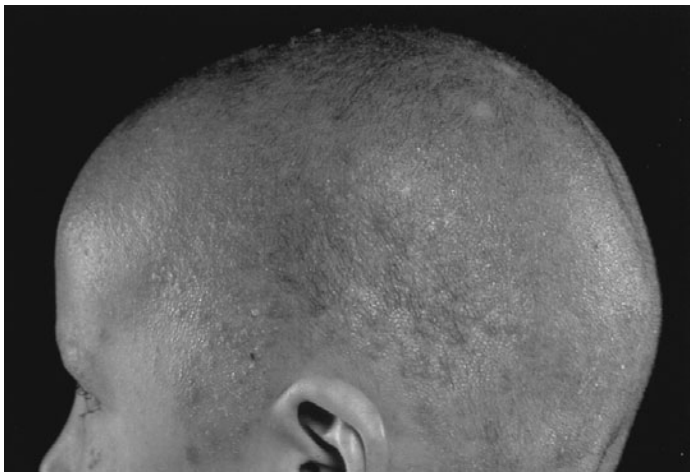

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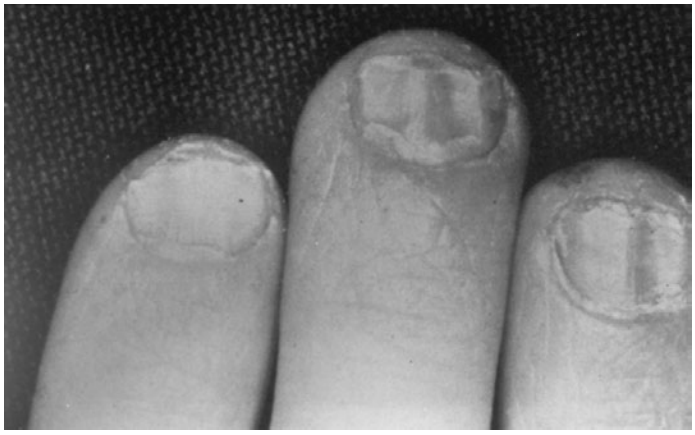


C

Fig. 13–170. *Trichothiodystrophy*. (A,B) Sparse broken eyebrows, eyelashes, and scalp hair; thickened epicanthic folds and protruding ears. (C) Dysplastic nails. (A,B courtesy of M Pittelkow, Rochester, Minnesota.)

ataxia, and erythrodontia. These patients may present as collodion babies in the newborn period (27).

Type F: (*p*hotosensitivity with IBIDS or PIBIDS). This group manifests all the features of group E, plus photosensitivity (27).

Type G: (trichothiodystrophy with immune defects). The anomalies of the hair are associated with chronic neutropenia or immunoglobulin deficiency. Mental retardation may or may not be present (27).

Two brothers were reported with a severe variant of trichothiodystrophy leading to death at 12 weeks and at 6 months, respectively. Clinical manifestations included brittle hair, failure to thrive, recurrent infections, cataracts, and angioendotheliomas of the liver at autopsy (19). There was also a report of a patient with TTD associated with urologic malformation and primary hypercalciuria (16).

It is important to remember that there is significant overlap in clinical manifestations of these groups. However, it is reported that 50% of TTD patients exhibit photosensitivity and deficiency in nucleotide excision repair (NER) (30). A classification based on specific mutations may be more reliable (vide infra). A good review is that of Tolmie et al (29a).

Anomalies of the hair. Under polarizing light, hairs show a pattern of light and dark bands (Fig. 13–171A) (20). The hair shaft may be twisted and nodes, as in trichorrhexis nodosa, may be observed. Scanning electron microscopy reveals abnormal cuticle formation (Fig. 13–171B) and irregular twisting and transverse fracturing of hairs (trichoschisis) (20). Abnormal whorled and irregular arrangement of microfibrils may be noted by transmission electron microscopy (9,12,27,30).

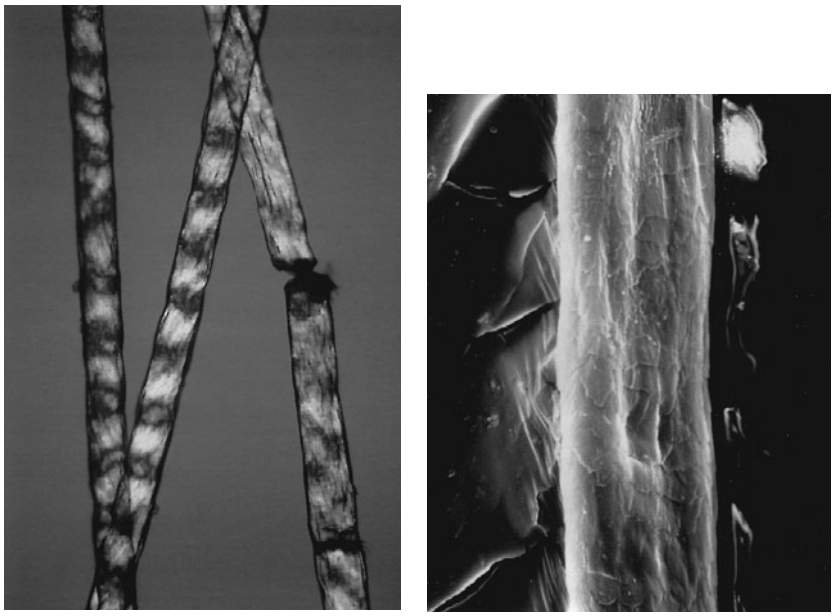
In all types of trichothiodystrophy, the hair shows a decrease in cystine to 10%–50% of normal, reflecting a decrease of ultrahigh sulfur proteins. The nails are deficient in high sulfur proteins as well (9,27).

Heredity. The photosensitive form of trichothiodystrophy (TTD) has autosomal recessive inheritance. Like xeroderma pigmentosum (XP), TTD is characterized by persistence of unrepaired DNA damage produced by exposure to UV light (6–8,17,23,24). However, unlike XP, TTD patients do not have an increased frequency of skin cancers (21).

Nucleotide excision repair (NER) (31) is the most versatile of DNA repair systems. It recognizes and eliminates a wide variety of DNA lesions, in particular those induced by ultraviolet light (1,10,14). NER requires the products of at least 20 genes (23). The NER process has five steps: recognition of the DNA lesion (by DNA-binding protein XPA), incision of the damaged strand on both sides of the lesion (by bidirectional helicases XPB and XPD), excision of the damaged oligonucleotide (by XPF and XPG), and DNA synthesis to fill the gap and ligation (Fig. 13–122) (23).

The NER defect of photosensitive TTD patients has been assigned to three complementation groups. The large majority of cases (90%) fall into the same group as XP-D and the TTD/XP-D group (23,25). The XP-D and the TTD/XP-D patients carry mutations on the same repair gene, mostly located in the C-terminal region (2,28). XPD is one of the subunits of the transcription/repair factor TFIIH. It interacts specifically with p44, another subunit of TFIIH. This interaction results in the stimulation of the $5' \rightarrow 3'$ helicase activity of XPD. Mutations in the XPD C-terminal domain prevent the interaction with p44, thus explaining the decrease in XPD helicase activity and the NER defects in TTD (3). No mutations on the XPD gene have been found in the nonphotosensitive TTD patients. Recently, one family was found to belong to the XP-B complementation group, called the TTD/XP-B group (32,34). A third kindred constitutes a distinct NER-deficient group, TTD-A (26). Because of strong evidence that most of the clinical features of TTD patients can be correlated with a defect in transcription, the notion of "transcription syndromes" has been proposed for TTD disease (3,10,18,32,34).

All cultured cells isolated from photosensitive TTD patients are sensitive to the killing effect of UVC irradiation and present a reduced level of DNA repair synthesis (22). In cell lines from photosensitive TTD patients, the extent of cellular responses to UV irradiation is remarkably heterogeneous, even within the same complementation group (15,23,25).



A B

Fig. 13–171. *Trichothiodystrophy*. (A) Microscopic views of hair from patient between cross-polarizers. Turning microscope stage about 10° (5° on each side of position of maximum extinction) causes dark patches to become bright and bright patches to become dark (arrows). (B) Scanning electron micrograph shows notable ridging and fleeting along longitudinal hair axis. Also note cuticle damage. (A courtesy of M Pittelkow, Rochester, Minnesota. B from VH Price et al, Arch Dermatol 16:1375, 1984.)

In spite of the sensitivity to UV irradiation, and in contrast to XP, TTD patients do not have a predisposition to cancer, even though they exhibit low DNA repair efficiency due to mutation in the same DNA repair gene, the XPD gene (23). It has been estimated that XP patients present more than a 200-fold increment in all forms of skin cancer, whereas no skin cancer has yet been reported to be associated with the TTD syndrome (23).

XPB and XPD proteins have a dual function, both in nucleotide excision repair of DNA damage and in basal transcription. Mutations in the XPD gene can result in three distinct phenotypes: XP, TTD, and Cockayne syndrome (CS). Studies revealed that most mutation sites differed between XP and TTD. However, there are three sites at which the same mutation is found in XP and TTD patients. Since the corresponding patients were all compound heterozygotes with different mutations in the two alleles, the alleles were tested separately. The mutations that are found in both XP and TTD patients behaved as null alleles, suggesting that the disease phenotype was determined by the other allele (29).

A slight transcription deficiency in a gene regulating a major pathway in immunosurveillance could be produced with "XP mutations," markedly reducing the natural killer activity of the cell. This may not occur with "TTD mutations" (23). Conversely, TTD-specific mutations on the XPD gene may affect pathways that result in the clinical features of the TTD syndrome, such as brittle hair, nail and dental anomalies, or developmental and mental retardation (23). The recently generated mouse model of TTD (4) should provide a suitable experimental model to shed additional light on the pathophysiologic processes of this condition.

The essential problem, then, is to find factors that may modify the response of cells to the deleterious effects of UV light in sun exposure, thus avoiding the development of cancer. In this respect, striking differences have been found between XP and TTD cells. Cells from XP patients are very low in catalase activity, whereas in TTD cells, catalase activity is normal (33). Low catalase activity results in the accumulation of H_2O_2 in XP cells. This can cause an overload of free radicals that damage DNA and favor tumor progression. The presence of low catalase activity, together with low DNA repair capability, may partly explain the increased risks of tumor production in XP as compared to TTD. It was recently reported that low catalase activity in XP fibroblasts is directly related to decreased intracellular levels of the cofactor, NADPH (11).

Moreover, among the major responses of human cells to DNA damage is accumulation of the p53 tumor suppressor protein, which plays a crucial role as a cell-cycle checkpoint. There is prolonged p53 protein accumulation in trichothiodystrophy fibroblasts dependent on unrepaired pyrimidine dimers on the transcribed strands of cellular genes (5).

Differential diagnosis. The conditions that should be considered in the differential diagnosis and ruled out are Netherton syndrome, Menkes disease, and Sjögren-Larsson syndrome.

Laboratory aids. Prenatal diagnosis is possible by measurement of repair of UV-induced DNA damage in chorionic villus cells or cultured amniocytes. Measurement of cystine in specimens of hair may also confirm a clinical diagnosis (9,27).

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CHIME neuroectodermal dysplasia syndrome

CHIME syndrome is a rare neuroectodermal disorder first described by Zunich and Kaye in 1983 (3–6). It presents with *C*olobomas of the eyes, *H*eart defects, *I*chthyosiform dermatosis, *M*ental retardation, and *E*ar defects. Six children with this syndrome have been reported (1).

The anomalies of the eyes include retinal colobomas, hypertelorism, and (1), in one case (2,4,5), cloudy corneas. The cardiac anomalies consist of tetralogy of Fallot, transposition of great vessels, peripheral pulmonic stenosis, and ventricular septal defect (1). The skin presents with a migratory ichthyosiform rash, associated with hyperproliferative overgrowth of the epidermis with thick palms and soles (1). Mental retardation is present in all patients. It may be associated with cerebral atrophy, seizures, and wide-based gait (1). The ears have overfolded helices, and conductive hearing loss is present in all reported patients (1).

Other anomalies associated with this condition may be neonatal macrosomia, brachycephaly, flat broad nasal root, short philtrum, wide mouth, full lips, and widely spaced teeth. Cleft palate was present in two patients. The nipples were small, low-set, and, in one patient, supernumerary (1). Skeletal anomalies included broad second toe, hyperextensible joints, clinodactyly, brachydactyly, deep plantar creases, or clubfoot (1). The urinary system presented with duplicated ureters in one case and obstruction of the ureteropelvic junction in another (1). One patient developed acute lymphocytic leukemia.

The cause of CHIME syndrome is still unknown. Autosomal recessive inheritance is possible. The diagnosis is important to make because of the potential for associated congenital heart disease, neurologic compromise, and possible development of malignancy (1).

The differential diagnosis includes Rud syndrome, Refsum disease, Sjögren-Larsson syndrome, Netherton syndrome, *KID syndrome*, and *trichothiodystrophy*.

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Chapter 14
Syndromes with Craniosynostosis: General Aspects and Well-Known Syndromes

The craniosynostoses are etiologically and pathogenetically heterogeneous. Premature sutural fusion may occur alone or together with other anomalies, making up various syndromes. Over 90 syndromes are known. Several reviews are available (1–4), the most exhaustive review being that of Cohen and MacLean (4).

Craniosynostosis has been observed in white, black, and Asian populations (1). Birth prevalence is approximately 343–476 per one million newborns (4–12). Sagittal synostosis is the most common type, with percentages ranging from 56% to 58%. Coronal synostosis occurs less frequently, with estimates varying from 18% to 29%. With sagittal involvement, the male-to-female preponderance is 3:1. With coronal involvement, there is usually, but not always, a slight predilection for females. Metopic and lambdoid synostoses are uncommon and lambdoid synostosis is frequently confused with posterior deformational plagiocephaly (1,4).

Most cases of isolated craniostenosis are sporadic, but familial instances are known: coronal, 14.4%; sagittal, 6%; metopic, 5.6% (6–10). Familial lambdoid synostosis is rare (6). Associated anomalies are more frequent in coronal series than in sagittal series. The types of anomalies most commonly associated with syndromic craniostenosis are limb defects, ear anomalies, and cardiovascular malformations (1,2).

The main craniosynostosis syndromes are discussed in this chapter. Other syndromes are discussed in Chapter 15.

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Apert syndrome (acrocephalosyndactyly)

Apert syndrome is characterized by craniosynostosis, midfacial malformations, and symmetric syndactyly of the hands and feet, minimally involving digits 2, 3, and 4 (4,9,14,17). Apert (2) is credited with the discovery of the syndrome, although the condition was reported earlier by Wheaton (61) and others. Park and Powers (43) reported an extensive study of the disorder in 1920. The most extensive reviews are those of Cohen and Kreiborg (7–16), Kreiborg et al (28–31), and Cohen and MacLean (17). In 1960, Blank (4), in examining 54 cases, divided acrocephalosyndactyly into typical and atypical clinical categories. Typical, or Apert type, included only those patients who had a middigital hand mass consisting of osseous and soft tissue syndactyly of digits 2, 3, and 4. More than 500 cases have been reported to date.

Birth prevalence of Apert syndrome is estimated to be 15–16 per one million newborns and the syndrome accounts for about 4%–5% of all cases of craniosynostosis (18,57). Although most cases are sporadic, representing new mutations, autosomal dominant transmission with complete penetrance has been reported many times (1,3,17,18,34, 49,50,58,59). Increased paternal age has been associated with sporadic cases (21,57). Wilkie et al (62) discovered two mutations in the linker region between IgII and IgIII on FGFR2: Ser252Trp and Pro253Arg. Origin of new mutations is exclusively of paternal origin (39). Ser252Trp accounts for approximately two-thirds of the cases; Pro253Arg is found in about one-third (18,52,62). Genotype/phenotype correlations have been reported by Slaney et al (52). Ser252Trp is more frequently associated with cleft palate and Pro253Arg is more commonly found with severe syndactyly (58a). Rarely, other Apert mutations are found: Pro252Phe (42), acceptor splice site mutation (44), and *Alu* insertions (41) (Fig. 14–1). The structure of the ectodomain has been reported (46a).

Craniofacial features. During infancy, there is a wide midline calvarial defect that extends from the glabella to the posterior fontanel that gradually fills in with bony islands that coalesce. The coronal area is fused at birth. Only the lambdoid suture forms interdigitations visible on radiographs and on dry skulls. Head circumference is larger than the 50th centile at birth (11,16,17,29).

Hyperacrobrachycephaly is commonly observed, and the occiput is flattened. The forehead is steep, and during infancy a horizontal groove that disappears with age may be present above the supraorbital ridges (Fig. 14–2A). Bulging at the bregma or slightly anterior to the bregma may be noted in some cases. The cranial base is malformed and often asymmetric (17,18,29). The anterior cranial fossa is very short. Shallow orbits expanded and prolapsed ethmoids, and orbital hypertelorism are associated. The clivus and anterior cranial fossa are short. The lesser sphenoidal wings slope upward and laterally. The great wings of the sphenoid are protruded. The cranial base angle is variable, but platybasia occurs most commonly (15). Cloverleaf skull may be observed in about 4% (15,17,22). The temporal fat pads are enlarged (53).

The middle third of the face is retruded and commonly hypoplastic, resulting in relative mandibular prognathism. The nasal bridge is depressed, and the nose is beaked (Fig. 14–2B). The nasal septum is often deviated (15,17,29).

Hypertelorism, proptosis, downslanting palpebral fissures, and, frequently, strabismus are observed. Absence of the superior rectus muscle

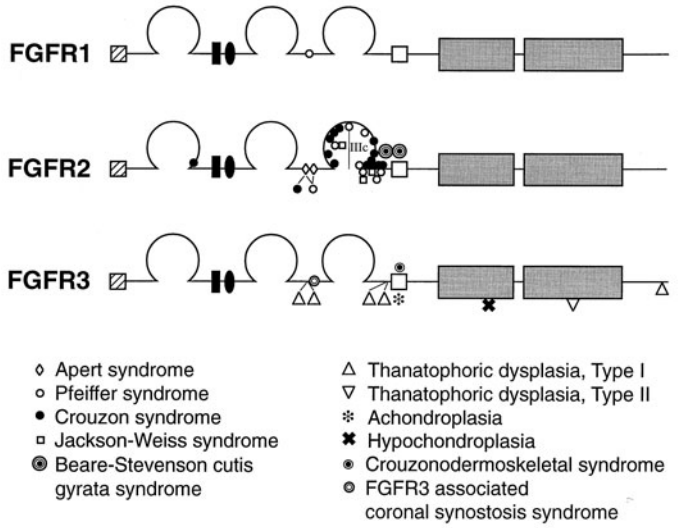


Fig. 14–1. Most mutations for major craniosynostosis syndrome are on FGFR2 with only one known mutation on FGFR1. Note mutations for short limb skeletal dysplasias (achondroplasia, hypochondroplasia, thanatophoric dysplasia, type I, and thanatophoric dysplasia, type II) on FGFR3. Fibroblast growth factor receptors 1,2,3. Hatched square = signal peptide. Solid oblong = acid box. Solid oval = CAM homology domain. Open square = transmembrane domain. Long oblongs = kinase domains 1 and 2. Three loops from left to right are immunoglobulin-like domains (IgI, IgII, IgIII). IIIc is alternatively spliced form of second half of IgIII. For clarity, only a few of the many mutations for Crouzon syndrome and Pfeiffer syndrome are shown on FGFR2. (From MM Cohen Jr, J Bone Min Res 12:322–331, 1997. Updated in: MM Cohen Jr, RE MacLean, Craniosynostosis: Diagnosis, Evaluation, and Management, 2nd ed., New York: Oxford University Press, 2000.)

has been reported (15,17,20,60). Structural alterations of the extraocular muscles have also been noted (9,15,17,35), indicating that ocular motility disturbances in the Apert syndrome may not be caused solely by mechanical factors. Albinoid findings have also been observed (36). Iris transillumination and depigmentation of the fundus are associated with absent or diffuse foveal reflexes. Unlike classical oculocutaneous albinism, however, visual acuity is not severely impaired, and pendular nystagmus is not observed. In some Apert syndrome patients, light hair color and pale skin are also noted (37).

The ears may appear low set in some instances. Minor anomalies of the ear may be noted on occasion (15,17). Otitis media is common in Apert syndrome. Middle ear disease is related to the high frequency of cleft palate (9,15,17) and may also be related to eustachian tube dysfunction compounded by obstruction of the epipharyngeal space (15). Congenital fixation of the stapedial foot plate has also been reported. The otologic manifestations have been reviewed by Bergstrom et al (3) and Gould and Caldarelli (23).

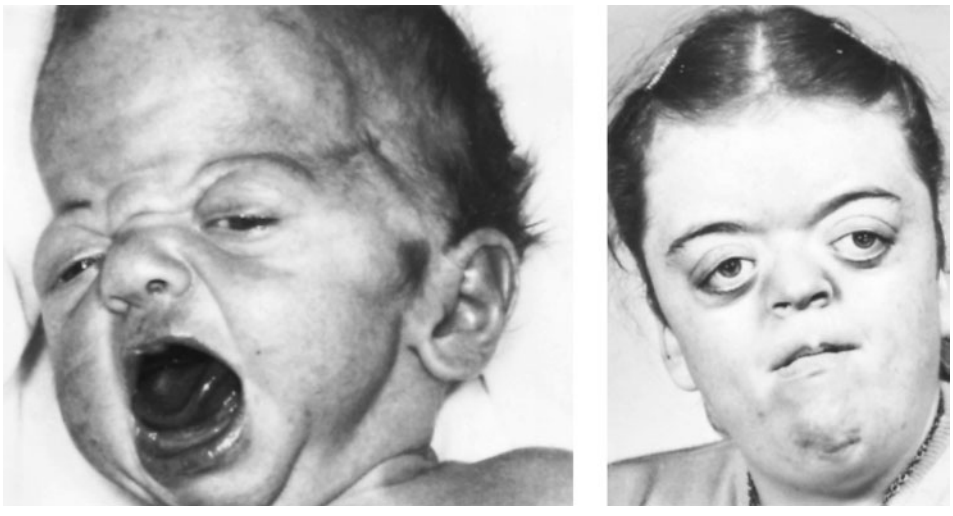
In the relaxed state, the lips frequently assume a trapezoidal configuration. The palate is highly arched, constricted, and usually has a median furrow (Fig. 14–3) (28,43,47,48). Lateral palatal swellings are present, which increase in size with age. These swellings have been shown to have excess mucopolysaccharide content, predominantly hyaluronic acid and, to a lesser extent, sulfated mucopolysaccharides (37,47). Cleft soft palate, or bifid uvula, is observed in 30% of cases (9,15,28). The hard palate is shorter than normal, but the soft palate is both longer and thicker than normal (9,15,28,47,48). Alterations in the nasopharyngeal architecture consist of reduction in pharyngeal height, width, and depth (15,47,48). The combination of reduced nasopharyngeal dimensions and decreased patency of the posterior nasal choanae poses the possible threat of respiratory embarrassment and cor pulmonale, especially in the young child (8,9,17). Solid cartilaginous trachea has been noted (17,38,40).

The maxillary dental arch is V-shaped with severely crowded teeth and bulging alveolar ridges. The maxillary hypoplasia, so frequently present in Apert syndrome, leads to compression of the dental arch, which becomes V-shaped. This results in irregular positioning of teeth and marked thickening of the alveolar process. Class III malocclusion is commonly present, with anterior open bite as well as anterior and posterior crossbite (28). Delayed dental eruption is a common finding (27,28).

Growth. Weight, length, and head circumference tend to be above the 50th centile in newborns. Birth measurements are explained by megalencephaly and increased head height (11).

The growth pattern in infancy and childhood consists of a gradual decrease in height so that most values fall between the 5th and 50th centiles. From adolescence to adulthood, the decrease in centiles becomes more pronounced. This two-step deceleration in height results from rhizomelic shortening of the lower limbs (11).

Central nervous system. The subject has been reviewed by Cohen and Kreiborg (7). A significant proportion of patients are mentally retarded. IQ has been studied at two large craniofacial centers. Lefebvre et al (32) assessed 20 children with a full battery of psychometric tests. Mean IQ was 73.6 with a range of 52–89. Patton et al (46) found that approximately half of their patients had an IQ greater than 70, although none had an IQ above 100 (n=29). Of 14 patients with IQs above 70, seven found suitable training or employment. Only 7% had IQs lower than 35. In patients who had craniectomies performed during the first year of life, no significant differences were found between retarded vs. nonretarded outcome. However, patients with normal intelligence and above average intelligence have been observed (17).



A B

Fig. 14–2. *Apert syndrome* (A) Note turribrachycephaly, proptosis, and horizontal grooves above supraorbital ridges. (B) Note turribrachycephaly, hypertelorism, downslanting palpebral fissures, beaked nose, midface hypoplasia, and relative mandibular prognathism. (B from A Kahn Jr and J Fulmer N Engl J Med 252:379, 1955.)

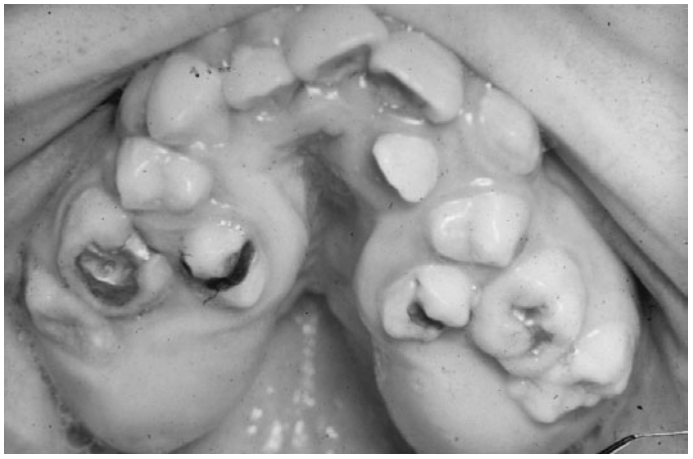


Fig. 14–3. *Apert syndrome*. Note Byzantine arch-shaped palate.

Cohen and Kreiborg (7) reported absent or defective corpus callosum, defects of limbic structures, or both. Other frequent findings in their neuropathology series included megalencephaly and gyral abnormalities. Hypoplasia of cerebral white matter and heterotopic gray matter were found in some cases.

Progressive hydrocephalus is uncommon and has frequently been confused with distortion ventriculomegaly (7,17), which is very common.

Hands and feet. The hands and feet have been studied extensively by Cohen and Kreiborg (14). A middigital hand mass minimally involving the second, third, and fourth fingers is nearly always observed (Fig. 14–4A,B), but exceptions occur (6,45). Associated synonychia is variable in degree. The first and fifth fingers may be joined to the middigital hand mass or may be separate. When the thumb is free, it is broad and deviates radially. Some degree of brachydactyly involving all five fingers is usually present. The interphalangeal joints become stiff by 4 years of age (14,17).

Radiographically, the first metacarpal is normal. The proximal phalanx of the thumb is short, frequently narrow, and sometimes delta-shaped. The distal phalanx of the thumb is enlarged and trapezoidal in shape. The second to fifth metacarpals are shorter than normal and tend to be uniform in length. The proximal ends of the fourth and fifth metacarpals may be unsegmented (Fig. 14–4C). Osseous symphalangism of the proximal interphalangeal joints is visible radiographically by 4–6 years of age. Synostosis of adjacent distal phalanges occurs with age, most frequently between the third and fourth distal phalanges, but also between the second to fourth distal phalanges. Unsegmented carpal bones, particularly the hamate and capitate, may be observed. Other bony abnormalities of the hands have also been noted (14,17,51).

In the feet, syndactyly involves the second, third, and fourth toes (Fig. 14–4D). The first and fifth toes are sometimes free and sometimes joined by soft tissue union to the second and fourth toes, respectively. Toenails may be separate or partially continuous. The great toes are broad, and hallux varus is commonly observed (5,14).

The distal phalanx of the great toe is enlarged and trapezoidal. The proximal phalanx of the great toe is malformed. The second phalanges of the second to fifth toes are often absent. The first metatarsal is broad, shortened in some instances, and may exhibit partial or tarsal bone duplication. Symphalangism, fusion of the tarsal bones, six metatarsals, and other bony abnormalities may be observed in the feet (14,17,51).

Progressive calcification and fusion of the bones of the hands, feet, and cervical spine becomes visible radiographically with age (14,17,33,51). Imaging of the hands and feet has been described (19,25).

Skin. Acne vulgaris with unusual extension to the forearms may be seen in more than 70% (n=19) of patients at adolescence and thereafter. Frank comedones and pustules occurring on the face, chest, back, and upper arms may be very severe and hyperseborrhea is especially common (13,17,54). Steffen (56) does not accept this as a true acne vulgaris.

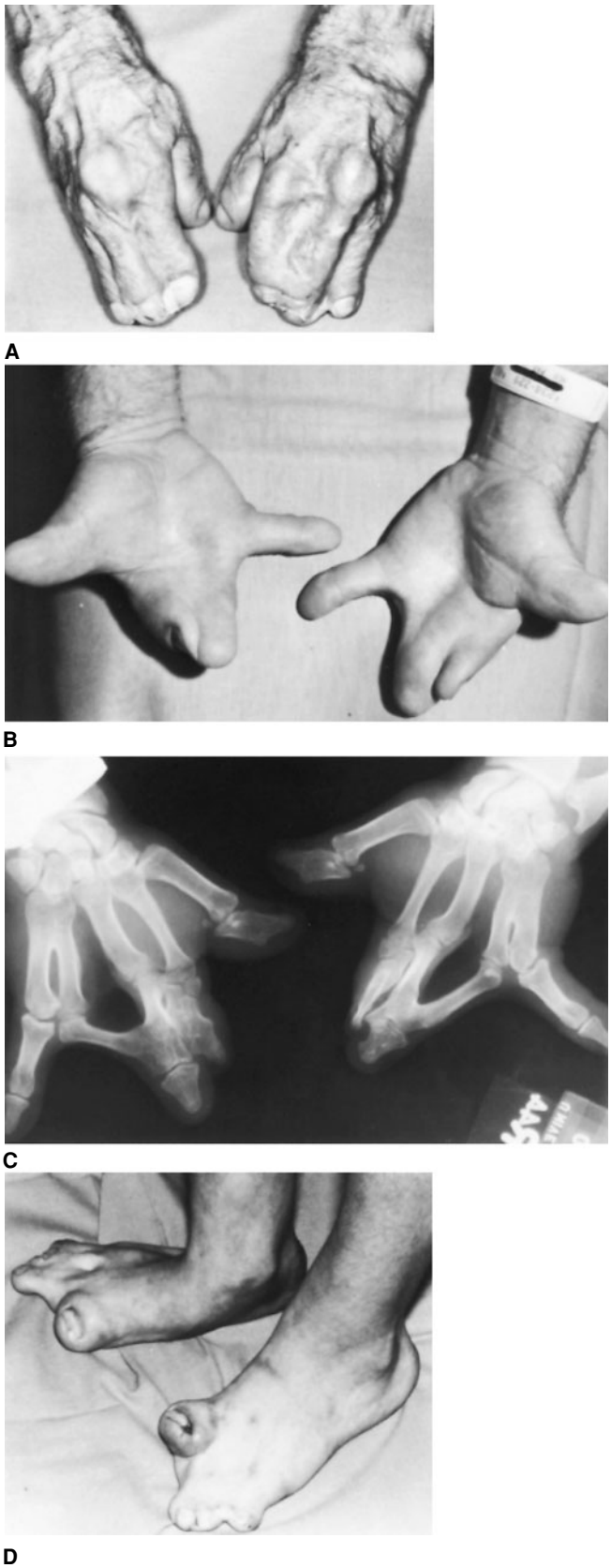


Fig. 14–4. *Apert syndrome*. (A) Syndactyly of second to fourth fingers. Note broad, radially deviated thumbs. (B) Mid-digital hand mass with first and fifth digits free. (C) Radiograph showing bony synostoses. (D) Syndactyly of second to fourth toes. Note broad, proximally placed halluces. (B and C from JM Opitz Helena, Montana. D courtesy of R Bauer, Innsbruck, Austria.)

Other findings. Final height attainment is commonly between the 5th and 50th centiles. This is due in part to mild rhizomelia of the lower limbs. Rhizomelia of the upper limbs may be more pronounced. In the series of Cohen and Kreiborg, 4% (n=55) exhibited severe rhizomelia (10). Progressive generalized bony dysplasia with limitation of motion at the shoulders with mild limitation at the elbows has been documented. Alterations in the pelvis have also been noted (10). Cardiovascular defects are found in about 10% and genitourinary anomalies are noted in approximately 10% (12). Cervical fusions, particularly involving C_5–C_6, have been found in 69% (30).

Differential diagnosis. Apert syndrome should be distinguished from *Pfeiffer syndrome, Saethre-Chotzen syndrome, Jackson-Weiss syndrome, Crouzon syndrome*, and *Carpenter syndrome*.

Prenatal diagnosis. Prenatal diagnosis of Apert syndrome has been reported (7,17,24,34). Diaphragmatic hernia has been noted as a presenting sign (63).

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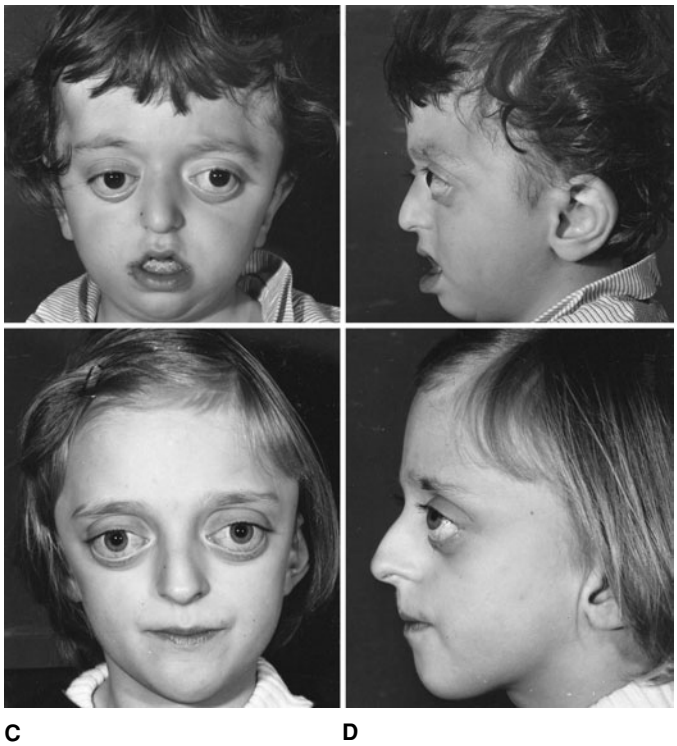
Crouzon syndrome (craniofacial dysostosis)

Crouzon syndrome is characterized by craniosynostosis, maxillary hypoplasia, shallow orbits, and ocular proptosis (Fig. 14–5). First described by Crouzon (12) in 1912, eighty-six published cases were reviewed by Atkinson (6) by 1937. Numerous publications on Crouzon syndrome have appeared (1–45), with the most complete study being Kreiborg's (26) monograph, which analyzes 61 cases. Cohen and MacLean (11) provided an exhaustive review.

Crouzon syndrome has autosomal dominant transmission. In Atkinson's review (6), 67% of the cases were familial and 33% were sporadic, representing new mutations. In Kreiborg's monograph (26), 44% were familial and 56% occurred sporadically. Increased paternal age at the time of conception was a statistically significant factor in new mutations in Kreiborg's study (26). Rollnick (40), Navarette et al (37), and probably Juberg and Chambers (23) reported examples of germinal mosaicism. Crouzon syndrome has a birth prevalence of 15–16 per one million newborns and Crouzon syndrome accounts for 4.5% of all cases of craniosynostosis (10). Variability of expression characterizes Crouzon syndrome. Nowhere is this more apparent than in the pedigree reported by Shiller (42; see also 20). The proband, the most severely affected member of the family, presented with cloverleaf skull. Several sibs manifested classic Crouzon syndrome. The affected mother and various other members of the family exhibited ocular proptosis and midface deficiency without craniosynostosis. In some instances, affected individuals with only subtle features of Crouzon syndrome are detected because they are related to a classically affected relative (11). On occasion, a normally appearing member of the family may harbor a Crouzon mutation (11).

Over 30 mutations for Crouzon syndrome are located on IgIII of FGFR2 (22) (Fig. 14–1). About half of a dozen of these are also found in Pfeiffer syndrome (9,11). Two extremely rare mutations have been reported: Tyr105Cys on IgI and Ser252Leu in the linker region between IgII and IgIII (9,11). A novel mutation, G362T, has been shown with apparent nonpenetrance (15a). The phenotype of the patient shown by Steinberger et al (43) does not resemble Crouzon syndrome. Spontaneous mutations are of paternal origin (18a).

Fig. 14–5. *Crouzon syndrome*. (A–D) Note various craniofacial shapes, shallow orbits, proptosis, divergent strabismus, hypertelorism, short upper lip, and midface hypoplasia. (Courtesy of P Tessier, Paris, France.)



Craniofacial features. Cranial malformation in Crouzon syndrome depends on the order and rate or progression of sutural synostosis. Brachycephaly is most commonly observed, but scaphocephaly, trigonocephaly, and, as already indicated, the cloverleaf skull may be observed (Fig. 14–5).

Craniosynostosis commonly begins during the first year of life and is usually complete by 2–3 years of age. In some cases, craniosynostosis may be evident at birth (11,26). Occasionally, no sutural involvement may be noted. Shallow orbits and ocular proptosis are diagnostic features of Crouzon syndrome. Diagnosis may be evident at birth or during the first year of life. On occasion, the phenotypic features of Crouzon syndrome may be absent and evolve gradually during the first few years of life. Various sutures may be prematurely synostosed, and multiple sutural involvement is found eventually in most cases (coronal and sagittal—20%; coronal, sagittal and lambdoidal—75%; sagittal and lambdoidal—4%) (26). Kreiborg et al (32) demonstrated earlier closure of sutures, fontanelles, and synchondroses in Crouzon syndrome than in Apert syndrome. Increased digital markings are common on skull radiographs (11,26). Anthropometric and cephalometric studies have been carried out (24,26,35,36).

Ocular proptosis, a feature occurring in 100% of the cases (n=61), is secondary to shallow orbits and results in a high frequency of exposure conjunctivitis or keratitis. Luxation of the eyeglobes has been observed in some cases. Exotropia is an extremely common finding (77%, n=60) (7,26). Poor vision occurs in approximately 46% (n=54), with optic atrophy found in 22% (n=45) and blindness in 7% (n=61) (26). Low-frequency findings include nystagmus, iris coloboma, aniridia, anisocoria, corectopia, microcornea, megalocornea, keratoconus, cataract, ectopia lentis, blue sclera, and glaucoma (6,11,26).

Approximately 50% (n=54) have lateral palatal swellings but only in a few instances are they large enough to produce the median pseudocleft palate appearance found so frequently in Apert syndrome (26,38). Cleft lip and cleft palate are anomalies of low frequency (26). Because of maxillary hypoplasia in Crouzon syndrome, the anteroposterior dimension of the maxillary dental arch is shortened. Dental arch width is also reduced, and the constricted arch gives the appearance of highly arched palate, although palatal height is normal by measurement. Unilateral or bilateral posterior crossbite is evident in two-thirds of Crouzon syndrome patients. Crowding of maxillary teeth is common, and ectopic eruption of maxillary first molars occurs in approximately 47% (n=17). Anterior open bite, mandibular overjet, and crowding of mandibular anterior teeth are also commonly observed. Aplasia of single teeth (rarely more), shovel-shaped maxillary incisors, and abnormal premolar morphology have been observed in Crouzon syndrome with the same low frequency found in the general population (26,38,39).

Central nervous system. Progressive hydrocephalus, chronic tonsillar herniation, and jugular foramen stenosis with venous obstruction occur with significant frequency (8,34). Headaches were found in 29% (n = 52) in Kreiborg's series (26). Seizures occurred in 12% (n = 52), and marked mental deficiency was found in only 3% (n = 61).

Other findings. Conductive hearing deficit is found in 55% (n=49) and atresia of the external auditory canals occurs in 13% (n=53) (26). Deviation of the nasal septum was observed in 33% (n=60) of Kreiborg's series (26). Calcification of the stylohyoid ligament was especially common, being found in 88% (n=60). Cervical spine anomalies were also common (30%, n=60). Fusion of C_2 with C_3 occurred with the highest frequency, but in some instances C_5 and C_6 were fused, and in still other instances, C_2–C_3 and C_5–C_6 fusions occurred in the same patient (31). Fusions were found in 18% in another series, and butterfly vertebrae were found (2). C_2–C_3 and C_5–C_6 were found with equal frequency. Solid cartilaginous trachea was reported by Devine et al (14), Sagehashi (41), and Davis et al (13). In Kreiborg's series (26), stiffness of the elbows was noted in 16% (n=61), and in two of these cases, subluxation of the radial heads was evident. Cubitus valgus was observed in one patient by VA McKusick (personal communication, 1982). Peromelia was recorded in one instance (18). Sacral, vertebral, and rib anomalies were also noted by Golabi et al (19). A tail was noted by Sagehashi (41).

Several radiographic studies of the limbs have been carried out (1–5,36). Carpal fusions were found in 12% (n = 34). Mild defects of the hands have been shown by using metacarpophalangeal profile patterning (1,5,36). Radiographic abnormalities of the elbows have been documented in some instances (3).

Differential diagnosis. Crouzon syndrome should be distinguished from simple coronal synostosis, craniosynostosis, *Apert syndrome*, *Pfeiffer syndrome*, *Saethre-Chotzen syndrome*, *Jackson-Weiss syndrome*, and particularly from *crouzonodermoskeletal syndrome*.

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Pfeiffer syndrome

In 1964, Pfeiffer (37) described a syndrome consisting of craniosynostosis, broad thumbs, broad great toes, and a variable feature, partial soft tissue syndactyly of the hands. Eight affected individuals in three generations were noted in Pfeiffer's report. Other pedigrees consistent with autosomal dominant transmission have been noted by several authors (27,36,43,53,55). Penetrance has been complete, and expressivity has been very variable (4,44). In some cases the thumbs may be normal (4,42). Sporadic cases have also been noted (1–3,10–12,14,19,22,24,25,52). The most exhaustive review is that of Cohen and MacLean (10).

Muenke et al (16,32,40,46) and others (23,28,35,42,45) showed that mutations causing Pfeiffer syndrome are found on FGFR1 and FGFR2 (Fig. 14–1). Only one mutation is found on FGFR1 in the linker region between IgII and IgIII: Pro252Arg. Multiple mutations are known on

FGFR2 clustering on IgIII. About half a dozen of these mutations have also been found with Crouzon syndrome (10). For about 45% of cases, no mutation has been identified. Common mutations involve Cys278 and particularly Cys342. Ser351Cys is also common, occurring with a severe phenotype. However, not all patients have either broad thumbs or broad great toes so, by definition, do not have Pfeiffer syndrome. Splice site mutations account for perhaps 10% of those identified (M Muenke, personal communication, 1999). A Cys278Phe mutation has been found with severe craniolacunae (48). Spontaneous mutations appear to be of paternal origin (13a). Genotype-phenotype correlation has been studied by Cornejo-Roldan et al (10a).

Rutland et al (42), Schell et al (46), and Robin et al (41) suggested that clinical differences might exist between the mutation on FGFR1 and those on FGFR2. Severe craniosynostosis and midface hypoplasia, more pronounced ocular proptosis, and perhaps broader thumbs are more likely to be associated with mutations on FGFR2 than with the single mutation on FGFR1, although there is some overlap.

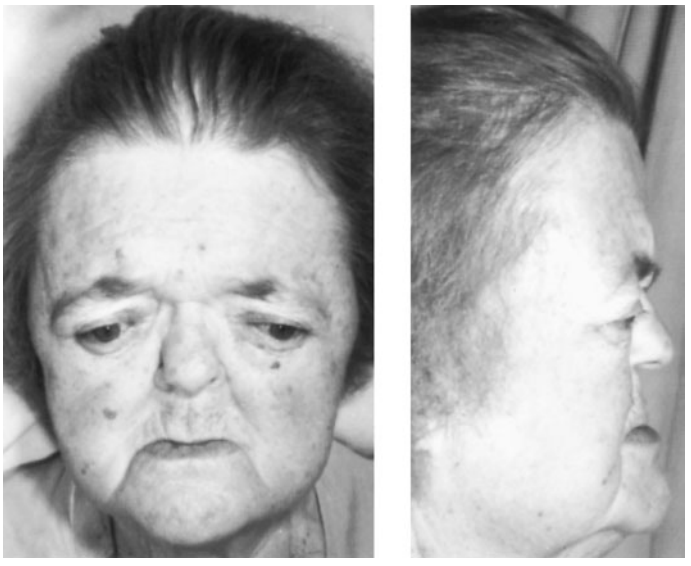
Clinical subtypes. Cohen (8) proposed three clinical subtypes of Pfeiffer syndrome with prognostic trends. He emphasized that such subtypes do not have genetic or nosologic status as separate entities; clinical overlap does occur (8,10).

Classic Pfeiffer syndrome (type 1) is likely to be compatible with life and normal or near normal intelligence in most cases, with mild mental deficiency occurring in others. Autosomal dominant families have been recorded (8) (Figs. 14–6 to 14–8).

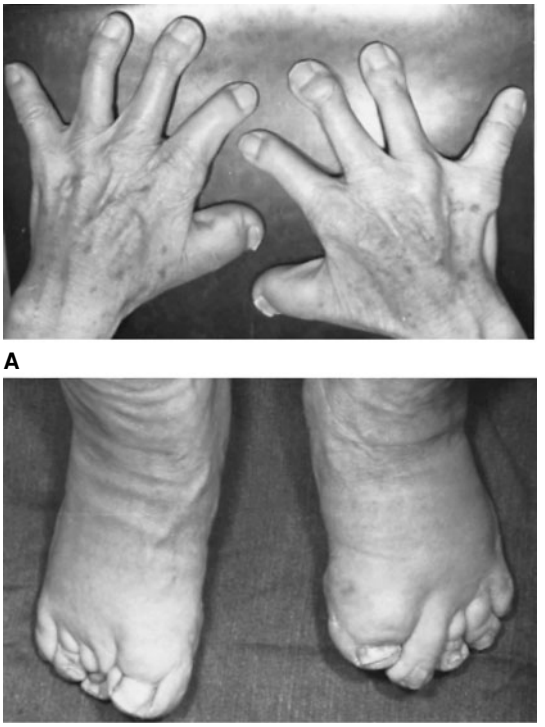
Type 2 Pfeiffer syndrome is characterized by cloverleaf skull, severe ocular proptosis, often severe CNS involvement such as hydrocephalus, elbow ankylosis/synostosis, broad thumbs and great toes, and a clustering of unusual low frequency anomalies that are frequently inconsistent from case to case (13,18,22,38,49,50) (Fig. 14–9A). The elbow ankylosis is not invariably present (1). All known cases have been sporadic (8). No classic type 1 pedigree has shown enough variability of expression to include a Pfeiffer cloverleaf case within the pedigree. One of us (MMC) cannot accept the example of the Pfeiffer syndrome mother and child reported by Soekarman et al (47). The son reportedly had cloverleaf skull, but the photographs do not suggest this interpretation.

Type 3 Pfeiffer syndrome is similar to type 2 but lacks cloverleaf skull (Fig. 14–9B). Hallmarks include severe ocular proptosis, shallow orbits, and marked shortness of the anterior cranial base. A clustering of unusual low frequency anomalies that are frequently inconsistent from case to case can be found with type 3 as well as with type 2. To date, type 3 cases have been sporadic (8,20).

Fig. 14–6. *Pfeiffer syndrome, type 1.* (A,B) Hypertelorism, downslanting palpebral fissures, and midface deficiency.



A B



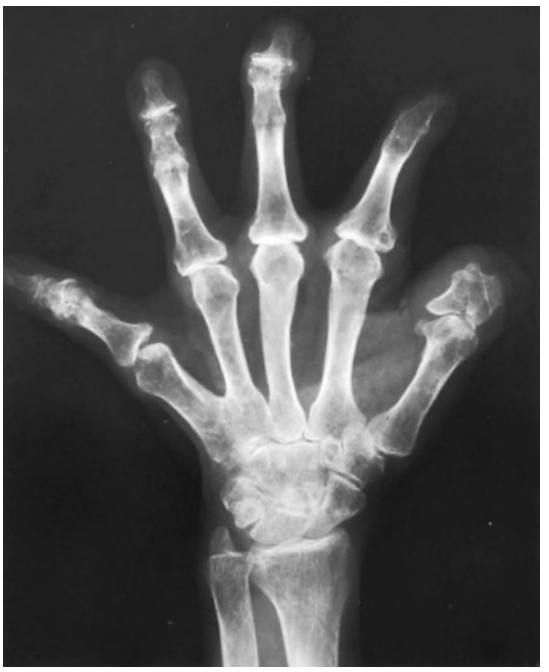
A

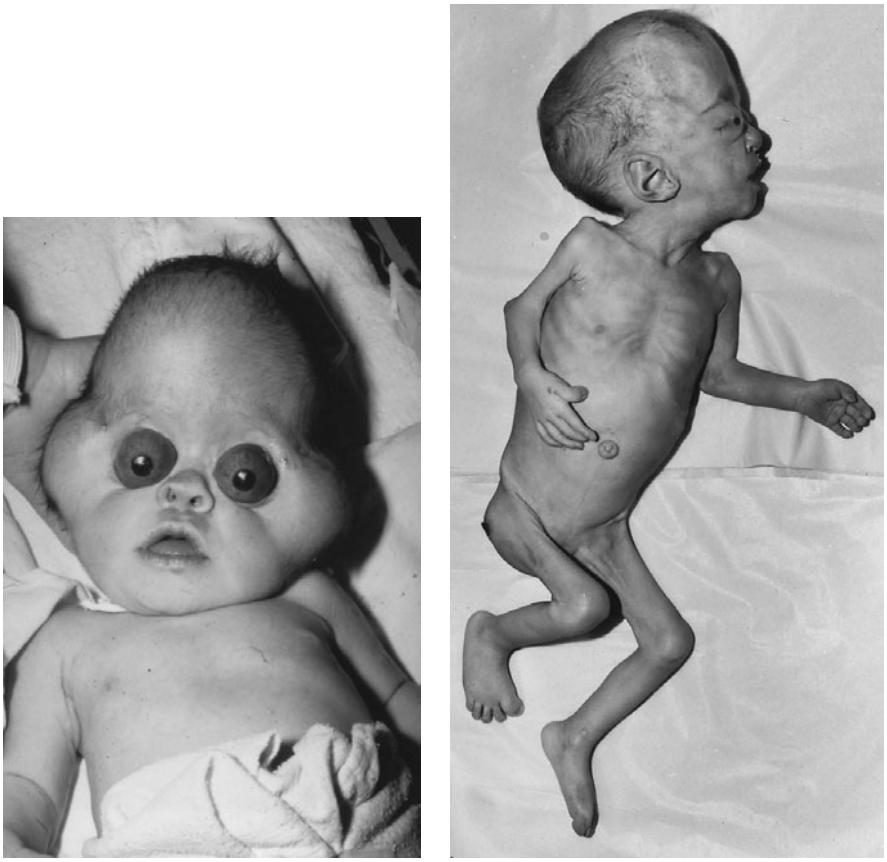
B

Fig. 14–7. *Pfeiffer syndrome, type 1.* (A) Broad radially deviated thumbs, brachydactyly, and clinodactyly of terminal phalanges. (B) Broad halluces and crooked toes.

Craniofacial features. The skull in type 1 is usually turribrachycephalic. Craniofacial asymmetry may be present in some instances. Maxillary hypoplasia and relative mandibular prognathism are observed. The nasal bridge is depressed. Hypertelorism, downslanting palpebral fissures, ocular proptosis, and strabismus are common (7,37,43) (Fig. 14–6).

Fig. 14–8. *Pfeiffer syndrome, type 1.* Radiograph showing malformed fused phalanges of thumbs, brachymesophalangy, symphalangism, fusion of proximal ends of fourth and fifth metacarpals.





A B

Fig. 14–9. *Pfeiffer syndrome*. (A) *Type 2*. Note cloverleaf skull and severe ocular proptosis. (B) *Type 3*. Premature synostosis of coronal suture. Note severe proptosis, hypoplastic supraoribtal ridges, and malar eminences, fixed hypertension of cervical spine, ankylosis of elbows, and pectus excavatum. Note broad thumb and great toes. (From MM Cohen Jr, Am J Med Genet 45:300, 1993.)

The nose may be beaked. The palate is highly arched, the alveolar ridges are broad, and teeth are crowded (7). Some affected individuals are fair and have prominent scalp veins. Natal teeth have been documented in type 3 Pfeiffer syndrome (2).

Central nervous system. Distortion ventriculomegaly, midline calvarial defect, progressive hydrocephalus, and cerebellar herniation are commonly encountered. Progressive hydrocephalus is found more frequently with Pfeiffer syndrome and Crouzon syndrome than with Apert syndrome (10,30). Central nervous system involvement occurs with much higher frequency in type 2 and type 3 patients than in type 1 patients (8,10). Gosain et al (15) reported morbidity and outcome of elevated intracranial pressure in patients with Pfeiffer syndrome. Mortality has been reported by Gosain et al (15) and Moore et al (29).

Hands and feet. The thumbs and great toes are broad (Fig. 14–7), usually with varus deformity (37). Mild soft tissue syndactyly may especially involve digits 2 and 3 and sometimes digits 3 and 4 of both hands and feet (7,37). Partial soft tissue syndactyly between toes 1 and 2 has also been reported (3,7,55). Brachydactyly may be observed and, in some cases, syndactyly is absent (7). Clinodactyly has also been noted (7,26,43).

Brachymesophalangy of both hands and feet is frequently present. Middle phalanges may be absent in some cases. The distal phalanx of the great toe is broad, and the proximal phalanx malformed. The first metatarsal is broad, may be shortened, and may be duplicated in some instances (7,26,27,37).

Accessory epiphyses in the first and second metatarsals and double ossification centers in the proximal phalanx of the great toe have been reported. Partial duplication of the great toe may be observed occasionally. Symphalangism of both hands and feet has been reported. Fusion of carpals and tarsals, in some instances involving the proximal ends of the metacarpals and metatarsals, respectively, has also been noted (7,27,36,55) (Fig. 14–8).

Other findings. Fused cervical vertebras and lumbar vertebras have been described (17,31). Shortened humerus, cubitus valgus, radiohumeral and radioulnar synostosis, abnormalities of the pelvis, coxa valga, and talipes calcaneovarus have been reported occasionally (7,10,27,43). Other abnormalities have included choanal stenosis, solid cartilaginous trachea, ventricular septal defect, patent ductus arteriosus, pyloric stenosis, umbilical hernia, malpositioned or imperforate anus, bifid scrotum, cryptorchidism, widely spaced nipples, ptosis of eyelids, corectopia, scleralization of the cornea, optic nerve hypoplasia, preauricular tag, absent external auditory canals, hearing deficit, bifid uvula, supernumerary teeth, and gingival hypertrophy (3,7,10,11,14,19,27,33,34, 43,49,51).

Differential diagnosis. Pfeiffer syndrome should be distinguished from *Apert syndrome*, *Crouzon syndrome*, *Saethre-Chotzen syndrome*, and *Jackson-Weiss syndrome*. Sporadic cases of Pfeiffer syndrome with coincidental stub thumb of normal thickness in the mother have been noted (21,39). Winter (54) suggested that several cases of Pfeiffer syndrome with prune belly (5,6,13) should be grouped as a separate syndrome, the Eaton-Bracero syndrome. However, Cohen and Barone (9) prefer to keep them in type 3, at least temporarily.

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FGFR3-associated coronal synostosis syndrome (Muenke craniosynostosis)

Muenke et al (10) and Bellus et al (2) reported a unique point mutation on fibroblast growth factor receptor (FGFR3) causing a newly recognized autosomal dominant condition characterized by unilateral or bilateral coronal synostosis, a variety of minor anomalies, and remarkably variable expressivity. Other cases with this mutation have been described (4–6, 9,11,12).

Genetics. The identified mutation, FGFR3 Pro250Arg (2,9,11) may be the highest transversion rate currently known in the human genome (9) (Fig. 14–1). Muenke et al (10) reported 61 cases; autosomal dominant inheritance was observed in 12 of the families. Expressivity is extremely variable, but it is more often expressed in females (8). Golla et al (2) described a patient with cloverleaf skull; another affected member of the family had unilateral coronal synostosis with marked facial asymmetry. Muenke et al (10) described two sibs with bilateral coronal synostosis; the affected father had macrocephaly only. Gripp et al (6) found four mutations (Pro250Arg) among 37 sporadic cases of unicoronal synostosis (11%). It is particularly noteworthy that three fathers of unicoronal probands tested positive for the mutation themselves. None of the three fathers had craniosynostosis and had never come to medical attention previously. They were unaware of their 50% risk of passing the mutation on to their other children. Nonpenetrance was also found by Robin et al (12). It must be emphasized that the 50% recurrence risk is for the mutation per se, not for the phenotype. The prevalence of the abnormal phenotype in mutation carriers is unknown at present.

Craniofacial features. The craniofacial phenotype is variable. Coronal synostosis, either unilateral or bilateral, is common. Some patients have macrocephaly without craniosynostosis. One of us (MMC) observed a patient with macrocephaly and unicoronal synostosis. Midface hypoplasia, downslanting palpebral fissures, ptosis of the eyelids, and highly

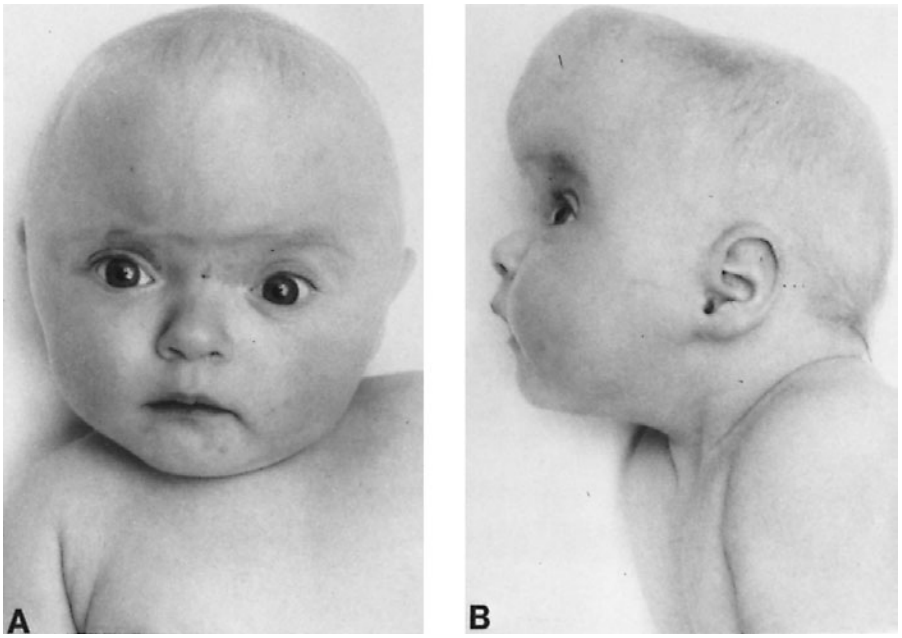

Fig. 14–10. *FGFR associated coronal synostosis (Muenke craniosynostosis).* (A,B) Unusual head form and facial asymmetry. (From IA Glass et al, Clin Dysmorphol 3:215, 1994.)

arched palate have been documented (10) (Fig. 14–10). Cloverleaf skull has been noted (4).

Performance. Developmental delay or learning disabilities have been found in 37% of patients (10). This is not related to craniosynostosis per se, but is part of the clinical spectrum in both familial and sporadic cases (11).

Other clinical findings. Brachydactyly has been observed in both the hands and the feet in some cases. Broad halluces have also been noted. However, medial or lateral deviation does not occur.

Radiographic findings. Thimble-like middle phalanges are particularly common in the hands. Cone-shaped epiphyses have been found in both hands and feet. Carpal and tarsal coalitions have been noted (5,10) (Fig. 14–11).

Diagnosis. All patients with nonsyndromic coronal synostosis, either bilateral or unilateral, should be screened for the Pro250Arg mutation in FGFR3. This is true for both sporadic and familial cases of coronal synostosis. Sporadic cases that test positive also require testing of the phenotypically normal parents. Some patients have macrocephaly without craniosynostosis. Patients with a mild Saethre-Chotzen-like phenotype or a Pfeiffer-like phenotype, who are FGFR1, FGFR2, and TWIST negative, should be screened for this particular mutation.

Adelaide type craniosynostosis (7), earlier reported as Jackson-Weiss syndrome (1) has been shown to have the Pro250Arg mutation in FGFR3 (10). The craniosynostosis-brachydactyly syndrome (3) has also been found to have this mutation (10). The large kindred of craniosynostosis suggestive of Saethre-Chotzen syndrome that did not map to 7p21 (13) also has this mutation (4).

Prenatal diagnosis. For molecularly proven families or sporadic cases, prenatal diagnosis is possible by chorionic villus sampling or amniocentesis.

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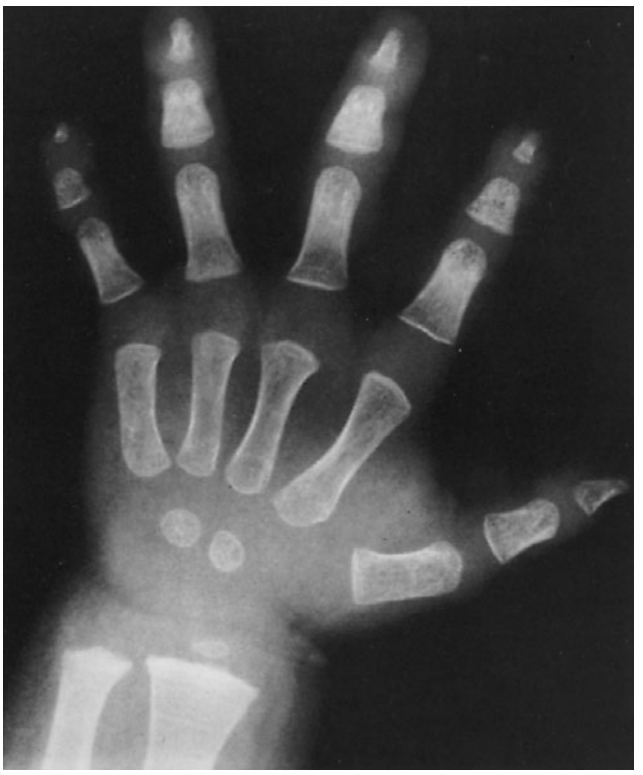
Fig. 14–11. *FGFR associated coronal synostosis (Muenke craniosynostosis).* Note enlarged middle phalanges with thimble form. (From IA Glass et al, Clin Dysmorphol 3:215, 1994.)



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Saethre-Chotzen syndrome

Saethre-Chotzen syndrome is characterized by a broad and variable pattern of malformations, including craniosynostosis, low-set frontal hairline, facial asymmetry, ptosis of eyelids, deviated nasal septum, brachydactyly, partial soft tissue syndactyly, especially of the second and third fingers, and various skeletal anomalies. Autosomal dominant inheritance is evident with a high degree of penetrance and variable expressivity (3,4,6,7,14,27,28). Incomplete penetrance was documented by Carter et al (6). A nice review of the present molecular status is that of Zackai and Stolle (45).

First recognized as an entity by Saethre (39) in 1931 and by Chotzen (7) in 1932, many authors have since reported affected families (1–4,6,7,11, 13,14,17,19,20,25–28,30,31,38,42). The most extensive early discussion and delineation of the syndrome was published by Pantke et al (28).

Saethre-Chotzen syndrome is caused by mutations in the *TWIST* gene located at 7p21 (5,23,24,32). The *TWIST* gene codes for a transcription factor containing a basic helix-loop-helix motif. Nonsense, duplication, missense, and frameshift mutations have been detected (9,16,29,35). Most mutations truncate the TWIST protein, resulting in haploinsufficiency. Loss-of-function may also be caused by missense mutations. Johnson et al (18) identified microdeletions of chromosome band 7p21.1 that are not detectable by conventional cytogenetic analysis unless a translocation is present. Balanced translocation has been reported (32,36,41,43). Both protein degradation and cellular mislocalization are causative mechanisms (9a).

Craniofacial features. Craniosynostosis is a facultative rather than an obligatory abnormality (1,14). When present, the time of onset and degree of craniosynostosis are quite variable. Brachycephaly or acrocephaly with coronal sutural synostosis is frequently observed, and involvement is often asymmetric, producing plagiocephaly and facial asymmetry (14) (Fig. 14–12). Trigonocephaly has also been observed (8,17). Cloverleaf skull was noted in one instance (RD Clark, personal communication, 1994). Frontal bossing, parietal bossing, and flattened occiput have been reported in various cases. Large late-closing fontanelles, large parietal foramina, ossification defects of the calvaria, and enlargement of the sella turcica have also been recorded (44). Calvarial hyperostosis was found in one family (1,7,14,28).

Low-set frontal hairline is commonly observed. Ptosis of eyelids, ocular hypertelorism, and strabismus are common. Occasionally, the forehead may be protuberant in association with metopic synostosis and hypotelorism. Blepharophimosis is evident in some cases. Tear duct stenosis may be a feature. Low-frequency findings have included epicanthic folds, optic atrophy, downslanting palpebral fissures, irregular eyelid margins, and sparse eyebrows medially with heavy eyebrows laterally (3,7,14,28).

The ears may be low-set, small, posteriorly angulated, or may have folded helices or prominent antihelical crura. Mild conductive hearing loss is common (10,28). Congenital atresia of the external auditory meatus has been documented (10).

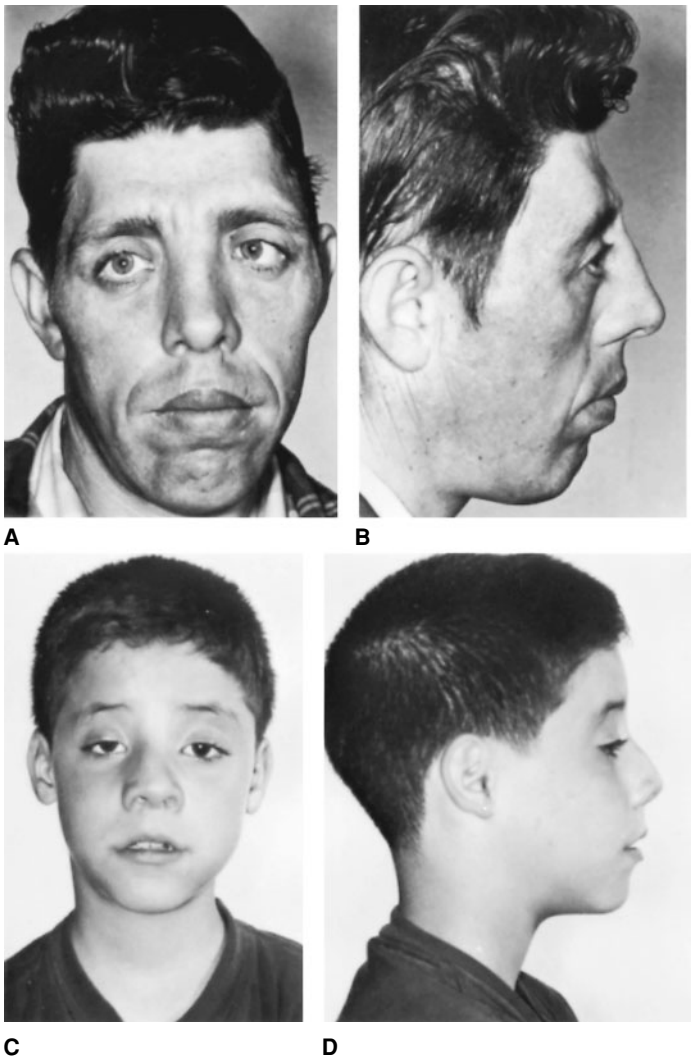

Fig. 14–12. *Saethre-Chotzen syndrome*. (A,B) Acrocephaly, facial asymmetry, low hairline. (C,D) Son of man seen in A and B. Note eyelid ptosis.

The nasofrontal angle may be flattened in some instances. Maxillary hypoplasia with relative mandibular prognathism may be evident. The midface may be broad and flat in some cases. Deviation of the nasal septum is often found (14,28).

Oral anomalies include narrow or highly arched palate, cleft palate on occasion, malocclusion, supernumerary teeth, enamel hypoplasia, and other dental defects (3,14,28).

Performance. Intelligence is usually normal. However, mild-to-moderate mental deficiency has been observed in a number of cases (3,7). Significant learning difficulties were found in the patients with microdeletions reported by Johnson et al (18). Neonatal seizures, epilepsy, and schizophrenia have also been noted (3,7,10,39).

Hands and feet. Some degree of brachydactyly may be observed (28). Partial cutaneous syndactyly is present in some instances, most frequently between the second and third fingers, but sometimes extending from the second to fourth fingers (3,7,26,39) (Fig. 14–13). Clinodactyly, especially of the fifth finger, has been found in some cases (1,14). The distal phalanges may be hypoplastic, and, on occasion, finger-like thumbs have been noted (14). Dermatoglyphic findings have included single palmar creases, distally placed axial triradii, increased frequency of thenar and hypothenar patterns, increased frequency of fingertip arch patterns, and low total ridge count (1,3,14,28).

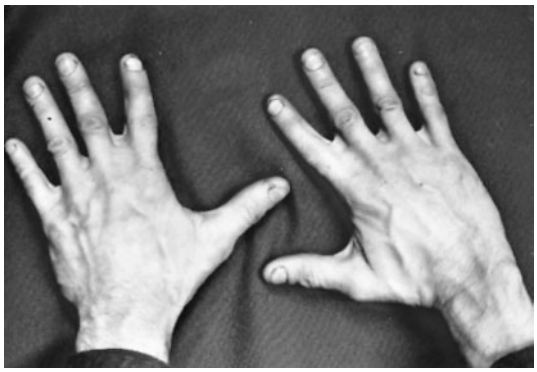

Fig. 14–13. *Saethre-Chotzen syndrome*. Soft tissue syndactyly between second and third fingers. (From CS Bartsocas et al, J Pediatr 77:267, 1967).

Partial cutaneous syndactyly between the second and third toes, but occasionally involving other toes, has been reported (3,7,22,39). Broad great toes and hallux valgus have been noted in some instances (14,28,39) and dorsiflexion of the fourth toes has been observed (3).

Radiographic features have been discussed by Anderson et al (2). The most common finding was an enlarged epiphysis of the distal phalanx of the thumb. Less commonly observed were pseudoepiphyses of the metacarpals. Bifid distal phalanges have been noted in some patients (19,22). Partial duplication of the first metatarsal has also been recorded (22).

Other findings. Short stature has been documented in some instances (1,28). Defects of the cervical and lumbar spine have been reported by several authors (7,28,39). Radioulnar synostosis was noted by Bartsocas et al (3) and short fourth metacarpals were reported by Aase and Smith (1). Friedman et al (14) documented short clavicles, limitation of motion at the elbows, small ilia, large ischia, and coxa valga. Legius et al (22) noted fused cervical vertebrae. Other findings have included cryptorchidism, renal anomalies, congenital cardiac defects, and imperforate anus (1,3,7,10,28). Escobar et al (11) reported a case with congenital adrenal hyperplasia. McKeen et al (26) observed an affected family in which multiple malignancies occurred, including nasopharyngeal carcinoma, Hodgkin's disease, and embryonal cell carcinoma of the testis. However, the Saethre-Chotzen syndrome and the familial malignancies were probably inherited independently. Etzioni et al (12) described a patient with Saethre-Chotzen syndrome and defective neutrophil chemotaxis. Boeck et al (4a) noted the co-occurrence of hyper IgE (Job) syndrome and Saethre-Chotzen syndrome. Russo et al (38) reported a case with renal tubular dysgenesis, which probably occurred coincidentally.

Differential diagnosis. Saethre-Chotzen syndrome is frequently confused with simple craniosynostosis. It is important to recognize that few anomalies in Saethre-Chotzen syndrome are obligatory and individual patients may not necessarily have craniosynostosis (14) or syndactyly or ptosis of the eyelids or facial asymmetry. The variability of expression found in Saethre-Chotzen syndrome can make clinical diagnosis difficult in some cases (29).

A patient with presumed Baller-Gerold syndrome with a *TWIST* mutation (15) had facial features of Saethre-Chotzen syndrome: craniosynostosis, brachycephaly, ocular hypertelorism, occipital ossification defect, and hallux valgus. The upper limb reduction defect was unilateral, which is not found in Baller-Gerold syndrome; limb defects are bilaterally symmetric. The father who also harbored the *TWIST* mutation had facial asymmetry and hallux valgus. Two conditions once thought to constitute separate nosologic entities—auralcephalosyndactyly (21) and Robinow-Sorauf syndrome seem to be examples of Saethre-Chotzen syndrome (22).

Diagnostic confirmation of Saethre-Chotzen syndrome is possible by identifying a mutation in the *TWIST* gene. Saethre-Chotzen-like patients who are *TWIST* negative should be tested for *FGFR3* Pro250Arg (*Muenke craniosynostosis*).

Laboratory aids. Fluorescent in situ hybridization (FISH) can be used to detect large deletions, but Gripp et al (15a), employing Southern blot analysis with a PCR generated probe, has improved the analytic methods of Johnson et al (18).

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Carpenter syndrome (acrocephalopolysyndactyly)

Carpenter syndrome is characterized by craniosynostosis, commonly but not always preaxial polysyndactyly of the feet, short fingers with clinodactyly, and variable soft tissue syndactyly, sometimes postaxial polydactyly, and other abnormalities, such as congenital heart defects, short stature, obesity, and mental deficiency (Figs. 14–14 to 14–16). First described by Carpenter in 1901 (3) and 1909 (4), the syndrome was not recognized as a distinct nosologic and genetic entity until Temtamy's report (35) in 1966. Extensive reviews are available (5–7), the most complete being that of Cohen andMacLean (8). Approximately 45 cases have been recorded to date (1–6,9–12,14,17,30,33–37).

Affected sibs (3–5,11,14,15,19,22,24,25) have been reported, and sporadic occurrences (6,9–11,20,23,33–37) have been described. Consanguinity was noted in the case recorded by Der Kaloustian et al (9) and may also have been present in the sibs described by Rudert (28). Carpenter syndrome clearly has autosomal recessive inheritance.

Height is usually below the 25th centile, but in some instances may be above the 60th centile. Weight is often above average. Obesity of the trunk, proximal limbs, face, and neck is common (35).

Craniofacial features. Craniosynostosis usually involves the sagittal and lambdoid sutures first, the coronal being last to close. The calvaria may be grossly malformed in some instances, but variable in shape

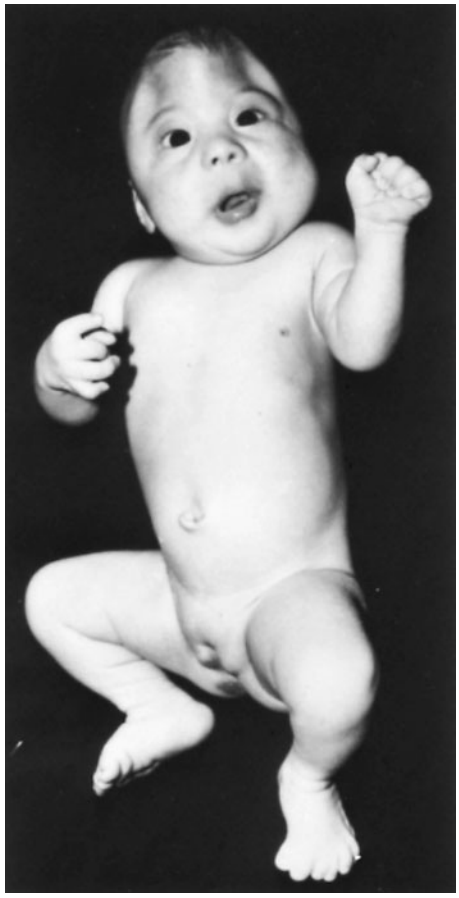
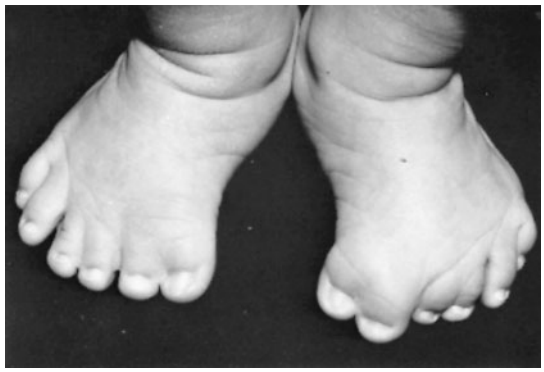


Fig. 14–14. *Carpenter syndrome*. Asymmetric tower-shaped skull, short neck, soft tissue syndactyly of third and fourth digits. (From V Der Kaloustian et al, Am J Dis Child 124:716, 1972.

(Fig. 14–14). In many cases, unilateral involvement of the coronal or lambdoid suture produces marked cranial asymmetry (6,8). Wormian bones were noted in the anterior fontanel in one case (20). The cloverleaf skull anomaly has been observed in association with Carpenter syndrome (6). One instance of otherwise classic Carpenter syndrome did not exhibit craniosynostosis (8). Dystopia canthorum and mildly downslanting palpebral fissures are observed. Epicanthic folds, microcornea, corneal opacity, slight optic atrophy, and blurring of the disc margins have been reported in some instances (3,4,18,35). The ears appear low set (33,35) and the neck is short. Preauricular fistulas have been

Fig. 14–15. *Carpenter syndrome*. General webbing as well as bilateral polysyndactyly of halluces. (From V Der Kaloustian et al, Am J Dis Child 124:716, 1972).



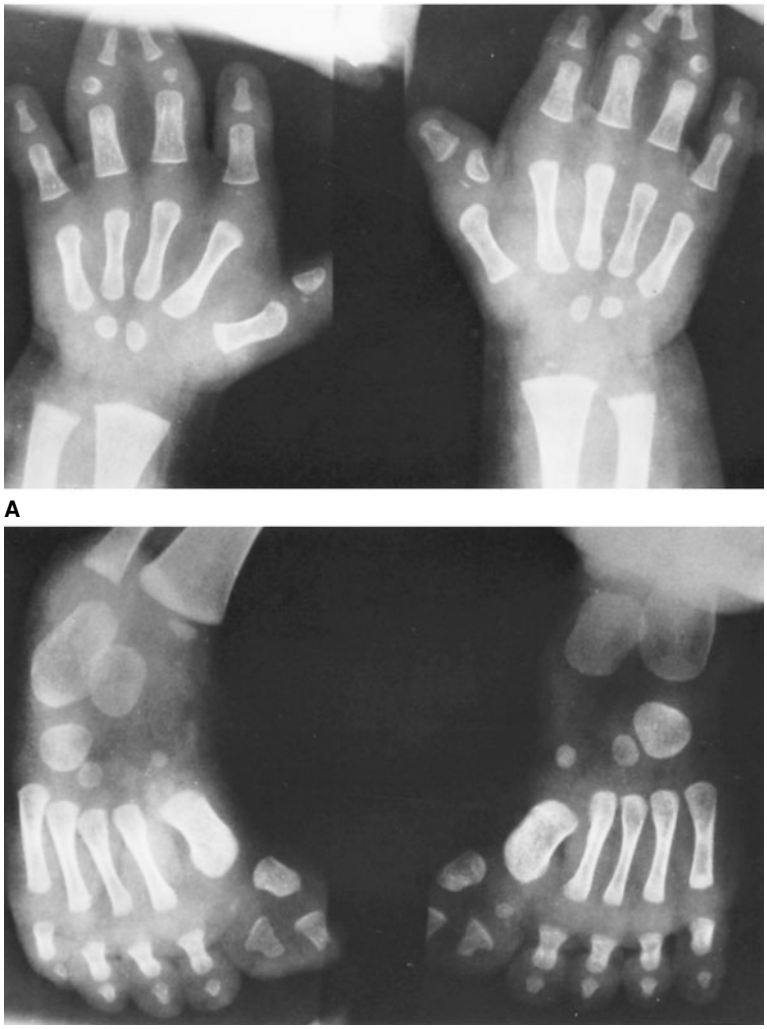


Fig. 14–16. *Carpenter syndrome*. (A,B) Note especially brachymesophalangy and agenesis of middle phalanges together with soft tissue syndactyly and clinodactyly of the third and fourth digits; also polysyndactyly of halluces, varus deformity, broadening of the first metatarsal, and absent middle phalanges. (From H Schönenberg and E Scheidhauser, Monatsschr Kinderheilkd 114:322, 1966).

noted (37). The mandible may be somewhat small, and the palate may be narrow or highly arched (8).

Performance and central nervous system. Mental deficiency has been a feature in many patients with Carpenter syndrome, but normal intelligence is also encountered (5,11,13,16,17,26,31,32,34,38). Warkany's patient was estimated to have an IQ of 70 (29). Early craniectomy may possibly prevent mental deficiency. However, normal intelligence has been observed without neurosurgical intervention. Furthermore, mental deficiency has been noted despite early craniectomy, suggesting a primary brain abnormality in at least some cases of Carpenter syndrome.

Hands and feet. The hands are short and the fingers stubby. Marked soft tissue syndactyly may be present, especially between the third and fourth fingers with less marked involvement between other fingers. In some cases, minimal or no syndactyly may be evident. Clinodactyly of the fingers, single flexion crease, and sometimes postaxial polydactyly may be observed. Radiographically, brachymesophalangy, or agenesis of the middle phalanges is evident (Fig. 14–16). A tongue-shaped projection may extend from the radial side of the epiphysis of the proximal phalanx of the second finger. Two ossification centers in the proximal phalanx of the thumbs have been reported (35,37).

Abnormalities of the feet include bilateral varus deformities and commonly but not always preaxial polydactyly with duplication of the second toes or halluces. Soft tissue syndactyly may be observed between the toes, and only two phalanges are present in each toe (35) (Fig. 14–15).

Cardiovascular anomalies. Congenital heart defects have been reported in approximately 33%. Anomalies have included VSD, ASD, PDA, pulmonic stenosis, and tetralogy of Fallot. Transposition of the great vessels and anomalous duplication of the superior vena cava have also been noted (7,8).

Other abnormalities. Genua valga and lateral displacement of the patellae are common. Other skeletal findings have included decreased hip-joint mobility, flaring of the ilia with poor development of the acetabula, coxa valga, absent coccyx, spina bifida occulta, and scoliosis (19,30,33,35). Umbilical hernia or omphalocele has been a feature in a number of cases. Other findings have included cryptorchidism, inguinal hernia, hydronephrosis, hydroureter, and accessory spleens (3,4,6,7,10,18,20,30,33,35,37).

Differential diagnosis. Carpenter syndrome is sometimes confused with *Apert syndrome, Bardet-Biedl syndrome*, and *Sakati syndrome*. The conditions known as Summitt syndrome (31,32) and Goodman syndrome or acrocephalopolysyndactyly type IV (13) represent examples of Carpenter syndrome (8,12,15). This problem is thoroughly analyzed elsewhere (8).

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Cloverleaf skull (Kleeblattschädel)

Classically, cloverleaf skull or Kleeblattschädel consists of a trilobular skull with craniosynostosis. However, the degree of severity varies and different sutures may be involved in different patients. Holtermüller and Wiedemann (25) first identified the condition in 1960 and noted several earlier cases. Over 90 cases of the subject are known (1–7, 21–65). The most extensive reviews are those of Cohen (9–16,18), and Cohen and MacLean (18). An early case was described by Vrolik (60) in 1849. Another possible early example is that of Nettleship (45) in 1887.

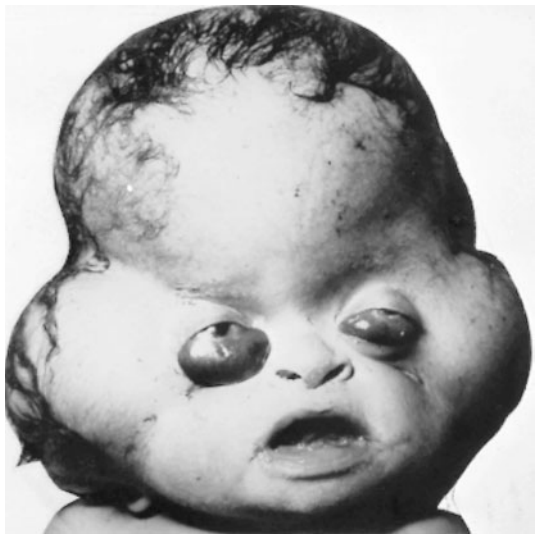
Synostosis may involve the coronal, lambdoid, and metopic sutures, with bulging of the cerebrum through an open sagittal suture or, in some cases, through open squamosal sutures. Synostosis of the sagittal and squamosal sutures with cerebral eventration through a widely patent anterior fontanel may also be observed. Finally, a trilobular skull may occur with complete synostosis of all cranial sutures in some instances or with widely patent sutures and no evidence of craniosynostosis at birth in other instances.

When cloverleaf skull is severe, the ears are displaced downward, facing the shoulders. Midface hypoplasia and relative mandibular prognathism are frequently encountered. The nasal bridge is low and, in some cases, the nose may be beak-like. Severe proptosis, hypertelorism, and downslanting palpebral fissures are common. The eyelids may fail to close, leading to corneal ulceration and clouding. Venous distention of the scleras, eyelids, periorbital areas, and scalp has been noted (2,11–15,18,24,30,31,41) (Figs. 14–17 and 14–18).

Radiographically, the skull has a trilobular contour with marked convolutional impressions and a thin, distorted vault, giving a honeycomb appearance. Synostosis and shortening of the cranial base have been reported. The posterior cranial fossa is small (4,52,64) (Fig. 14–19). In some cases, shortening of the cranial base with concomitant distortion of the hindbrain may be responsible for cerebrospinal fluid obstruction at the level of the fourth ventricle (2,31), leading to hydrocephaly, which is commonly found with cloverleaf skulls. Obstruction of the cerebral aqueduct has been demonstrated in one instance (23). Hypoplasia and malformation of orbits, sphenoid, ethmoid, nasal bones, and maxilla are common. In one case (19), the orbits and zygomatic arches were absent.

Early demise has been noted in most cases, although there have been exceptions (23,64). One patient is known to have been 14 years old (23).

Fig. 14–17. *Cloverleaf skull*. Classical trefoiling of skull. Note subluxation of eyeballs. (Courtesy of RT Guzman, Mexico City, Mexico.)



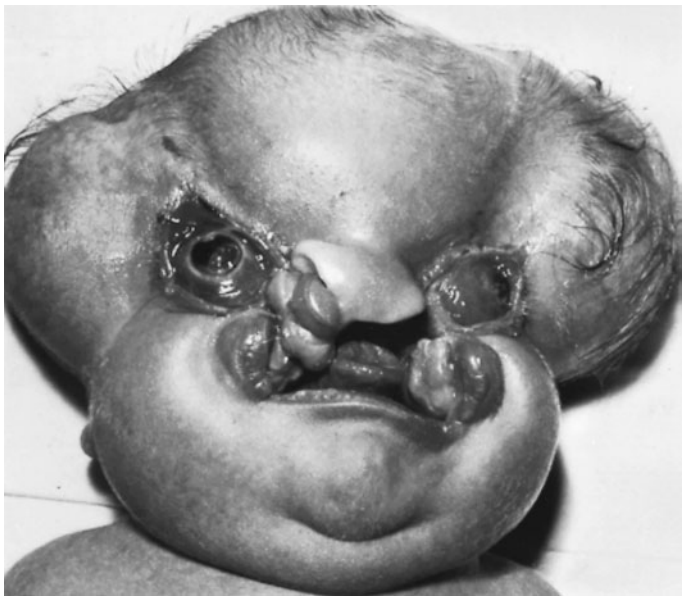
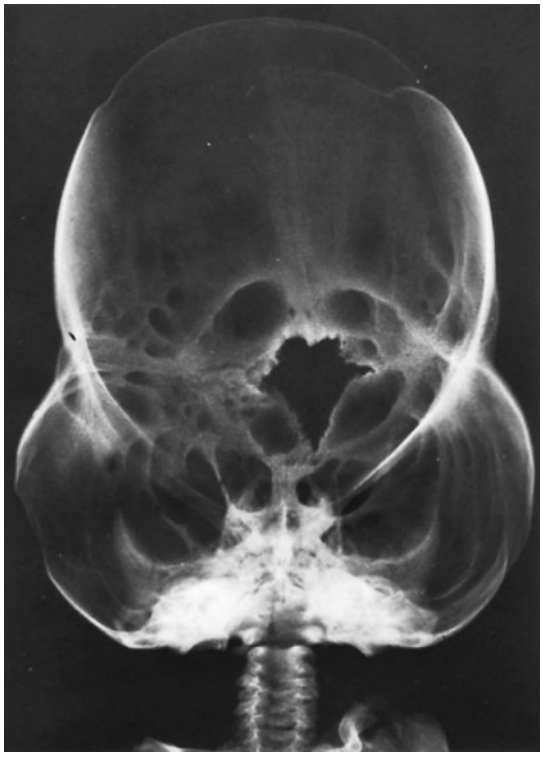


Fig. 14–18. *Cloverleaf skull*. Cloverleaf skull in infant with bilateral oblique facial clefts. Child also had intrauterine amputation of digits. (From A Schuch and HJ Pesch, Z Kinderheilkd 109:187, 1971).

Changes in skull shape were noted with age. At birth the skull was trilobular, but by 14 years of age, skull shape had changed dramatically.

As mentioned above, hydrocephaly is common (2,19,31). Psychomotor retardation (2,62), small cerebellum (2), cerebellar herniation, polymicrogyria (30), and various other brain anomalies (32) have been reported. Other findings have included iris colobomas, blindness, obstructed nasolacrimal ducts, absent external auditory canals, macrostomia, macroglossia, oblique facial clefting, cleft lip-palate, bifid uvula, highly arched palate, natal teeth, malocclusion, PDA, ASD, bicuspid aortic valve, common mesentery, absent lesser omentum, hypoplastic gallbladder, single umbilical artery, and omphalocele (2,10,18,19,20,23,30).

Fig. 14–19. *Cloverleaf skull*. Radiograph showing classic trilobular skull. (From MW Partington et al, Arch Dis Child 46:656, 1971.)



Cloverleaf skull is known to be both etiologically and pathogenetically heterogeneous (9,12,14,18,30). Kokich and co-workers (38) demonstrated heterogeneity at the anatomic and histologic levels in two different cloverleaf specimens. Although both exhibited premature fusion of the coronal, sagittal, and lambdoid sutures, the interrelationships and spacial orientation of their respective articulations and skeletal components differed markedly.

Etiologic heterogeneity has been demonstrated repeatedly (9,11–18). Cloverleaf skull is nonspecific—that is, the condition may be observed as an isolated anomaly or together with other anomalies making up various syndromes known to have different causes. Diagnosis is made on the basis of the overall pattern of anomalies. Syndromes associated with the cloverleaf skull anomaly include amniotic rupture sequence (57,63), Apert syndrome (51), Beare-Stevenson cutis gyrata syndrome (28), Carpenter syndrome (9), Crouzon syndrome (27,58), COH syndrome (18), osteoglophonic dysplasia (36), dup 4p (50), dup(13q) syndrome (42), dup(15q) syndrome (47), type 2 Pfeiffer syndrome (18,20,30,62), Saethre-Chotzen syndrome (8), Say-Poznanski syndrome (56), type 2 thanatophoric dysplasia (18,40,46), rarely type 1 thanatophoric dysplasia (18), Cumming syndrome (49), FGFR3-associated coronal synostosis syndrome (25), Loschge syndrome (43,44), osteocraniostenosis (59), Shprintzen-Goldberg syndrome (53), and Boston type craniosynostosis (61). Cloverleaf skull with "campomelic dysplasia of the craniosynostosis type" (37) may represent an example of Antley-Bixler syndrome. Cloverleaf skull has been reported with hypochondroplasia (3). Although craniosynostosis was evident, a rare finding, we cannot agree that there was cloverleaf skull.

It has been estimated that approximately 40% (n = 51) of all cloverleaf skull malformation cases represent thanatophoric dysplasia and about 20% represent Pfeiffer syndrome (30). The great variety of other malformations reported in association with the cloverleaf skull anomaly suggests that several unknown genesis syndromes in this group may become further delineated in the future (10,12,18). Ultrasonographic evaluation of affected fetuses may permit correct antenatal diagnosis of cloverleaf skull (4,6).

References [Cloverleaf skull (Kleeblattschädel)]

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Chapter 15
Syndromes with Craniosynostosis: Miscellaneous Syndromes

Acrocephalospondylosyndactyly

Wells et al (277), in 1990, described a male infant with craniosynostosis, acrobrachycephaly, syndactyly of all extremities, midface hypoplasia, parrot-beak nose, exophthalmos, hypertelorism, exotropia, huge pinnae, and short upper lip. The hands and feet resembled those of Apert syndrome. In addition, there were block thoracic vertebrae with progressive loss of intervertebral discs and platyspondyly. The thin posterior ribs had a fan-like configuration.

Other extremity anomalies included: flared metaphyseal ends of humeri, dislocated radii with immobile elbows, a tail-like structure, and a solid cartilaginous tracheal wall.

The syndrome may represent a severe example of *Apert syndrome*, but molecular delineation remains unknown.

Acrocraniofacial dysostosis

Kaplan et al (139) reported an oculo-oto-palato-digital syndrome in two sisters. Features consisted of short stature, craniosynostosis involving the coronal suture, ocular hypertelorism, ocular proptosis, ptosis of the eyelids, downslanting palpebral fissures, high nasal bridge, anteverted nostrils, short philtrum, cleft palate, micrognathia, mixed hearing loss, proximally placed thumbs and great toes, bulbous digits, metatarsus adductus, and other abnormalities (Fig. 15–1). Consanguinity was noted, strongly suggesting autosomal recessive inheritance.

Antley-Bixler syndrome

Characteristic features of Antley-Bixler syndrome are craniosynostosis, dysplastic ears, arachnodactyly, radiohumeral synostosis, femoral bowing, and joint contractures. Antley and Bixler (11) reported a case in 1975 and Lacheretz et al (155) reported one a year earlier. Over 30 cases have been observed to date (10a,11,12,21,23,34,60,66–68,79,113, 116,124,123,144,155,162,175,204,216,222,224,234,241,280,283). Extensive reviews are those of Crisponi et al (60), Hassell and Butler (113), and Poddevin et al (207). The syndrome has also been known as trapezoidocephaly-multiple synostosis syndrome (11), multisynostotic osteodysgenesis (68), and acrocephalosynankie (6,155,273). Cohen coined the term Antley-Bixler syndrome in 1977 (41) and used it again in 1979 (44).

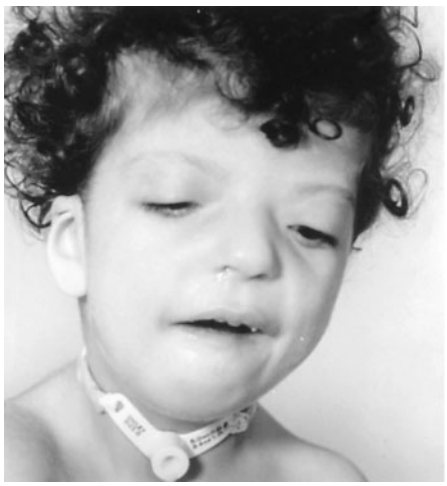
The syndrome has been observed in sibs four times (162,175, 241,280) and consanguinity has been noted in several instances (79,155, 175,257,283). Thus, autosomal recessive inheritance is supported. Reardon et al (214) have noted that 7 of 16 patients had abnormal steroid biogenesis, and R Kelley (personal communication, 2000) noted a block at the level of lanosterol 14-alpha-demethylase, the site of action of the azole antifungals that cause a phenocopy (vide infra). Virilization of a female due to disturbed androgen metabolism has been noted (226a).

Prenatal diagnosis (134,234) has been made by ultrasound, with immobility and flexion at the elbows being essential findings. Polyhydramnios has been noted as a feature of pregnancy.

Respiratory obstruction leads to early demise in about 55% (11,68, 222,224). However, there have been long term survivors. The prognosis for intellectual development may be reasonable in some cases with appropriate multidisciplinary management (175).

Craniosynostosis usually involves the coronal and lambdoid sutures, resulting in a brachycephalic head shape (Fig. 15–2). When viewed from the top, head shape may be trapezoidal. Craniofacial features include large anterior fontanelle, frontal bossing, ocular proptosis, low nasal bridge, large nose, midface hypoplasia, choanal atresia or stenosis, and

Fig. 15–1. *Acrocraniofacial dysostosis*. (A) One of two sisters with acrocephaly, hypertelorism, shallow orbits, ptosis, downslanting palpebral fissures, dysmorphic pinnae. Both had cleft palate and pectus excavatum. (B) Feet of one sib showing metatarsus adductus and fingerlike halluces. (C) Radiograph of feet of older sib showing metatarsus adductus and severe hypoplasia of first metatarsal and digital phalanges. (A–C from P Kaplan et al, Am J Med Genet 29:95, 1988.)



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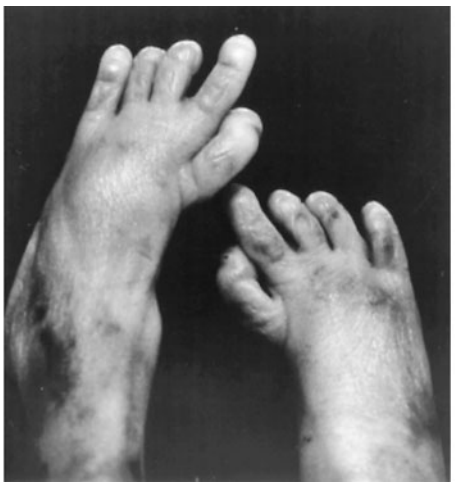

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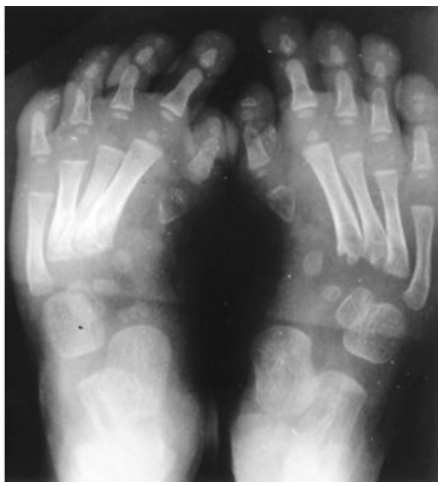

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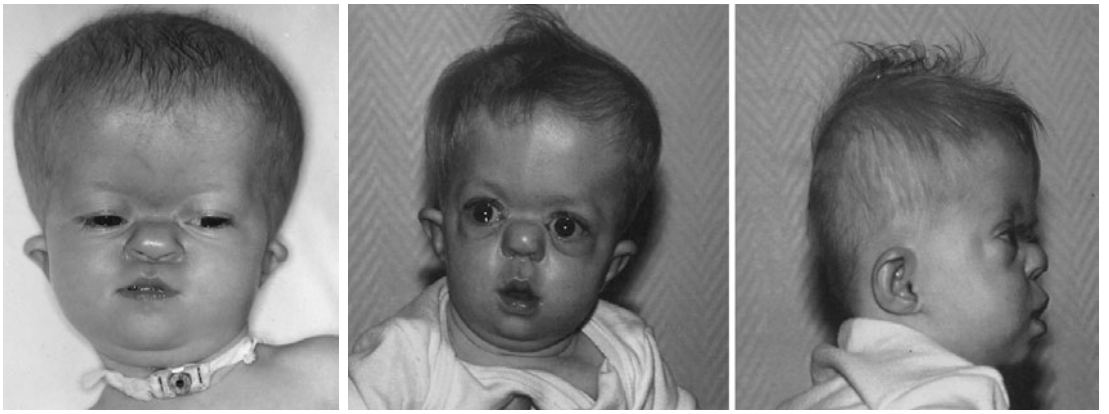


A B C

Fig. 15–2. *Antley-Bixler syndrome*. (A) Brachycephaly, biparietal bossing, malformed ears, and low nasal bridge. (B,C) Compare with child in A. (B,C from L Bottero et al, Ann Chir Plast Esthet 42:48, 1997.)

low-set protruding ears (11,68) (Table 15–1). Arnold-Chiari malformation has been found in one case (34a).

Trunk abnormalities consist of a tower-shaped rib cage, gracile ribs, narrow pelvis, vertically slanted ilia, limited hip abduction, and/or hip dislocation. Limb anomalies include radiohumeral synostosis, joint contractures, medially bowed ulnas, synostosis of carpal bones, arachnodactyly with camptodactyly, femoral bowing, femoral fractures, synostosis of tarsal bones, rocker-bottom feet, and camptodactyly of the toes (11,12,68,222,224,241) (Fig. 15–3). Crisponi et al (60) reported a case with radioulnar synostosis and Chabchoub et al (34) without radiohumeral synostosis.

Congenital heart defects and urogenital anomalies (absent and/or ectopic kidney, duplication of kidney and ureter, dilated ureter, hypoplasia of labia majora, fused labia minora, lower vaginal atresia and/or urogenital sinus and clitoromegaly) have been observed in some instances. Other abnormalities include atresia of the external auditory canals, absent nipples, imperforate anus, vertebral anomalies, and lumbar meningomyelocele (113,116,222,241,283). Feigin et al (79) reported a patient who had, in addition, esophageal atresia and trisomy 21 syndrome. An increased frequency of fingertip whorl patterns has been noted (216).

Table 15–1. *Antley-Bixler syndrome*

Findings	%
Craniofacial	
Brachycephaly/trapezoidocephaly	100
Frontal bossing	100
Proptosis	100
Deep nasal bridge	100
Midface hypoplasia	100
Dysplastic ears	100
Pear-shaped nose	100
Small mouth	100
Long philtrum	90
Wide anterior fontanel	90
Choanal atresia	60
Stenotic ear canals	40
Skeletal	
Long fingers, long palm	85
Femoral bowing	100
Radiohumeral synostosis	100
Neonatal fractures	100
Multiple joint contractures	90
Abnormal toe position	70
Rocker-bottom feet	70
Urogenital	
Renal malformation	50
Vaginal atresia	50
Fused labia minora	30
Hypoplastic labia majora	30

(Adapted from LF Escobar et al, Am J Med Genet 29:829, 1988.)

Differential diagnosis. Bowing of long bones is also found with *campomelic syndrome*. Keutel (143) reported two male sibs with radiohumeral synostosis, mesomelia, microcephaly, patent sutures, downslanting palpebral fissures, broad nasal bridge, micrognathia, dysplastic ears, micropenis, and cryptorchidism. Consanguinity was established.

Chun et al (39) reported a patient with presumed Antley-Bixler syndrome. The patient had very few of the anomalies of the syndrome but had several that were at variance with it. Clearly, the patient does not have Antley-Bixler syndrome. Chun et al (39) found a mutation on FGFR2 (Ser351Cys). Gripp et al (106) and Palleyn et al (212a) reported two other patients with the same mutation.

Fluconazole embryopathy resembles Antley-Bixler syndrome (4a, 164a,206).

Pincus et al (206) reported the otolaryngologic manifestations of Antley-Bixler syndrome. One photograph (their Figure 2) shows clear-cut Apert syndrome with mitten syndactyly. The patient also had radiohumeral synostosis, which can be found in Apert syndrome.

Iida et al (127) reported a patient with many of the features of Antley-Bixler syndrome, but radiohumeral synostosis was not observed and Iida's patient had cleft soft palate.

Armendares syndrome

Armendares and co-workers (15,16) described a heritable syndrome consisting of growth deficiency, craniosynostosis, retinitis pigmentosa, and other anomalies. Bone age was delayed, but intelligence was normal. Craniosynostosis involved both the coronal and sagittal sutures. Craniofacial features included microcephaly, cranial asymmetry, small face, scant eyebrows, short obtuse nose, micrognathia, highly arched palate, and either prominent or malformed auricles. Ocular findings included ptosis of the eyelids, epicanthic folds, primary telecanthus, downslanting palpebral fissures, diminution of visual acuity, irregular dispersion of the retinal pigment resulting in atypical retinitis pigmentosa, constriction of the visual fields, and narrowing of the retinal arteries. Limb anomalies consisted of short fifth fingers with clinodactyly, wide fourth interdigital spaces, and single palmar creases.

The syndrome was reported in three male sibs from a Mexican mestizo family, and consanguinity was evident. Thus, autosomal recessive inheritance seems likely. However, X-linked recessive inheritance cannot be ruled out at present. The reporting of other affected families should resolve the mode of inheritance.

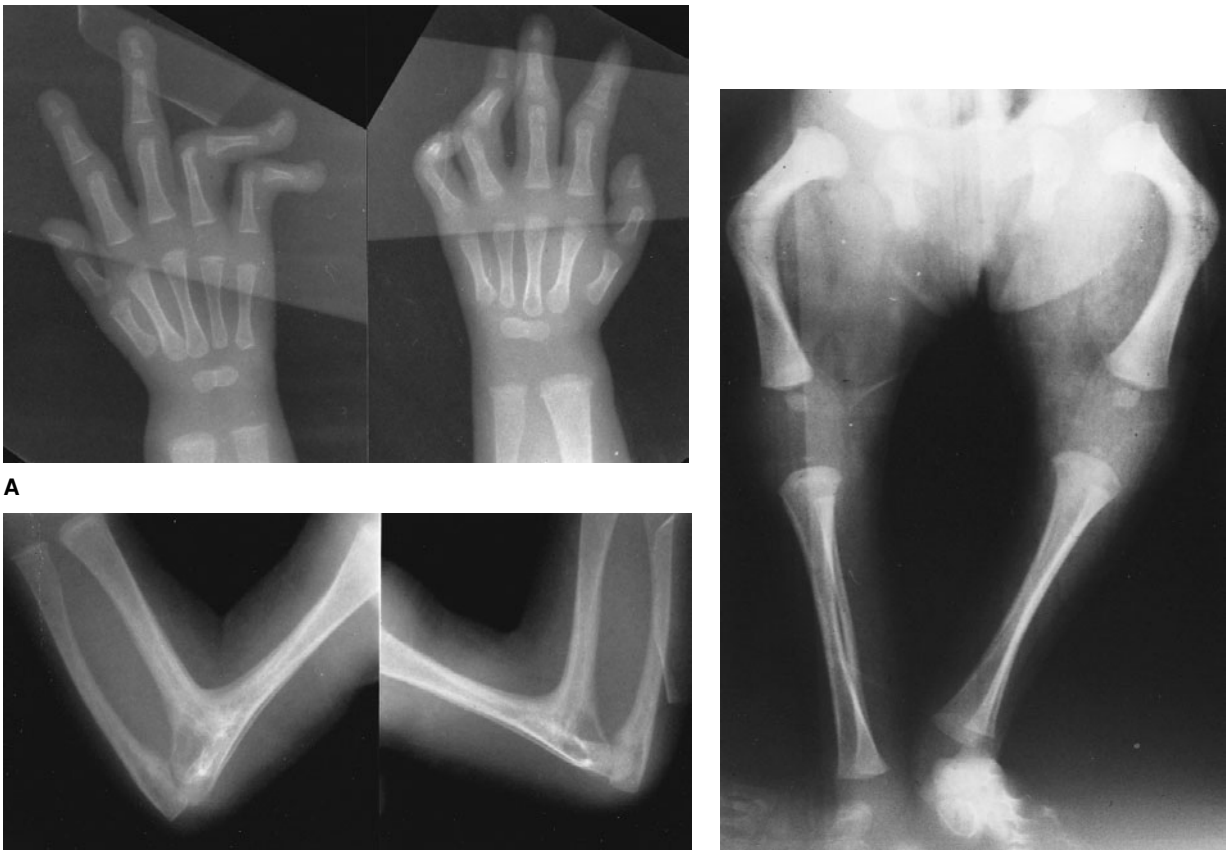


Fig. 15–3. *Antley-Bixler syndrome*. Radiographs. (A) Contractures, hypoplasia of terminal phalanges, and hamate-capitate fusion. (B) Bilateral radiohumeral synostosis. (C) Pronounced femoral bowing in a 6-week-old infant. (A,B from R Antley and D Bixler, Birth Defects 11(2):397, 1975. C from LK Robinson et al, J Pediatr 101:201, 1982.)

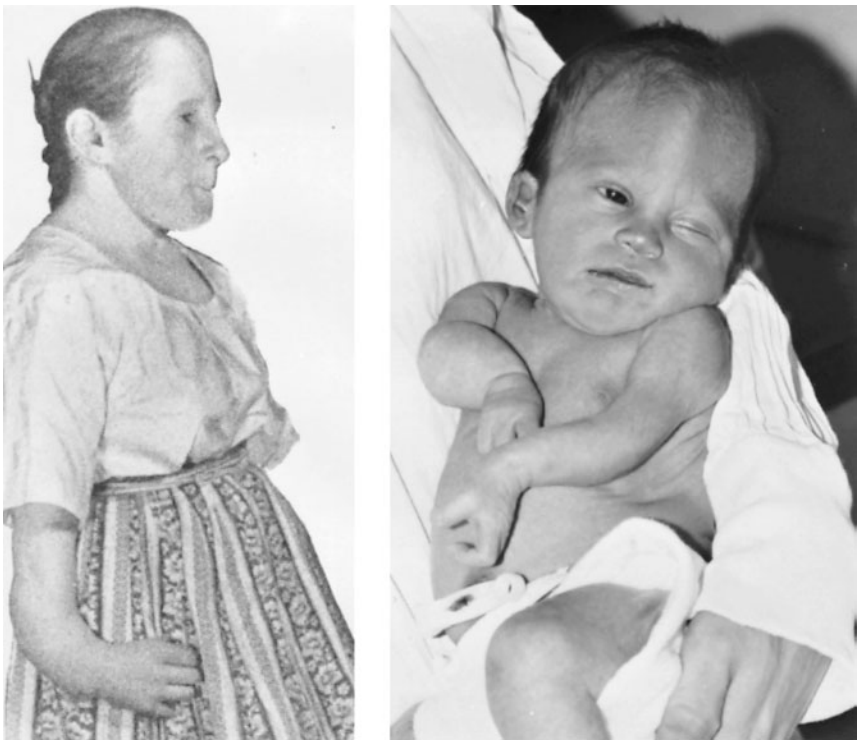


Fig. 15–4. *Baller-Gerold syndrome*. (A) Craniosynostosis and radial aplasia. (B) Note metopic ridging, short forearms (absent radii), and three fingers on each hand. (A from F Baller, Z Menschl Vererb Konstit-Lehre 29:782, 1950.)

Baller-Gerold syndrome

The original patients of Baller (17) and Gerold (96) had primary craniostenosis and preaxial upper limb malformations and, except for minor facial dysmorphism in one patient affecting the ear and the mandible, no other abnormalities were present (Fig. 15–4). The name Baller-Gerold syndrome was coined by Cohen in 1979 (45).

The delineation of the syndrome since then shows the addition of a large number of associated abnormalities including, among others, anal stenosis and/or malposed anus, and anomalies of the cardiovascular, genitourinary, skeletal, and central nervous systems (14,15,24,63,93,104,136, 164,167,194,200,213,217,219,231,232,246,262,268,282). Savarirayan et al (232) reported a congenital portal venous malformation in a 2-year-old patient.

Baller-Gerold syndrome has autosomal recessive inheritance. Verloes and Van Maldergem (271) reported that four of six sibs were affected. Gerold (96) also noted affected sibs. Consanguinity was documented by Gerold (96) and Pelias et al (200). Affected like-sexed dizygotic twins were described by Woon et al (282) and affected monozygotic twins were reported by Franceschini et al (85).

Diagnosis of Baller-Gerold syndrome can be more difficult than perhaps initially apparent (Table 15–2). The syndrome has phenotypic overlap with Fanconi anemia (78,226,265), VACTERL association (208,226), Roberts syndrome (118,126,191), and Rothmund-Thomson syndrome (209). Critical review of phenotypic overlap and differential diagnosis has been provided by Cohen and Toriello (58).

A patient with presumed Baller-Gerold syndrome with the only *TWIST* mutation known in the post-Helix II domain at this writing (Glu181Stop) (105), had facial features of Saethre-Chotzen syndrome. Furthermore, the upper limb reduction defect was unilateral, which is not found in Baller-Gerold syndrome; limb defects are bilaterally symmetric. Other family members with this mutation had no limb reduction defects (105), but did have several features of Saethre-Chotzen syndrome.

The work-up for this spectrum of patients should have the widest possible latitude; the diagnosis of Baller-Gerold syndrome is one of exclusion (58). Evaluation should include cytogenetic testing for Roberts syndrome and periodic hematologic screening for abnormalities suggestive of Fanconi anemia, which can first appear up to 10 years of age (232). VACTERL association has been discussed by Froster et al (86).

Table 15–2. Features of the *Baller-Gerold syndrome*

Features	Frequency
Growth	
Deficiency	8/9
Performance	
Sudden infant death	3/10
Mental and/or motor retardation	2/5
Cranial	
Craniosynostosis	10/10
Polymicrogyria	1/10
Facial	
Epicanthic folds	3/8
Prominent nasal bridge	3/9
Midline capillary hemangioma	2/7
Malformed ears	5/9
Low-set ears	2/9
Cleft palate	2/10
Bifid uvula	2/10
Highly arched palate	2/10
Micrognathia	2/10
Prominent mandible	2/10
Upper limbs	
Absent thumbs, radial hypoplasia or aplasia, associated limb defects	10/10
Other anomalies	
Cardiac[a]	2/10
Renal[b]	2/6
Anal[c]	4/7
Skeletal[d]	7/9

[a] Ventricular septal defect; subaortic valvular hypertrophy.
[b] Pelvic kidney; crossed renal ectopia.
[c] Anteriorly placed anus; imperforate anus; imperforate anus with perineal fistula.
[d] Lordosis at junction of skull and cervical spine; limited range of motion at shoulders, elbows, and knees; rib fusions and flat vertebrae in the dorsal area; absent vertebral bodies; sacral anomaly; anomalies of pelvic girdle and lower limbs; absent middle phalanges in fingers 2 and 5; absent middle phalanges in toes 2-5; metatarsus adductus.
(From MM Cohen Jr, Craniosynostosis: Diagnosis, Evaluation, and Management. Raven Press, New York, 1986.)

Beare-Stevenson cutis gyrata syndrome

In 1992, Hall et al (109) delineated the Beare-Stevenson cutis gyrata syndrome. Earlier cases had been reported by Beare et al (19), in 1969, and Stevenson et al (251) in 1978. Other cases were published by Andrews et al (10), Bratanic et al (26), and Krepelová et al (150).

Features consist of corrugated skin furrows, acanthosis nigricans, craniosynostosis, ear defects, anogenital anomalies, skin tags, and prominent umbilical stump. Cutis gyrata can affect the scalp, forehead, face, preauricular area, neck, trunk, hands, and feet (Fig. 15–5). Craniofacial appearance may be Crouzonoid or cloverleaf and some patients have been diagnosed initially as having Crouzon syndrome.

Intrauterine growth has been normal in all cases. Performance and life expectancy appear to be related to the presence or absence of cloverleaf skull. All cases to date have been sporadic.

Przylepa et al (212) reported two mutations for Beare-Stevenson syndrome on FGFR2: Tyr375Cys and Ser372Cys. Calda et al (31) also noted a case with Tyr375Cys. At this writing, there are three cases with Tyr375Cys and one with Ser372Cys.

Berant syndrome

In 1973, Berant and Berant (20) described a syndrome consisting of craniosynostosis involving the sagittal suture and radioulnar synostosis. Autosomal dominant inheritance with variable expressivity seems likely. Radioulnar synostosis was unilateral in some affected individuals and bilateral in others (Fig. 15–6).

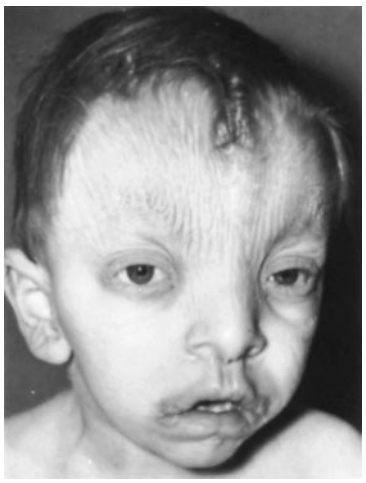
Isolated sagittal synostosis may occur sporadically or may sometimes follow an autosomal dominant mode of transmission. Radioulnar synostosis may occur as an isolated abnormality, may be inherited as an autosomal dominant trait, or may occur as a broader pattern of anomalies, as in *XXXXY* or *XXXXX syndrome*.

CAP syndrome

Flanagan et al (82) reported two male sibs with *c*raniosynostosis, *a*nal anomalies, and *p*orokeratosis (CAP). The syndrome possibly has autosomal recessive inheritance, but X-linked inheritance and gonadal mosaicism cannot be ruled out at this writing.

Features include microbrachycephaly, bifid scrotum, anteriorly placed, imperforate anus, and erythematous plaques with central clearing on the cheeks, ears, fingers, toes, and posterior scalp (82).

Porokeratosis is characterized by annular, parakeratotic plaques with central atrophy. Many types are known including linear porokeratosis, punctate porokeratosis, and Mibelli porokeratosis. Patients with CAP syndrome cannot be classified as having any of these types but most closely appear to have the Mibelli type (82).



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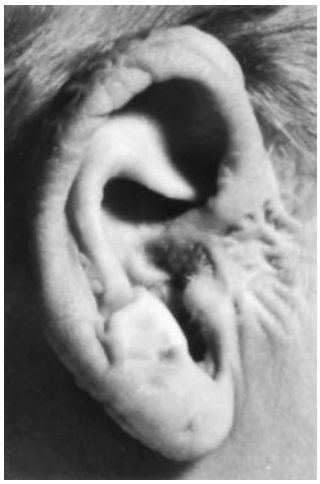

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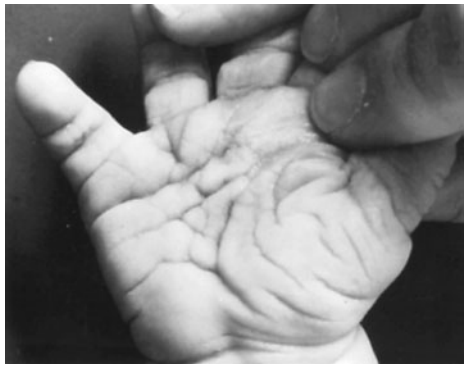

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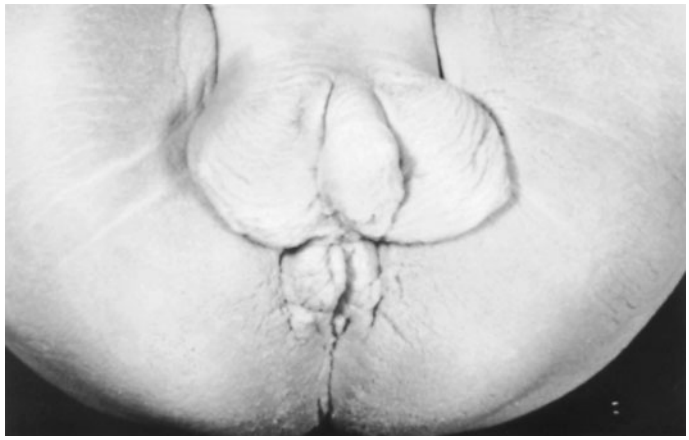


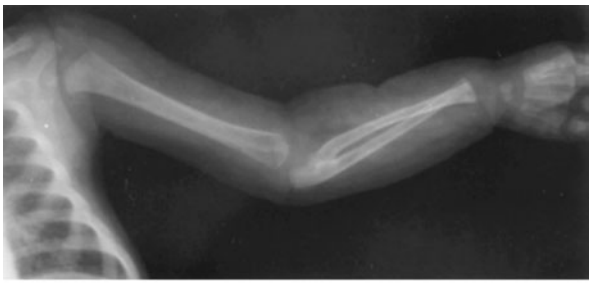
D

Fig. 15–5. *Beare-Stevenson cutis gyratum syndrome.* (A) Patient with cutis gyratum of facial skin, acanthosis nigricans. Note broad nasal bridge and unusual hairline. Patient also had cleft palate and natal teeth, but no evidence of craniosynostosis. (B) Malformed pinna showing indentation marks around tragal area in same patient. (C) Note palmar cutis gyratum. (D) Marked acanthosis nigricans in anogenital area of same patient. (A,B,D from JM Beare et al, Br J Dermatol 81:241, 1969. C from MM Cohen Jr, Am J Med Genet Suppl 4:99, 1988.)

Autosomal dominant inheritance of porokeratosis has been described in some instances. Porokeratosis may also be associated with UV light exposure, infectious disease, trauma, and immunosuppressive therapy.

Anal anomalies may be found in *Baller-Gerold syndrome* and *FG syndrome*. Porokeratosis has been reported in some instances of *trisomy 21 syndrome*. Poikiloderma is found in *Rothmund-Thomson syndrome* and *Bloom syndrome*.

Fig. 15–6. *Berant syndrome.* (A,B) Radioulnar synostosis in two affected members of the same family. (A,B from M Berant and N Berant, J Pediatr 83:88, 1973.)



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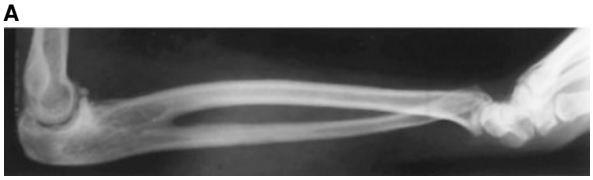

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Calabro syndrome

Calabro et al (30) reported a sporadic instance of a patient affected with synostosis of the coronal and metopic sutures, unilateral ulnar aplasia and oligodactyly, downslanting palpebral fissures, micrognathia, short neck, micropenis, cryptorchidism, and pulmonic stenosis.

Radial aplasia occurs with secondary ulnar involvement in *Baller-Gerold* syndrome. Radial aplasia and shortened ulnas are observed in *Herrmann syndrome*.

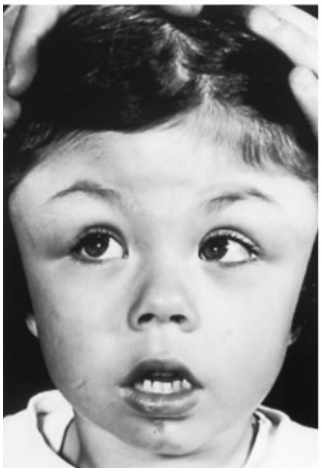
Calvarial hyperostosis

Pagon et al (198) reported an X-linked recessive form of calvarial thickening (Fig. 15–7). The cranial base, maxilla, and mandible were not affected. Although the coronal and sagittal sutures closed early, producing a Lückenschädel appearance, there was no evidence of increased intracranial pressure. Calvarial bone biopsy showed vacuolated histiocytes, suggesting a storage disease; however, at 18 years of age, one patient showed no evidence of neurologic deterioration or hepatosplenomegaly.

Chitayat hypophosphatemia syndrome

Chitayat et al (35) reported a syndrome in two brothers. The main features were renal hypophosphatemia, minor facial dysmorphism, intracerebral calcifications, and nonrachitic bone changes. Inheritance may be autosomal recessive or X-linked.

Abnormalities included dolichocephaly, sagittal synostosis, high forehead, malar hypoplasia, long philtrum, choanal stenosis, and dentin



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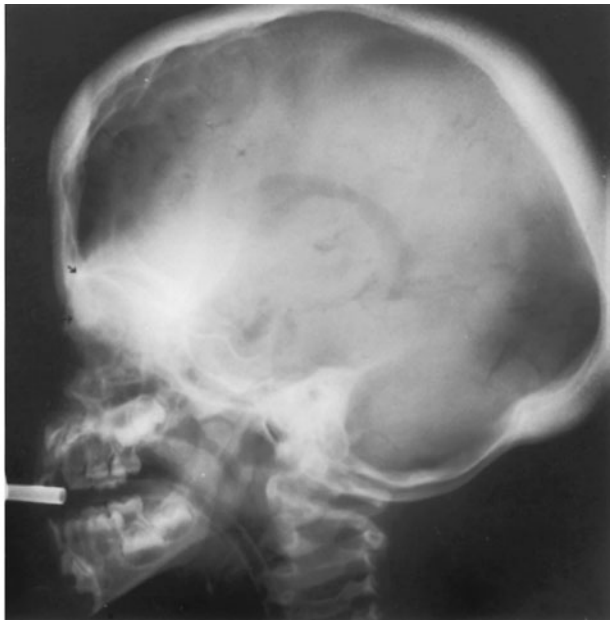

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Fig. 15–7. *Calvarial hyperostosis*. (A) Age 3.6 years. Note lateral frontal prominences. (B) Radiograph showing thickening in the basifrontal area (arrow) and supraoccipital bone. (From RA Pagon et al, Clin Genet 29:73, 1986.)

dysplasia with abscessed teeth. Intracerebral calcifications and nonrachitic bone changes were associated with hypophosphatemia, elevated serum alkaline phosphatase, and normocalcemia (35). Several renal hypophosphatemic syndromes are known including autosomal dominant, X-linked dominant, or autosomal recessive types (176).

Christian syndrome

In 1971, Christian et al (37) reported an autosomal recessive disorder consisting of microcephaly, craniosynostosis, arthrogryposis, and cleft palate. To date, the disorder has usually been referred to as the "adducted thumbs syndrome" (37,81,152), a term that Cohen found too nonspecific. Many features of the syndrome are secondary to abnormal development of the central nervous system. Ten cases have been recorded to date (37,81,152) (Table 15–3). Microcephaly, secondary craniosynostosis, and prominent occiput are accompanied by hypotonia, seizures, and mental deficiency. Ororespiratory problems include dysphagia, laryngomalacia, and pneumonia. An early demise is common. Facial features include a myopathic face, downslanting palpebral fissures in some instances, cleft palate or bifid uvula, micrognathia, low-set and posteriorly angulated ears, and torticollis (Fig. 15–8). Limb abnormalities include adducted thumbs, camptodactyly, limited extension at the elbows, wrist, and knees, and talipes equinovarus or calcaneovalgus. Hirsutism is frequently found.

Neuropathologic studies of one affected infant (37) showed dysmyelination with widespread glial proliferation in both the spinal cord and the brain. However, muscle biopsy in another patient (152) showed changes consistent with a myopathy rather than a neurogenic atrophy.

COH syndrome

COH syndrome represents a sporadically occurring case of cloverleaf skull, polymicrogyria, absent olfactory tracts and bulbs, proptosis, low nasal bridge, short upturned nose, downturned mouth, narrow palate, thumb duplication, small fifth fingers, micropenis, bifid scrotum, agenesis of the cervical thymic lobes, and bilobed lungs (Fig. 15–9). Chromosomes were normal. The mother, an unmarried primigravida, was normal and knew of no relatives affected with a similar set of anomalies. COH stands for Children's Orthopedic Hospital where the patient was seen as a newborn (48).

Table 15–3. *Christian syndrome*

Findings	Frequency
Performance	
Hypotonia	4/4
Seizures	6/10
Mental deficiency	5/5
Early demise	7/10
Ororespiratory	
Dysphagia	10/10
Respiratory problems	7/7
Pneumonia	5/5
Laryngomalacia	2/2
Craniofacial	
Microcephaly	8/10
Craniosynostosis	7/10
Prominent occiput	5/7
Myopathic face	3/3
Downslanting palpebral fissures	3/6
Ophthalmoplegia	6/6
Cleft palate, bifid uvula, or highly arched palate	9/9
Micrognathia	4/4
Abnormal ear placement	9/9
Torticollis	2/4
Limbs	
Adducted thumbs	10/10
Camptodactyly	3/3
Short first metacarpal	1/3
Limited extension at elbows, wrists, and knees	4/6
Talipes equinovarus or calcaneovalgus	9/10
Other	
Pectus excavatum	3/5
Hirsutism	6/6

(From MM Cohen Jr, Craniosynostosis: Diagnosis. Evaluation, and Management. Raven Press, New York, 1986.)

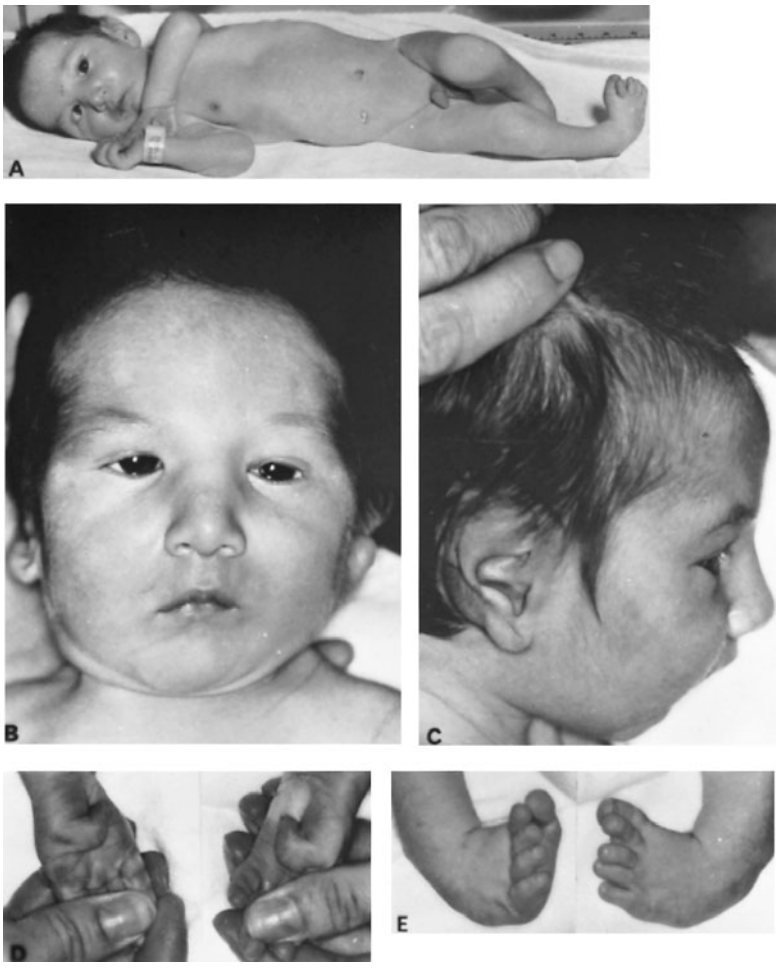


Fig. 15–8. *Christian syndrome*. (A–E) Pectus excavatum, facial asymmetry with telecanthus and downslanting palpebral fissures, hirsutism, micrognathia, posteriorly angulated ears, adducted thumbs, and talipes equinovarus. (From JC Christian et al, Clin Genet 2:95, 1971.)

Cranioectodermal dysplasia (Sensenbrenner syndrome)

Cranioectodermal dysplasia was first described by Sensenbrenner et al (243) in 1975 and named and expanded by Levin et al (163) in 1977. Over 10 cases have been recorded (9,73,94,95,161,163,233,243,266, 267,285). The syndrome consists of craniofacial, ectodermal, and skeletal abnormalities. Inheritance is autosomal recessive (73,163,285).

Development and intelligence are normal. Height is between the 3rd and 10th centiles. Several children have died before 7 years of age, usually from chronic renal failure with hypertension and proteinuria resulting from tubulointerstitial nephropathy (59a,73,233,266,267). Cardiac arrhythmia and interstitial pneumonia have caused death in two cases. Seizures may be noted on occasion.

The skull is scaphocephalic with synostosis of the sagittal suture. Frontal bossing and ocular hypotelorism are also found. Epicanthic folds, hyperopia, myopia, and nystagmus have been documented (59a,163). A symptomatic retinal photoreceptor dystrophy manifests during the first years of life as night blindness (73,267). The nose is small with anteverted nares. The lower lip is everted (163) (Fig. 15–10A–D).

Ectodermal abnormalities include fine, sparse, slow-growing hair with absence of the central pigment core of the hair shaft, short nails, and single palmar creases (285). Hypodontia, fused deciduous teeth, taurodontism, and microdontia have been noted (163).

Skeletal defects include generalized osteopenia, short narrow thorax, pectus excavatum, joint laxity, short limbs, stubby digits, fifth finger clinodactyly, and soft tissue syndactyly of the fingers and toes. The upper extremities exhibit more rhizomelic shortening than the lower extremities (163) (Fig. 15–10E).

Radiographic changes involve metaphyseal widening with flattened epiphyses of most long bones. However, the capital femoral epiphyses are small and round and ossify late. The fibulas are short and the semilunar notches of the ulnas are small (Fig. 15–10F,G). The vertebral bodies have short pedicles and convex superior and inferior surfaces. The sutures of the body of the sternum fuse prematurely (163).

Lammer et al (159) reported a boy with phenotypic features of cranioectodermal dysplasia but with different abnormalities of hair and bone. Growth, development, height, and limb lengths were normal. Bone changes consisted of indistinct medullary-cortical transition, particularly in the metacarpals, "bone within bone" changes in the vertebral bodies, and sclerosis of the anterior part of the vertebral bodies. Histologic study of the hair showed abnormalities of the internal root sheath of the hair follicle and hair shaft. In contrast, the change in cranioectodermal dysplasia consists only of absence of the central pigment core of the hair shaft.

Craniofacial dyssynostosis

Neuhäuser et al (189) described two affected sisters and five sporadic instances of craniosynostosis involving the lambdoidal and posterior sagittal sutures together with growth disturbance of the cranial base and minor facial anomalies (Fig. 15–11). They termed the condition craniofacial dyssynostosis. One of the seven patients had synostosis of the coronal suture as well. Four exhibited mental deficiency. Agenesis of the corpus callosum and interventricular lipoma were noted in one patient. Still another had PDA with possible VSD. All seven patients were of short stature. Spanish ancestry in four of seven patients and the occurrence of the disorder in two sibs suggest autosomal recessive inheritance. Other cases were reported by Al-Torki et al (7) and Morton (184a).

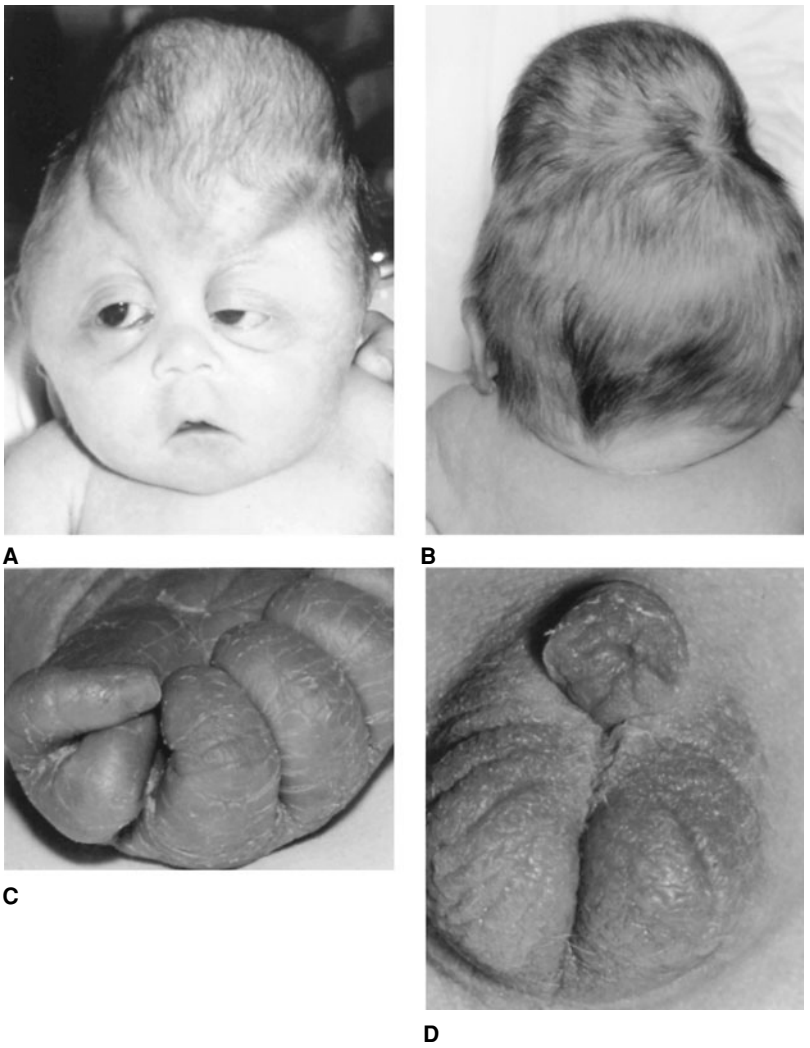


Fig. 15–9. *COH syndrome*. (A,B) Craniosynostosis, cloverleaf skull, and facial anomalies. (C) Preaxial polydactyly. (D) Micropenis and bifid scrotum. (From MM Cohen Jr, The Child With Multiple Birth Defects, Raven Press, New York, 1982.)

Craniofrontonasal syndrome

Craniofrontonasal syndrome (CFNS) was identified as a subpopulation of frontonasal dysplasia patients by Cohen (44), who also coined the term craniofrontonasal dysplasia. The condition was reported earlier by Reich et al (217) and at the same time as Cohen (44) by Slover and Sujansky (247). Craniofrontonasal syndrome has been reviewed elsewhere by Cohen (47), Young (284), Grutzner and Gorlin (107), and Saavedra et al (228).

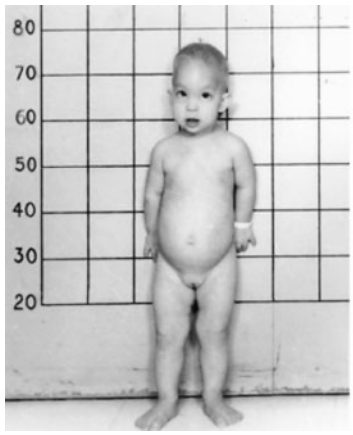
Craniofacial features include brachycephaly, coronal synostosis, craniofacial asymmetry, frontal bossing, dry curly or frizzy hair, coronal ocular hypertelorism, broad nasal bridge, bifid nose, pterygium colli, sloping shoulders, and longitudinally grooved nails (Fig. 15–12). Other reported findings include mild soft tissue syndactyly, clinodactyly of the fifth fingers, hyperextensible joints, and scoliosis. Malocclusion, ear anomalies, broad toes and hallucal duplication, minor vertebral anomalies, unusual dermatoglyphics, developmental delay, curly hair, short clavicles, downsloping shoulders, pectus excavatum, and unilateral breast hypoplasia have also been noted (44,121,142,211,220,228,247).

Although most cases are sporadic and occur in females who are generally more severely affected than the few reported males, pedigrees showing vertical transmission have been recorded [44,71,107,121 (see Figure 1, pedigree 1),123,140,142,151,180,183,210,211,218,220,228, 236,250]. Male-to-male transmission has not been observed in any publications to date, although Reich et al (198) noted two instances in an abstract that has yet to appear as a documented publication. Many suggestions have been put forth including X-linked dominant inheritance (192,201,225), metabolic interference (205), and a semilethal mutation with similarities to the T-locus in the mouse (216). Craniofrontonasal dysplasia has been mapped to Xp22 (74).

Females make up the majority, with males being fewer in number and tending to be less severely affected (42,99,208,216) (Fig. 15–12D). Manifestations in males are confined to the craniofacial region, consisting of ocular hypertelorism, cleft lip and/or palate in several cases, and malocclusion (cross-bite or posterior open-bite) (208). Severely affected males are very uncommon. One of us (MMC) knows of two such males in the Netherlands. A third affected male from Australia is shown in the monograph of David et al (65). The patient shown by David et al (65) (p. 24, Fig. 15), through correspondence from David et al to MMC, was found to be male. Natarajan et al (187) reported two severely affected brothers.

Craniofrontonasal syndrome can be distinguished from *frontonasal dysplasia*. The female patient with presumed frontonasal dysplasia and Klippel-Feil anomaly reported by Fragoso et al (84) probably had CFNS. The patient reported by Reardon et al (214) with craniosynostosis and Poland anomaly is similar to the patient of Webster and Deming (276) and, as suggested by Reardon et al (214), probably had CFNS. The patient described by Erdogan et al (75) with craniofrontonasal dysplasia, Poland anomaly, and polythelia most likely had CFNS, not a newly recognized syndrome, as suggested by these authors.

The proband reported by Kwee and Lindhout (153) as an example of CFNS probably had *Greig cephalopolysyndactyly*. Since the latter syndrome has autosomal dominant inheritance, the severely affected male, presumed to have CFNS by Kwee and Lindhout (153,154) and seconded by Young and Moore (286), cannot be used as evidence for autosomal dominant inheritance of CFNS.



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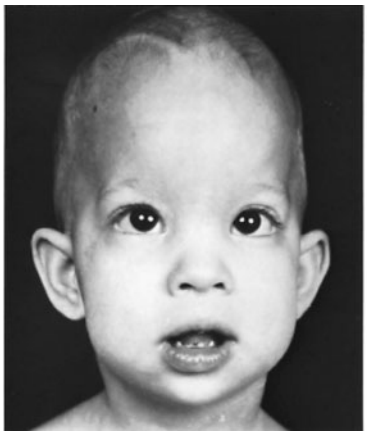

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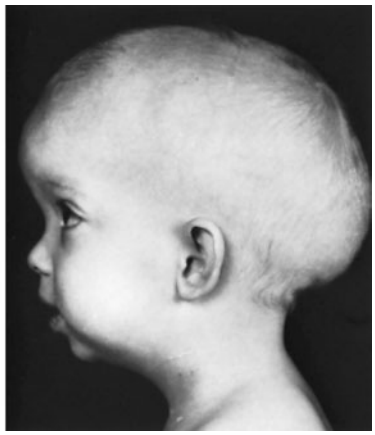

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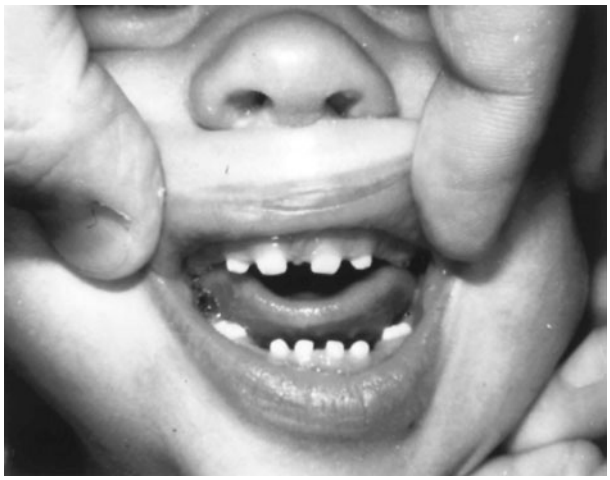

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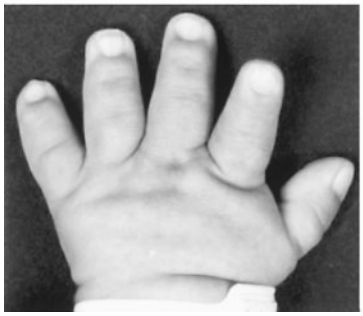

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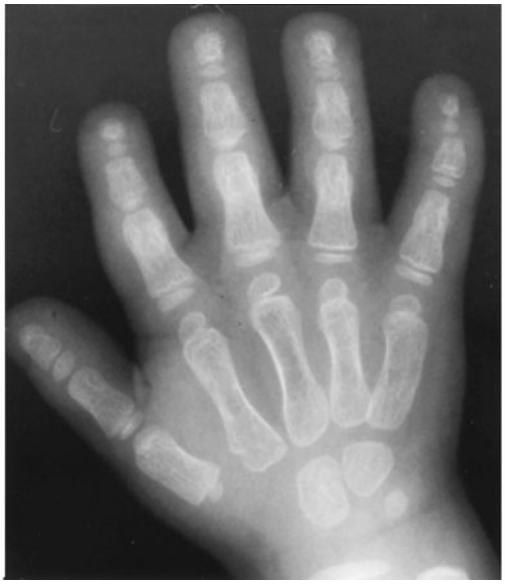

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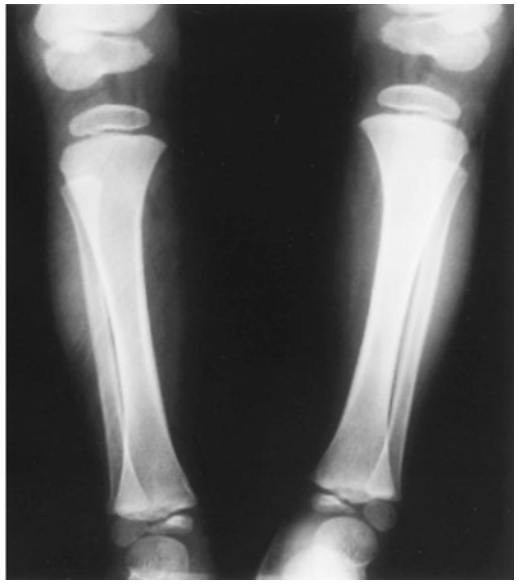


G

Fig. 15–10. *Cranioectodermal dysplasia.* (A) Age 23 months. Note rhizomelic shortening of limbs, especially upper limbs; small, narrow thorax with mild pectus excavatum; and dolichocephaly with short, thin hair. (B,C) Note dolichocephaly, short thin hair, frontal bossing, epicanthic folds, hypertelorism, and everted lower lip. (D) Microdontia (E) Brachydactyly. (F) Hand–wrist radiograph at age 4 years. Brachydactyly, osteoporosis with thin cortices and coarse trabeculae and mild clinodactyly of the fifth finger. (G) Radiograph showing flat irregular epiphyses and shortening of fibulae, both proximally and distally. (From LS Levin et al, J Pediatr 90:55, 1977.)

The family with three affected males and two affected females reported by Morris et al (184) has having CFNS probably represents another disorder. In their family, of six patients, only one had craniosynostosis, and affected males had manifestations such as short stature, delayed bone age, shawl scrotum, and hypospadias. Possibly their patients may have had *brachycephalofrontonasal dysplasia*, a dominantly inherited syndrome described by Teebi (260) and Stratton (252).

Craniomicromelic syndrome

Barr et al (18) reported a newly recognized lethal syndrome in two sisters who had coronal synostosis, relative macroturricephaly, short palpebral fissures, pinched nose with anteverted nares, protruding anterior nasal spine, low-set posteriorly angulated ears, micrognathia, microstomia, cleft palate in one sib, short limbs, hypoplastic lungs, absent/hypoplastic

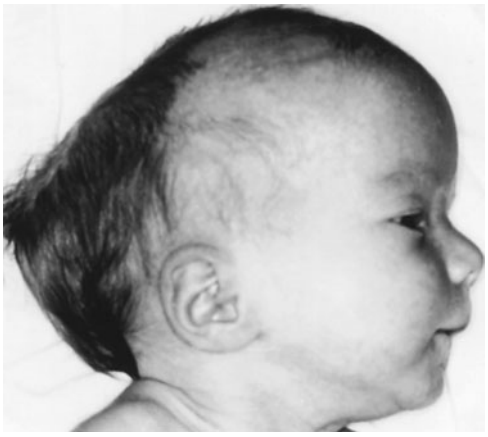


Fig. 15–11. *Craniofacial dyssynostosis*. Posterior sagittal and lambdoidal synostosis. (Courtesy of JM Opitz, Helena, Montana.)

gallbladder, short intestine with ileal distention, hypoplastic uterus, and intrauterine growth retardation. Another example is that of Baralle and Firth (17a). Inheritance is probably autosomal recessive.

The combination of craniosynostosis, short limbs, and lethality limits the differential diagnosis. Both *thanatophoric dysplasia* and *Ives-Houston syndrome* have all three of these characteristics. However, both have more dramatically short limbs and distinctive radiographic features.

Craniorhiny

Mindikoğlu et al (181,182) reported an autosomal dominant syndrome of craniosynostosis and striking nasal abnormalities. MM Cohen Jr coined the name "craniorhiny." The skull shape was oxycephalic with recessed forehead and lack of nasofrontal angle (Fig. 15–13). Synostosis of the coronal suture was found radiographically with digital impressions in the anterior portion of the skull. Characteristic nasal changes consisted of a wide nose, anteverted nares, nasal hirsutism, and bilaterally symmetrical, spherical almond-sized cyst-like structures with small fistulas just below the nose. The nasolacrimal ducts were absent. Of four reported Turkish sibs, three were affected, as was the mother (181).

Craniosynostosis, Boston type

Boston type craniosynostosis is an autosomal dominant disorder with variable expression. Most commonly observed are fronto-orbital recession or turribrachycephaly. Less commonly observed are cloverleaf skull or frontal bossing (275). The disorder is caused by a mutation in MSX2: Pro148His (56a,131,186). Three other mutations on MSX2 cause parietal foramina by haploinsufficiency.

Craniosynostosis/ectopia lentis

Cruysberg et al (61) described craniosynostosis and ectopia lentis in monozygotic twin sisters. One sister had sagittal synostosis, the other

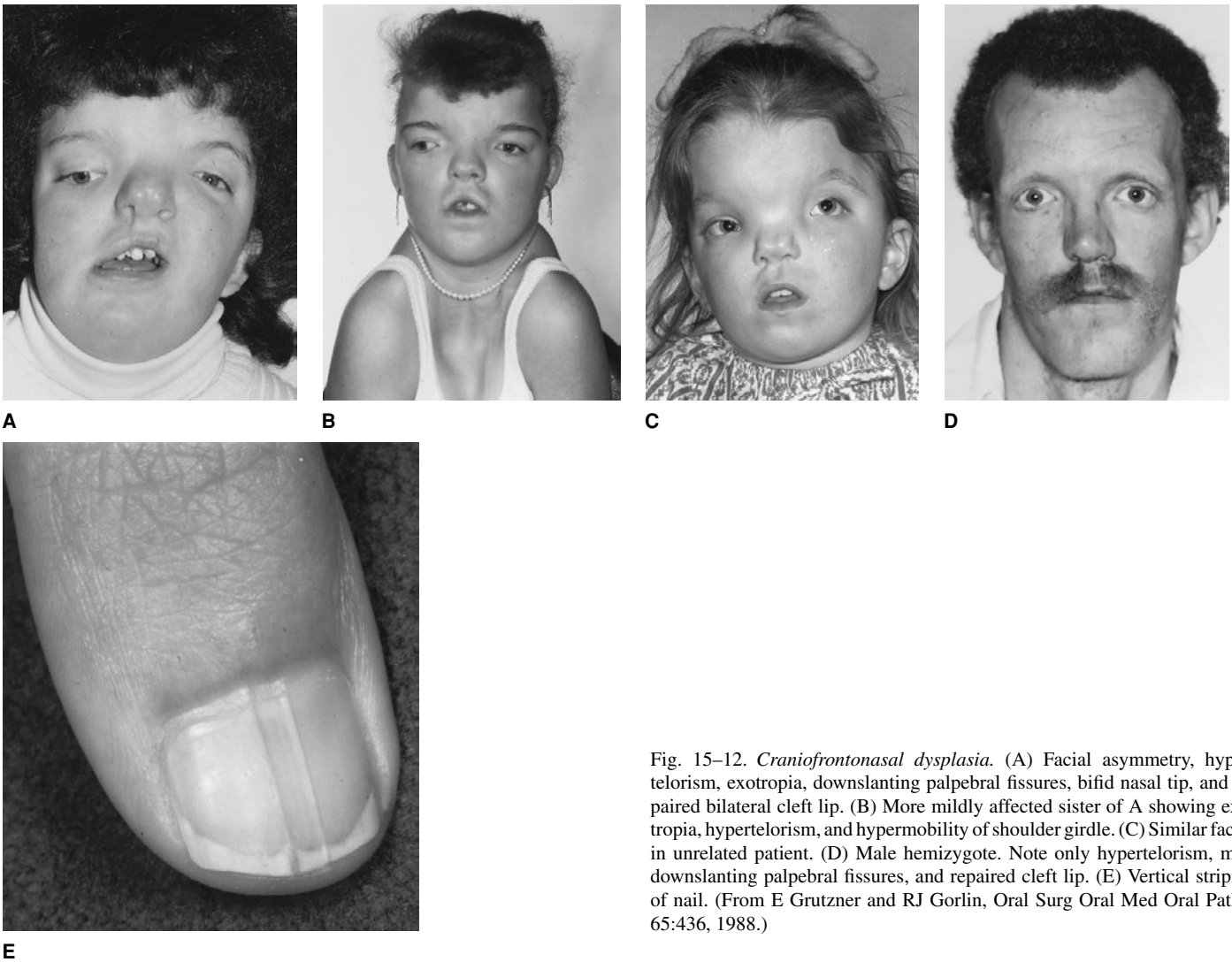
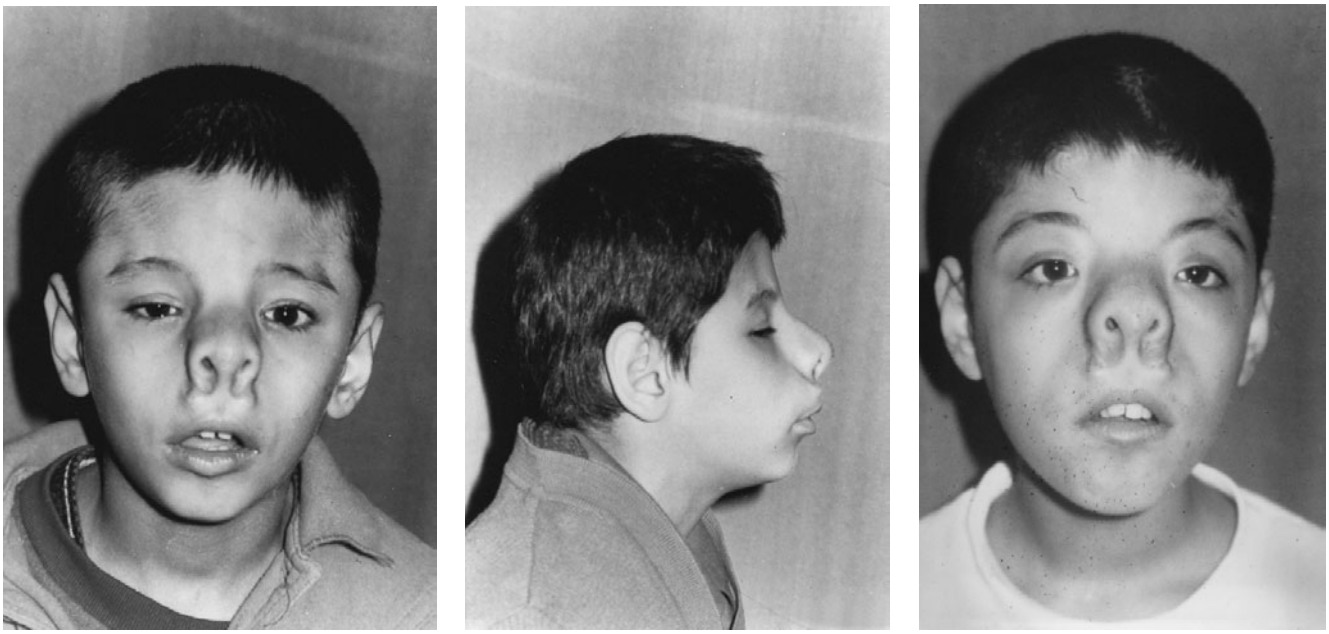


Fig. 15–12. *Craniofrontonasal dysplasia.* (A) Facial asymmetry, hypertelorism, exotropia, downslanting palpebral fissures, bifid nasal tip, and repaired bilateral cleft lip. (B) More mildly affected sister of A showing exotropia, hypertelorism, and hypermobility of shoulder girdle. (C) Similar facies in unrelated patient. (D) Male hemizygote. Note only hypertelorism, mild downslanting palpebral fissures, and repaired cleft lip. (E) Vertical striping of nail. (From E Grutzner and RJ Gorlin, Oral Surg Oral Med Oral Pathol 65:436, 1988.)



A B C

Fig. 15–13. *Craniorhiny.* (A–C) Coronal synostosis with lack of nasofrontal angle, wide nose, anteverted nares, and bilateral symmetrical spherical cyst-like formations just below nose. (From AN Mindikoğlu et al, Am J Med Genet 40:250, 1991.)

metopic synostosis. Both had hirsutism on the back, mild hyperlaxity of the elbows and knees, and hypoplastic toe nails. Inheritance may be autosomal dominant, possibly due to a new mutation; possibly autosomal recessive; or possibly X-linked, lethal in the male.

Ectopia lentis is rare in isolated cystathionine synthase and rare in *Crouzon syndrome* (47). It is common in *Marfan syndrome, cystathionine synthase deficiency*, and *Weill-Marchesani syndrome*.

Craniosynostosis, Philadelphia type

Robin et al (223) reported a five-generation autosomal dominant pedigree with a distinctive combination of sagittal synostosis and syndactyly. Dolichocephaly was found in seven of ten affected individuals. Nonpenetrance for craniosynostosis occurred only in females. The face was usually normal except for two patients who exhibited downslanting palpebral fissures. Soft tissue 2–5 syndactyly was found in most cases (7/8) with 3–4 syndactyly occurring in only one patient. Complete soft tissue 1–5 syndactyly of the feet was observed in all cases. Hand and foot lengths were below the 3rd centile.

Craniotelencephalic dysplasia

Jabbour and Taybi (130) and Daum et al (64) reported sporadic instances of a condition known as craniotelencephalic dysplasia. In both cases, premature closure of the sagittal, coronal, and metopic sutures occurred together with protuberance of the frontal bone and retarded neurologic development. A paramedian frontal encephalocele was present in one case (64) (Fig. 15–14).

Two affected sisters were reported by Hughes et al (120). One had septooptic dysplasia, absent olfactory nerves, agenesis of the corpus callosum, and lissencephaly. The occurrence of craniotelencephalic dysplasia in association with such central nervous system anomalies suggests that this combination probably represents a distinct autosomal recessive syndrome.

Because detailed studies of the brain were not possible in the two sporadic cases of craniotelencephalic dysplasia reported by Jabbour and Taybi (130) and Daum et al (64), it is not known whether they had similar central nervous system anomalies and therefore represent the same overall condition reported by Hughes et al (120). Final judgment as to the specificity or nonspecificity of craniotelencephalic dysplasia will have to await further studies.

Crouzonodermoskeletal syndrome

The association of Crouzon syndrome with acanthosis nigricans has been known for a long time (27,96a,145,215,256) (Fig. 15–15). H Curth, in private conversation with one of the authors (RJG), noted this association in 1948. More recently, an FGFR3 transmembrane mutation, Ala391Glu, has been reported (174a,179,186a,186b,242a,278). A still different variant, more resembling thanatophoric dysplasia or severe achondroplasia (SADDAN = *S*evere *A*chondroplasia with *D*evelopmental *D*elay and *A*canthosis *N*igricans), has another FGFR3 mutation, (Lys 650 Met) (259).

Cohen (56) indicated that this condition is completely separate from Crouzon syndrome for two reasons. First, it is caused by a highly specific mutation, which is 11 amino acids away from the common mutation for achondroplasia. In contrast, in exons 7 and 9 of the third immunoglobulin-like loop of FGFR2, more than two dozen mutations are known to cause Crouzon syndrome (55). Second, the phenotypes are entirely different. The FGFR3 Ala391Glu mutation is associated not only with acanthosis nigricans, but also with cementomas of the jaws (215,255,256). Furthermore, the interpediculate distances have been reported to narrow progressively from the upper to the lower spine, as in achondroplasia (255) (Fig. 15–16). There is also jugular foramen stenosis and intracranial venous hypertension and dilated scalp veins (186a). At this writing, the frequency with which vertebral alterations and cementomas occur in this syndrome is unknown because clinical manifestations have not been evident. Jugular foraminal stenosis with dilated scalp veins has also been described (145a). Certainly when a diagnosis of Crouzonoid phenotype and acanthosis nigricans is made, radiographic study should be instituted.

A mild disorder due to K650Q mutation in the FGFR3 gene has been reported (184a).

To call this disorder "Crouzon syndrome with acanthosis nigricans" shows that we are prisoners of our own conventional terminology. A specific mutation with a specific phenotype requires a specific name.

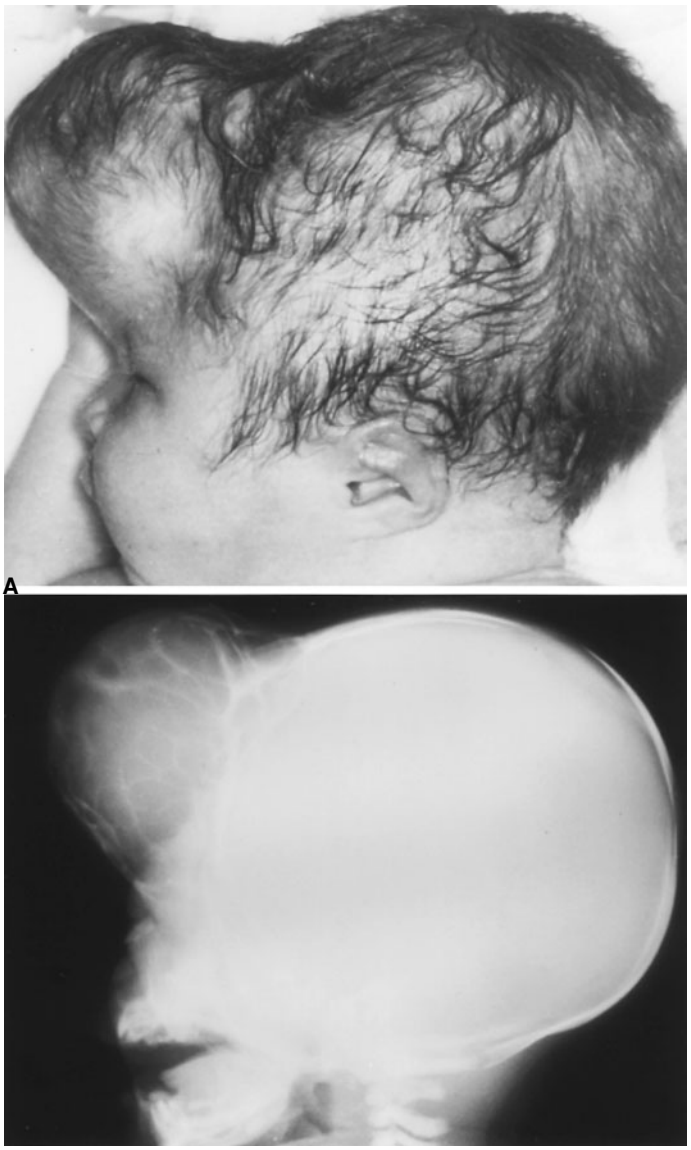


Fig. 15–14. *Craniotelencephalic dysplasia.* (A,B) Premature closure of the sagittal, coronal, and metopic sutures with protuberance of frontal bone. (From HE Hughes et al, Am J Med Genet 14:557, 1983.)

Elsewhere (56), Cohen proposed the name "Crouzonodermoskeletal syndrome." The term includes the Crouzonoid phenotype (*Crouzono*) acanthosis nigricans (*dermo*), and jaw cementomas and vertebral alterations (*skeletal*).

Curry-Jones syndrome

Temple et al in 1995 (261) reported five children with the Curry-Jones syndrome characterized by craniosynostosis (usually unilateral involving the coronal suture), facial asymmetry, preaxial polydactyly, variable syndactyly, and unusual skin lesions. The first two cases were presented at the David W. Smith Workshop on Malformations and Morphogenesis in 1986 and 1987. One case was described by Curry et al (62), the other by Jones (138). The name Curry-Jones syndrome was coined by Cohen in 1988 (48).

Affected skin is initially erythematous. Lesions then become pearly white and raised and finally become pale and atrophic with areas of scarring and hair growth. Distribution is linear and skin appears pigmented in a streaky or lace-like pattern. Some patients have freckling of the plantar surfaces of the feet (Fig. 15–17).

Agenesis of the corpus callosum and developmental delay have been found in three patients. Gastrointestinal obstruction has been associated with myelofibrosis of the bowel and the mesentery in some patients.

Elejalde syndrome

In 1977, Elejalde and his co-workers (74) described a spectacular overgrowth syndrome. Birthweights in three patients ranged from 4300g to 7500g. Features included a swollen globular body, omphalocele, short limbs, redundant neck skin, craniosynostosis, hypoplastic nose, and rudimentary auricles (Fig. 15–18). Three affected individuals in two sibships were recorded for which consanguinity was established. Thus, the Elejalde syndrome has autosomal recessive inheritance. Cell kinetic studies showed that fibroblasts from Elejalde syndrome patients completed the cell cycle in 63% of the normal cell cycle time. Since Elejalde's original cases were described, four other instances have been reported (36,174,190,264) (Table 15–4).

Autopsy findings showed enlarged kidneys with a thick fibrous capsule, lack of clear-cut differentiation between the cortex and the medulla, and multiple cysts. Excessive connective tissue was found throughout the body, except for the central nervous system. It was most prominent subcutaneously in the media of blood vessels, in the walls of the viscera, and interstitially in organs such as the pancreas and kidneys. Perivascular proliferation of nerve fibers was found in many viscera, particularly the spleen, thymus, colon, heart, and adrenal glands (49).

Fontaine-Farriaux syndrome

In 1977, Fontaine et al (83) described a sporadic occurrence of a newly recognized syndrome consisting of craniosynostosis, phalangeal hypoplasia with anonychia of the third, fourth, and fifth fingers, patches of lipodystrophy at the antecubital and popliteal fossae, aplasia of the abdominal muscles, genital hypoplasia, hypospadias, and cryptorchidism. Growth deficiency of prenatal onset and an early demise at 3.5 months were reported. Karyotype was normal. Autopsy findings included VSD, absence of the common mesentery, lissencephaly, absent interhemispheric fissure, and disorganization of the basal ganglia.

Fontaine-Farriaux syndrome is named after the first two authors of the report (83) to clearly distinguish it from another condition already known as Patterson-Stevenson-Fontaine syndrome, an autosomal dominant disorder characterized by micrognathia, dysplastic ears, ectrodactyly and syndactyly of the feet, and, in some instances, submucous cleft palate and mental deficiency (43).

Frydman trigonocephaly syndrome

In 1984, Frydman et al (87) reported a newly recognized autosomal dominantly inherited trigonocephaly syndrome. The proband had trigonocephaly, premature metopic synostosis, ridging of the metopic suture, mild synophrys, hypotelorism, S-curved lower eyelids, preauricular tag, omphalocele, large phallus, and a hemivertebra at L5. Mental development was normal. The father of the proband had trigonocephaly with marked ridging of the metopic suture, mild microcephaly, mild synophrys, S-curved lower eyelids, and hypotelorism. Intelligence was normal. Four other affected members of the family had trigonocephaly and normal intelligence.

Fryns craniosynostosis syndrome

Fryns et al (90) reported a mother and son with synostosis of the coronal and metopic sutures, an asymmetric long face, high narrow forehead, short upper lip, and highly arched palate. Sensorineural hearing loss of 35–45 dB in the low and middle frequencies was present in both mother and son.

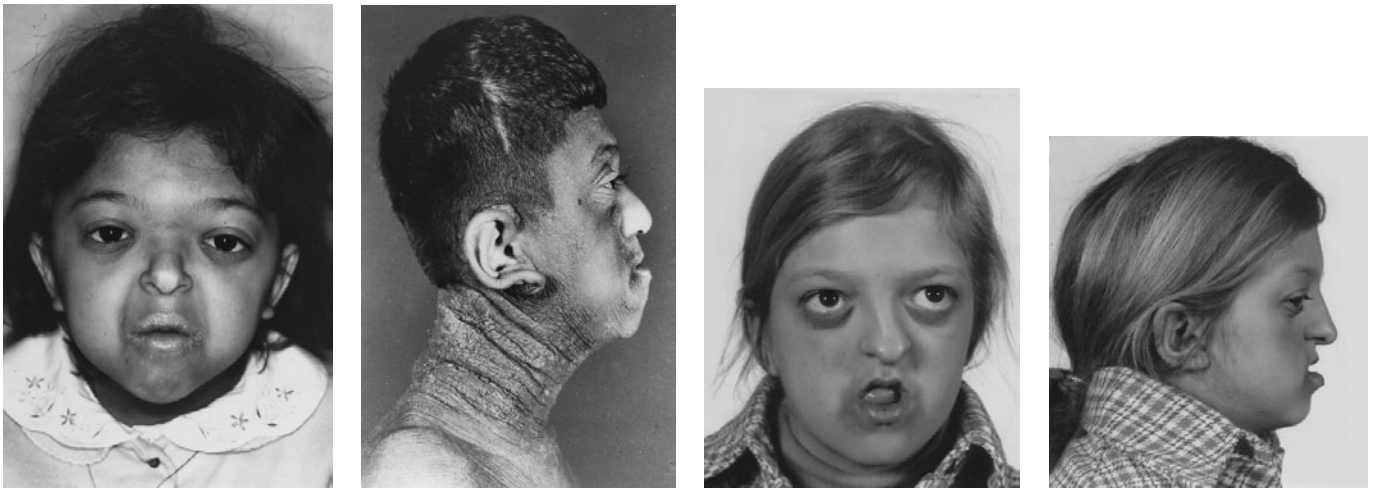
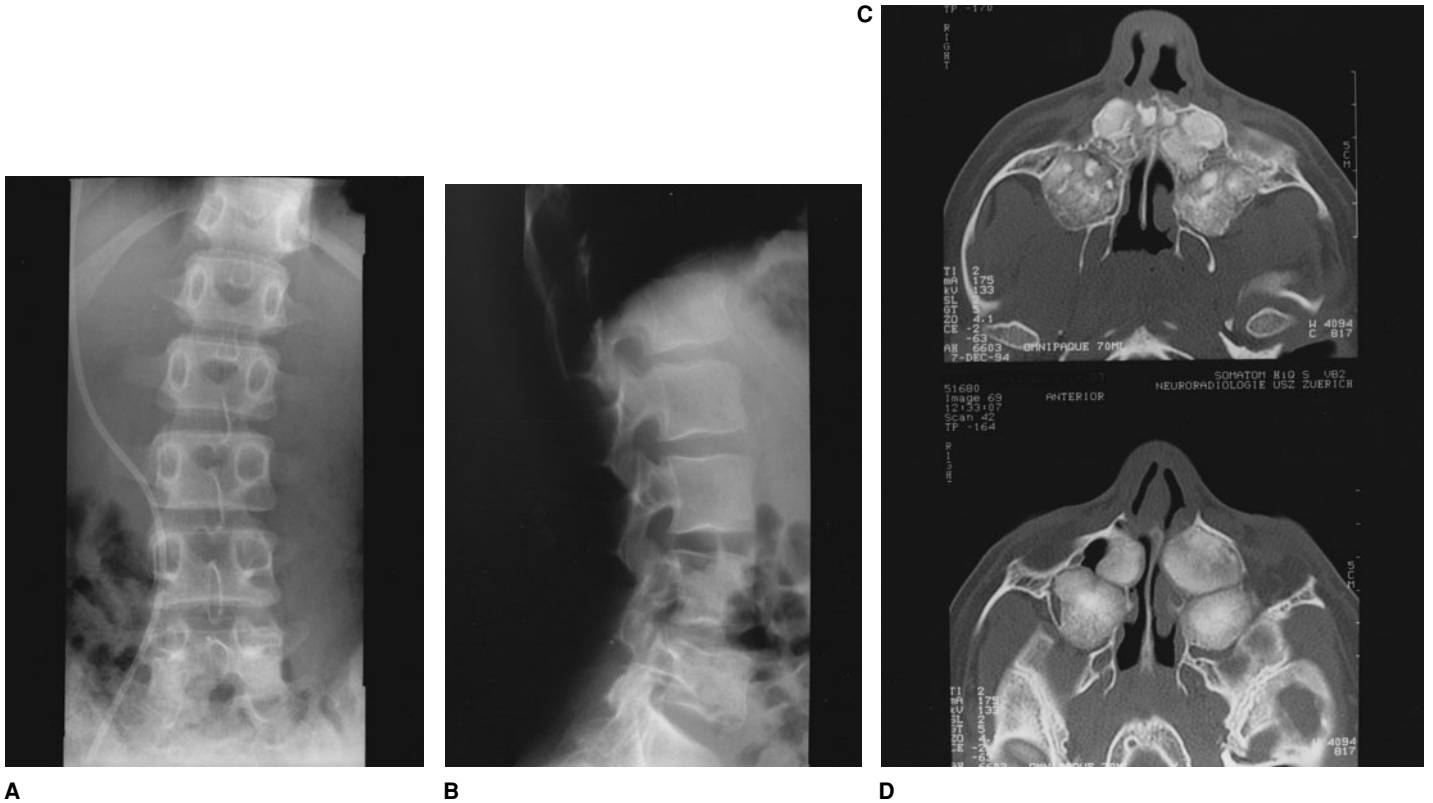


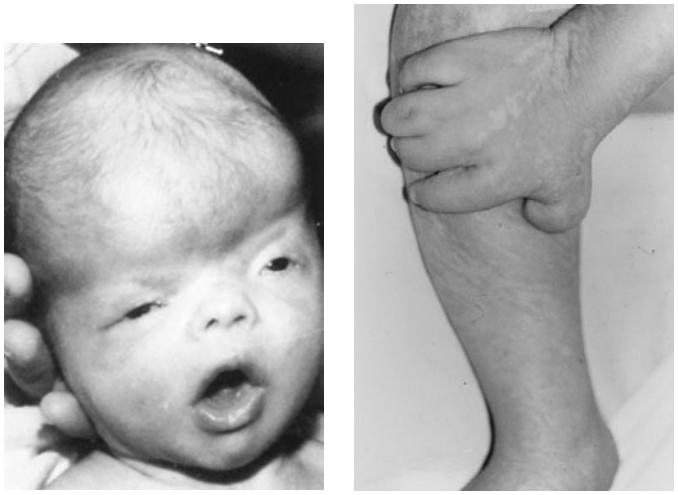
Fig. 15–15. *Crouzonodermoskeletal syndrome.* (A) Note Crouzon-like facies with relatively mild acanthosis nigricans. (B) Marked brachycephaly, extensive acanthosis nigricans. (C,D) Typical Crouzonoid facies and acanthosis nigricans, especially evident circumorally. (A courtesy of J Mulliken, Boston, Massachusetts. B from BSN Reddy et al, J Dermatol 12:85, 1985. C,D courtesy of A Superti-Furga, Zürich, Switzerland.)

Gomez-López-Hernández syndrome (cerebello-trigeminal-dermal dysplasia)

Gomez-López-Hernández syndrome is a distinctive condition consisting of craniosynostosis, ataxia, trigeminal anesthesia, pons-vermis fusion, mental deficiency, short stature, parietal alopecia, ocular hypertelorism, corneal opacities, midface hypoplasia, low-set posteriorly angulated ears, clinodactyly, and hypoplastic labia majora (Fig. 15–19). Two unrelated Mexican girls were reported by López-Hernández (169). Chromosomes were normal in each girl. In both families, the parents were normal, consanguinity was denied, and there were no affected sibs. Another earlier case was reported by Gomez (98) who recognized the disorder as a distinct entity and named it cerebellotrigeminodermal dysplasia. Gomez (97) reviewed the subject extensively. To date, eight sporadic cases have been described, and males as well as females have been affected (27a,98,141,169,199,205) (Table 15–5). Only two of the six affected individuals had craniostenosis, which appears to be secondary to microcephaly, a variable feature of the syndrome (Fig. 15–20).

Fig. 15–16. *Crouzonodermoskeletal syndrome.* (A,B) A–P and lateral radiographs showing decreasing interpediculate distances as one goes down the lumbar spine. (C,D) Numerous cementomas of maxilla. (Courtesy of A Superti-Furga, Zürich, Switzerland.)





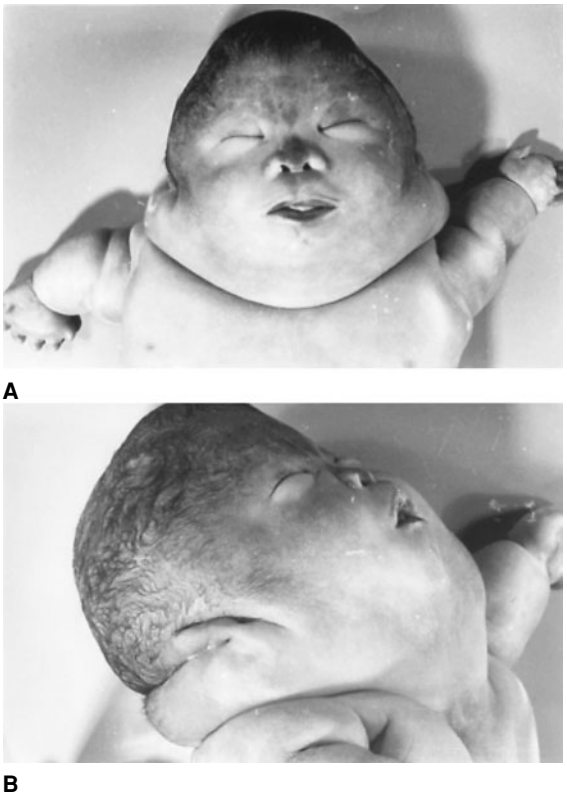
A B

Fig. 15–17. *Curry-Jones syndrome.* (A) Brachyplagiocephaly, unilateral microphthalmia. (B) Streaky lace-like pigmentation. (A courtesy of CJR Curry, Fresno, California. B courtesy of K Temple, Southampton, England.)

Gorlin-Chaudhry-Moss syndrome

In 1960, Gorlin et al (100) described a syndrome in two female sibs consisting of craniosynostosis, midface hypoplasia, hypertrichosis, and anomalies of the eyes, teeth, heart, and external genitalia. The name Gorlin-Chaudhry-Moss syndrome was coined by Cohen in 1975 (41). Autosomal recessive inheritance seems likely. Other cases have been observed (128). The condition should be distinguished from *Crouzon syndrome* and *Saethre-Chotzen syndrome* (209a).

Fig. 15–18. *Elejalde syndrome*. (A,B) Complete fusion of all cranial sutures, closure of fontanels, epicanthic folds, downslanting palpebral fissures, hypoplastic nose, rudimentary auricles, and redundant tissue around neck. [From BR Elejalde, Birth Defects 13(3B):53, 1977.]



A B

Table 15–4. Features of *Elejalde syndrome*

Findings	Patient 1	Patient 2
Growth		
Gigantism	+	+
Abdominal/genitourinary		
Omphalocele	+	+
Accessory spleen	−	+
Megaureter	+	+
Megabladder	+	+
Megavagina	−	+
Redundant connective tissue	+	+
Proliferation of perivascular nerve fibers	+	+
Craniofacial		
Craniosynostosis	+	+
Ocular hypertelorism	+	+
Epicanthic folds	+	+
Downslanting palpebral fissures	+	+
Hypoplastic nose	+	+
Rudimentary auricles	+	+
Limbs		
Short limbs	+	+
polydactyly	−	+
Other		
Redundant neck skin	+	+
Hypoplastic lungs	+	+

[Based on data from BR Elejalde et al: Birth Defects 13(3B):53, 1977.]

Table 15–5. *Gomez-López-Hernández syndrome*

Features	Patient 1	Patient 2
Growth		
Short stature	+	+
Performance		
Mental deficiency	+	+
Central nervous system		
Pons-vermis fusion	+	+
Atresia of fourth ventricle	+	+
Cerebellar ataxia	+	+
Trigeminal anesthesia	+	+
Craniofacial		
Craniosynostosis	+	+
Parietal alopecia	+	+
Ocular hypertelorism	+	−
Corneal opacities	+	+
Midface deficiency	+	+
Low-set, posteriorly angulated ears	+	+
Limbs		
Clinodactyly	+	+
Genitalia		
Hypoplastic labia majora	+	+

(From MM Cohen Jr, Craniosynostosis: Diagnosis, Evaluation, and Management, Raven Press, New York, 1986.)

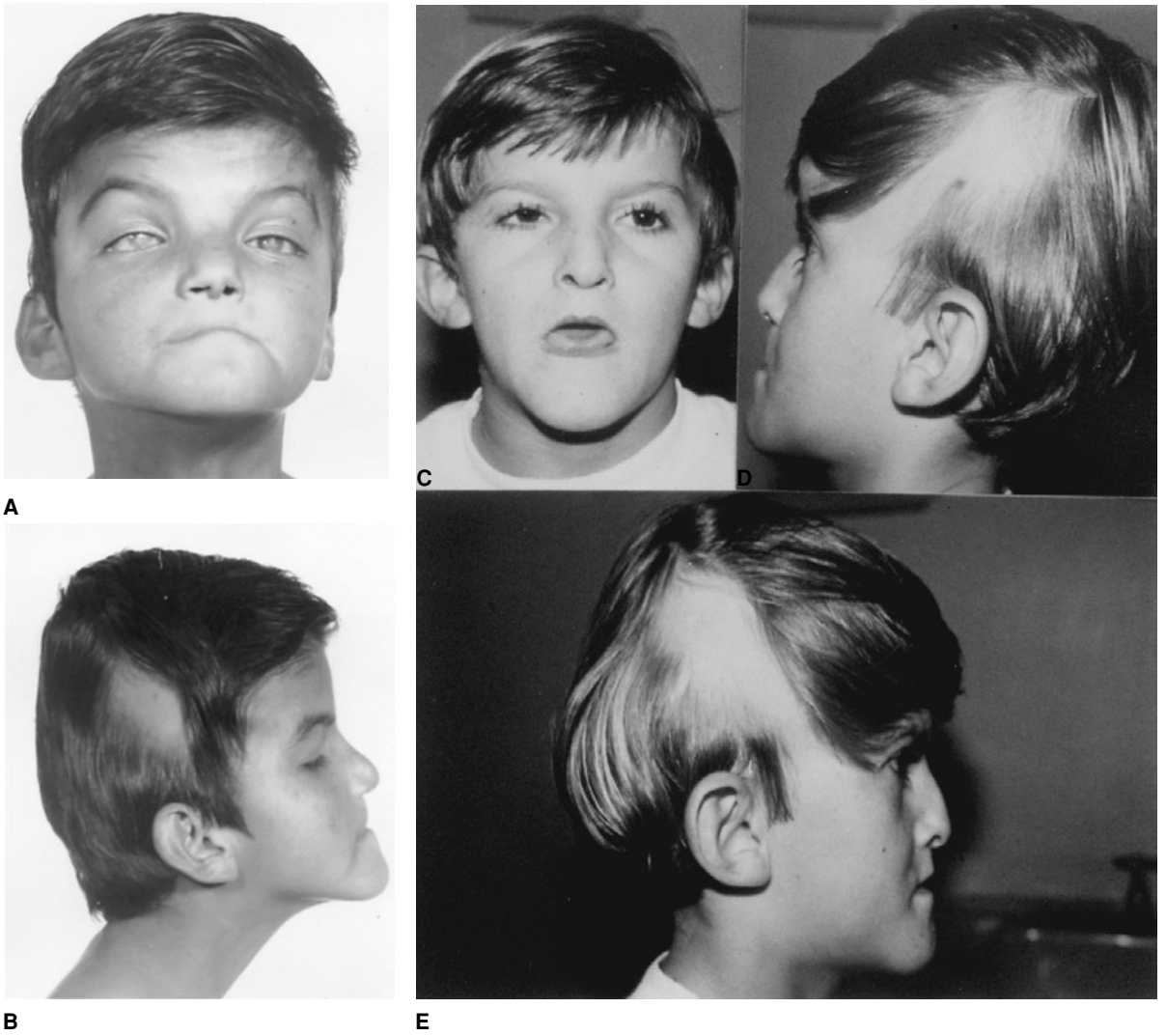


Fig. 15–19. *Gomez-López-Hernández syndrome* (*cerebello-trigeminal-dermal dysplasia*). (A,B) Craniosynostosis, focal parietal alopecia, low-set posteriorly angulated ears, and midface deficiency with relative mandibular prognathism. Note corneal opacities. (C–E) Frontal and side views. (A,B from A López-Hernández. Neuropediatrics 13:99, 1982. C–E from MV Muñoz et al, Am J Med Genet 72:34–39, 1997.)

The original sibs were short and of stocky build. Both held their heads in mild anteflexion when walking. Midface hypoplasia and depressed supraorbital ridges were observed but were more pronounced in the older sib. Hypertrichosis of the scalp, arms, legs, and back was noted. The scalp hairline was lower than normal. Downslanting palpebral fissures, inability to fully open or close the eyes, upper eyelid colobomas, microphthalmia, and hyperopia were reported. The younger sib had unilateral persistence of the iridopupillary membrane. Bilateral conductive hearing deficit was noted in both sibs (Fig. 15–21A–C).

Oral anomalies consisted of class III malocclusion, highly arched narrow palate, hypodontia, microdontia, and abnormally shaped teeth. Other findings included patent ductus arteriosus, pronounced hypoplasia of the labia majora, and umbilical hernia (Fig. 15–21D).

Radiographic examination of the skull showed premature synostosis of the coronal suture, brachycephaly, hypoplastic maxillary and nasal bones, ocular hypertelorism, lordosis of the petrous ridges, hypoplasia of the clivus, and elevation of the lesser sphenoidal wings.

Hall syndrome

In 1974, JG Hall (111) observed a patient with craniosynostosis and a Turner-like phenotype. Growth, however, was rapid, both height and weight being at the 97th centile. Mild mental deficiency was evident.

Significant dysmorphic features included unilateral synostosis involving the coronal suture, craniofacial asymmetry, downslanting and narrow palpebral fissures, midface deficiency, small ears, mild webbing of the neck with redundant skin, broad chest, low-placed and widely set nipples, and pudgy hands with mild hypoplasia of the nails (Fig. 15–22).

No similar condition was known in any member of the family. Both parents were normal, and consanguinity was denied. Chromosomes were normal. However, the proband was born following six second-trimester spontaneous abortions.

Herrmann syndrome

Herrmann et al (114) described a provisionally unique-pattern syndrome consisting of craniosynostosis, severe symmetrically malformed limbs, and cleft lip-palate. A chromosome study was normal.

The skull was microbrachycephalic. Synostosis involved mainly the coronal suture; the sagittal and lambdoid sutures remaining partially open. The metopic suture was patent. Ocular hypertelorism, occipital capillary stain, protruding dysplastic ears, deviation of the nasal septum, and cleft lip-palate were reported. Severe mental retardation was noted.

Radial aplasia and shortened ulna were observed bilaterally. The hands were in valgus position. Both fused and missing carpal bones were evident. Three metacarpals and three fingers were present on each hand,

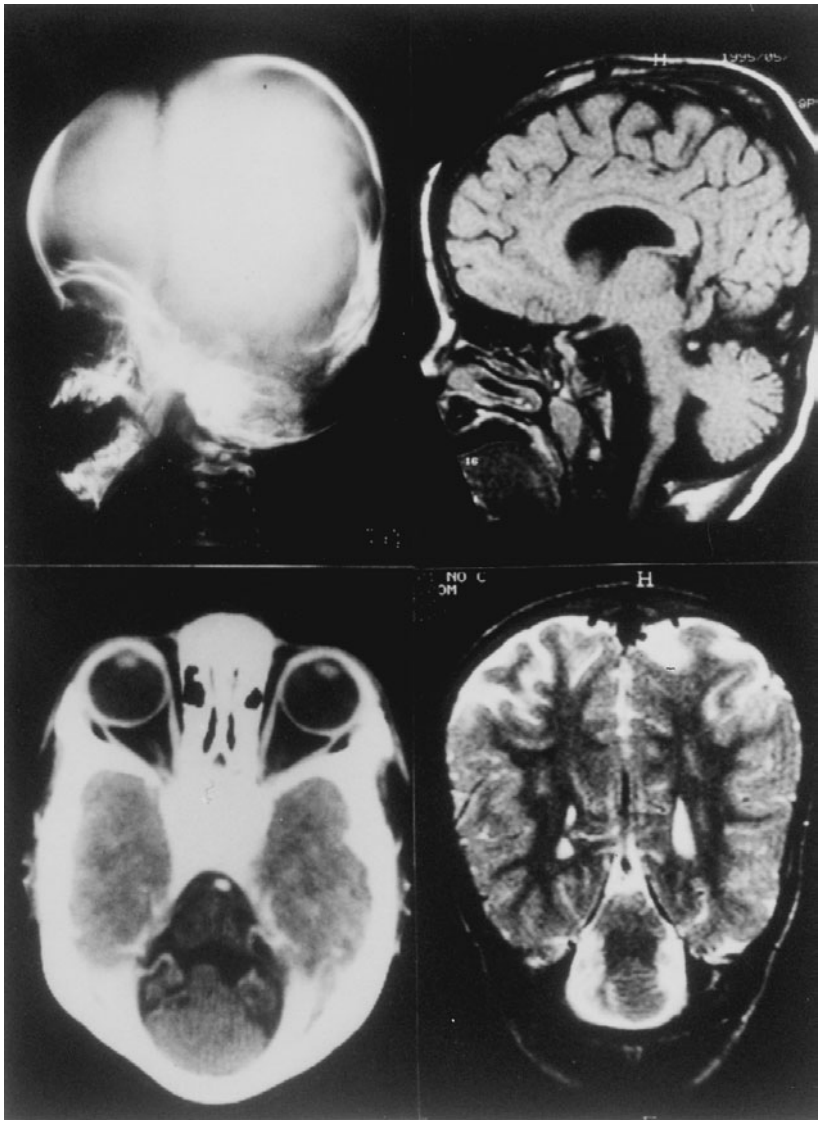


Fig. 15–20. *Gomez-López-Hernández syndrome* (*cerebello-trigeminal-dermal dysplasia*). Top left: Skull, plain radiograph showing a tower-like ridging of the occipital endocranial surface. Top right: Axial CT. Bottom left: Coronal MRI, long TR and long TE. Bottom right: Coronal MRI, short TR and short TE, showing small cerebellum and rhombencephalosynapsis. (From MV Muñoz et al, Am J Med Genet 72:34–39, 1997.)

the fourth and fifth metacarpals and fingers being absent. Two epiphyses were present in each metacarpal. The third finger was split with two separate fingernails (Fig. 15–23).

Congenital hip dislocation, dysplasia of the femoral heads and necks, ankylosis of the knees, and absent fibulas were reported. The feet were held in varus position, and the third and fourth toes on each foot were hypoplastic.

Other findings included narrow shoulders and thorax, slight depression of the lower sternum, and cryptorchidism. A remarkably similar patient was reported by Ladda et al (158).

Hersh syndrome

Hersh et al (115) described a syndrome in a brother and sister consisting of coronal synostosis in the brother, dolichocephaly in the sister, and shared features such as sensorineural hearing deficit, ocular hypertelorism, flat nasal bridge, broad nasal tip, micrognathia, and sparse curly hair. There was no evidence of syndactyly. Intellectual abilities and language skills were normal in the sister. The brother had low-average nonverbal intelligence with significant language delay and autistic-like behavior. Consanguinity was evident; the parents were first cousins. Thus, autosomal recessive inheritance of the Hersh syndrome seems likely.

Holoprosencephaly/craniosynostosis syndrome (Genoa syndrome)

Camera et al (32) reported two sibs with semilobar holoprosencephaly and primary craniosynostosis. Autosomal recessive inheritance is likely.

Both holoprosencephaly (50,51,57) and craniosynostosis (47,48) are heterogeneous. The face predicts the brain in about 80% of holoprosencephalic cases (69). In 20%, including the patients reported by Camera et al (32), the face is nondiagnostic. Craniosynostosis may occur secondarily in holoprosencephaly because of the associated microcephaly. The metopic suture may be fused specifically in some cases of holoprosencephaly. However, in the cases of Camera et al (32), craniosynostosis is both primary and multisutural.

Hunter-McAlpine syndrome

Hunter et al (122) described a syndrome in 1977 consisting of a characteristic facial appearance together with microcephaly, mental retardation, short stature, minor acral skeletal anomalies and, less commonly, craniosynostosis and congenital heart defects (Fig. 15–24). Autosomal dominant inheritance with reduced penetrance was evident. Thomas et al (263) reported a case with more severe skeletal abnormalities than previously described together with interstitial deletion of chromosome 17q. A third

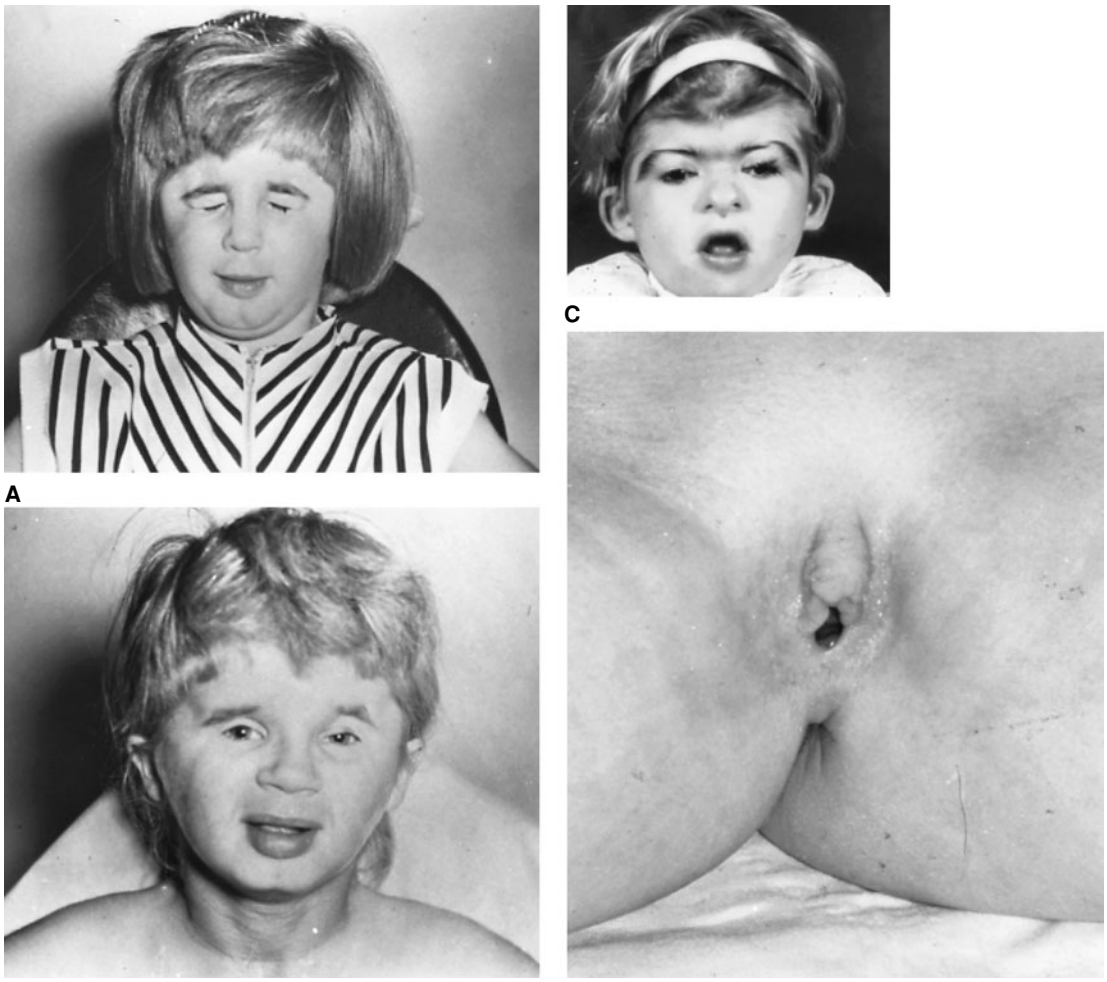


Fig. 15–21. *Gorlin-Chaudhry-Moss syndrome*. (A–C) Note hypertrichosis, severe midface hypoplasia, and eyelid ptosis. Patient in C is reminiscent of de Lange syndrome. (D) Hypoplasia of labia majora. (A,B,D from RJ Gorlin et al, J Pediatr 56:778, 1960. C courtesy of W Lenz, Münster, Germany.)

family was described (2). By using both the first and second authors' names from the original paper (122), Cohen proposed the designation "Hunter-McAlpine syndrome" to avoid confusion with mucopolysaccharidosis, types II-A and II-B (Hunter syndrome).

Facial features included almond-shaped eyes, small nose, and small downturned mouth. When craniosynostosis occurred, the coronal and lambdoid sutures were involved. Strabismus and mildly low-set ears were encountered in some instances. Skeletal anomalies included brachydactyly, cone-shaped epiphyses of the middle phalanges, clinodactyly, incomplete extension at the elbows, and spina bifida occulta in the lumbosacral region. Low-frequency findings included ASD and inguinal hernia.

The degree of mental deficiency ranged from mild, with minor motor and speech delay, to severe retardation, requiring institutional care. Affected individuals were frequently below the 3rd centile for head circumference and below the 3rd centile for height as well.

Hypomandibular faciocranial syndrome

Hypomandibular faciocranial syndrome consists of craniosynostosis, prominent eyes, deficient midface and zygomatic arches, short nose with anteverted nares, protruding lower face, minute oral aperture, persistent buccopharyngeal membrane, severe mandibular hypoplasia, and various extracephalic anomalies (Fig. 15–25). Several papers have been published (173,188,240). The disorder has been reviewed by Ludman et al (173). Two more examples were reported by Wilson and Kerr (280a).

Polyhydramnios is probably due to inability to imbibe significant amounts of amniotic fluid during intrauterine life. Early death occurred in two of the three recorded cases. One child was still living at age 4 1/2 years with severe mental deficiency.

Craniosynostosis is variable, affecting only the coronal suture in the two sibs observed by Schimke et al (240), but affecting multiple sutures in the case described by Ludman et al (173). The tongue was hypoplastic in one case and found as a remnant in another (240). In the patient of Ludman et al (173), the tongue was small but well developed except for a bifid tip, indicating incomplete fusion of the lateral lingual tubercles.

The term "hypomandibular faciocranial dysostosis" was coined by Cohen in 1988 (48), and the arranged order of the term ("hypomandibular faciocranial" rather than "craniofacial hypomandibular)" was used to emphasize the lower facial abnormalities, which are the most striking features of the condition. The findings of ASD, PDA, prominent labia minora, and bicornuate uterus demonstrate that extracephalic anomalies may also occur.

Affected sibs (188,223a,240) suggest autosomal recessive inheritance. However, gonadal mosaicism for a dominant mutation or an undetected microdeletion cannot be ruled out at this writing.

The condition is so distinct that differential diagnosis is academic. In *otocephaly*, severe hypognathia, hypoglossia, and microstomia occur together with low-set and sometimes fused ears.

Fig. 15–22. *Hall syndrome*. Unilateral synostosis involving coronal suture, craniofacial asymmetry, downslanting and narrow palpebral fissures, midface deficiency, mild neck webbing, and broad chest. Note Turner-like phenotype. (Courtesy of JG Hall, Vancouver, British Columbia.)

Ives-Houston syndrome

Ives and Houston (129), in 1980, reported a lethal, autosomal recessive syndrome consisting of intrauterine growth retardation, marked microcephaly with craniosynostosis, and severe malformations of the limbs, such as greatly shortened forearms, fused elbows, and the presence of two-to-four abnormal fingers (Fig. 15–26). The syndrome was discovered in a highly inbred, predominantly Cree Indian community in Northern Saskatchewan with 14 known instances.

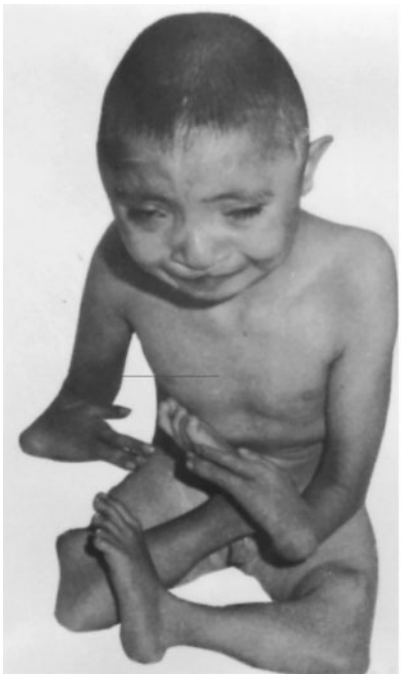
Growth deficiency of prenatal onset was marked; birth weights varied from 450g to 1390g. At least six infants were in breech position at delivery. Four infants were stillborn; seven expired within 20 minutes following severe gasping; and three died of recurrent apneic episodes.

Severe microcephaly with complete craniosynostosis was evident in every case. Each had a small brain with primary sulci and gyri. Absence of the corpus callosum was noted in three instances. Facial features included short palpebral fissures, small eyes, prominent broad nose, micrognathia, and microstomia. Cleft soft palate was reported in one instance.

Upper limb anomalies were severe and consisted of fixed elbows and markedly shortened forearms. In four cases, only a single forearm bone was present, and it was not possible to determine whether it was a radius or an ulna. An abnormal and variable pattern characterized the hands. Two-to-four malformed digits were present. Most commonly, three digits were observed; two were well-developed central digits with a less well-developed index finger. A fifth finger, when present, had a tendency to arise from a bifid fourth metacarpal. A thumb was noted in only one instance. The legs were less severely affected. First metatarsals and great toes were shortened. The fourth and fifth toes were either hypoplastic or absent. Short legs and absence of the fibulas were noted in one case. Other findings included two or more narrow ribs, sacral segmentation defects, and, in some instances, hip dislocation.

Jackson-Weiss syndrome

Jackson and Weiss (133), in 1976, reported an autosomal dominant syndrome consisting of craniosynostosis, midfacial hypoplasia, and



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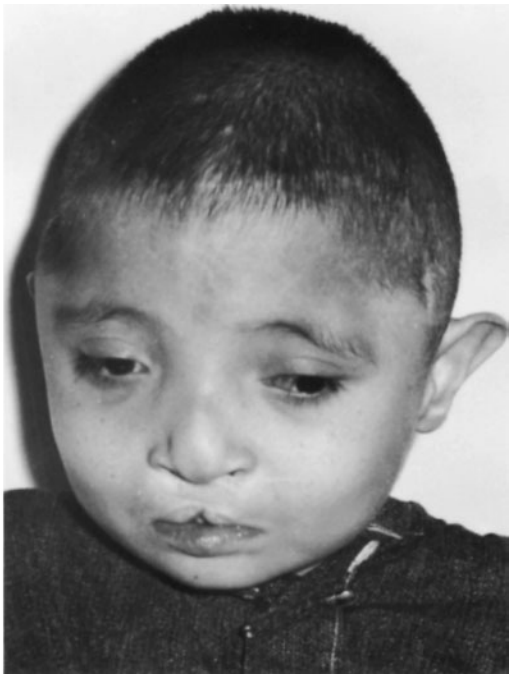


B

Fig. 15–23. *Herrmann syndrome*. (A,B) Note symmetric limb malformations, microbrachycephaly, hypertelorism, repaired cleft lip. (From J Herrmann et al, Rocky Mt Med J 66:45, 1969.)

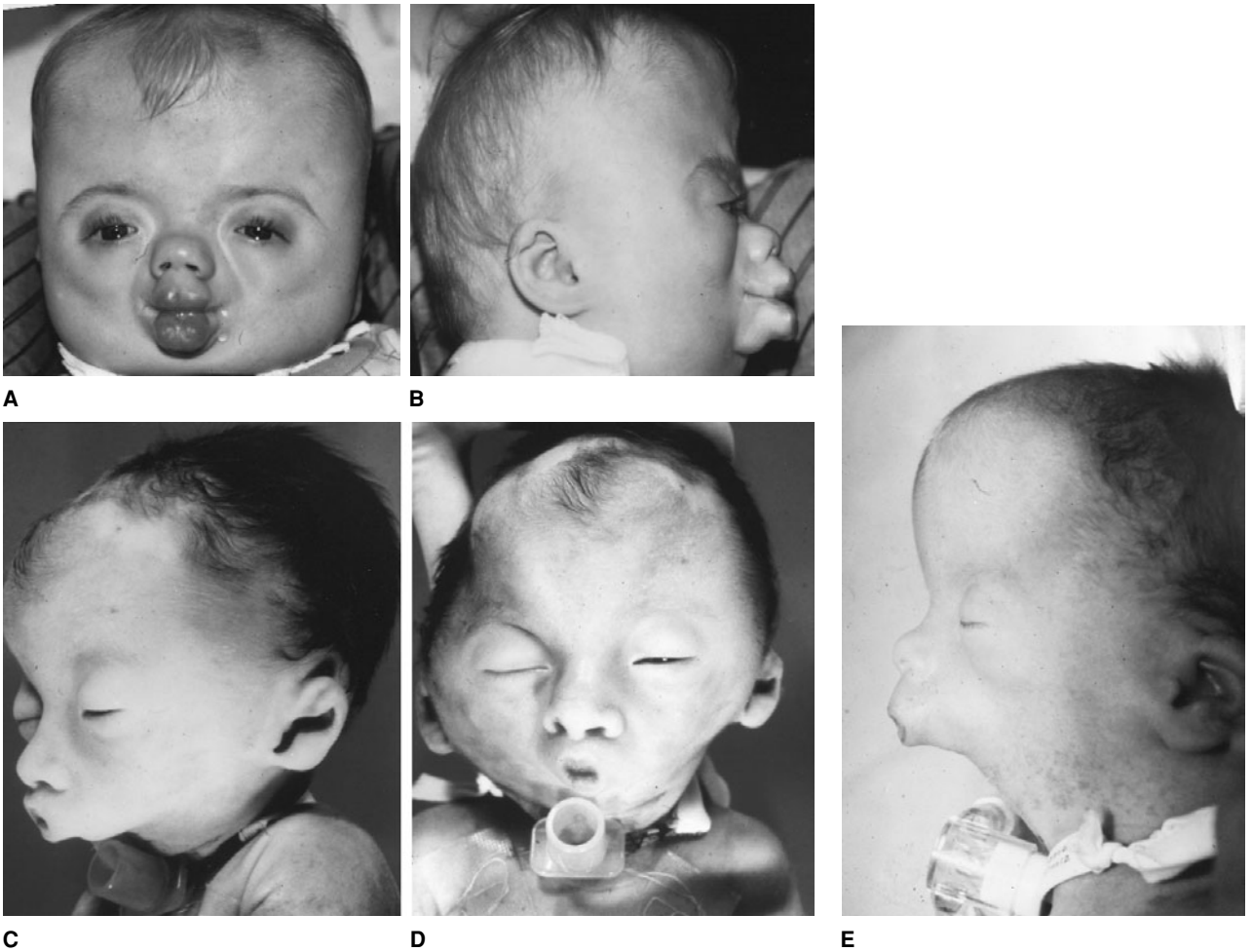
A B C

Fig. 15–24. *Hunter syndrome*. (A–C) Characteristic facial appearance in same patient at different ages. (Courtesy of W Lenz, Münster, Germany.)

abnormalities of the feet (Figs. 15–27 and 15–28). Eighty-eight affected individuals were examined and another 50 were reliably reported to be affected, thus making a total of 138. Penetrance was extremely high, and great variability in expression was observed. Some affected individuals had syndactyly of the second and third toes, usually mild, and broad great toes that deviated medially. The only consistent manifestation was some abnormality in the clinical or radiographic appearance of the feet. Minimal manifestations included short, broad first metatarsal, abnormally shaped tarsal bone, and calcaneocuboid fusion. In some instances, the first and second metatarsals were fused, the second and third metatarsals were partially fused, the tarsal bones were abnormally shaped, and fusion of the navicular and first cuneiform bone occurred. Some affected individuals showed no clinical or radiographic abnormalities of the face or skull. Only one instance each of 3–4 syndactyly of the fingers, preaxial polydactyly of the feet, and fusion of the phalanges in the thumb were observed. No mentally retarded individuals were detected in this family.

Escobar and Bixler (76) reported an autosomal dominant pedigree in which the "classic forms of the Pfeiffer and Apert syndromes as

Fig. 15–25. *Hypomandibular faciocranial syndrome.* (A–E) Absence of mandible, minute mouth aperture with pursing of lips, hypoplasia of maxilla and zygomatic arches, deficiency of orbits and midface, and coronal synostosis. (A,B,E from RN Schimke et al, Am J Med Genet 41:102, 1991. C,D from MD Ludman et al, Am J Med Genet 47:352, 1993.)



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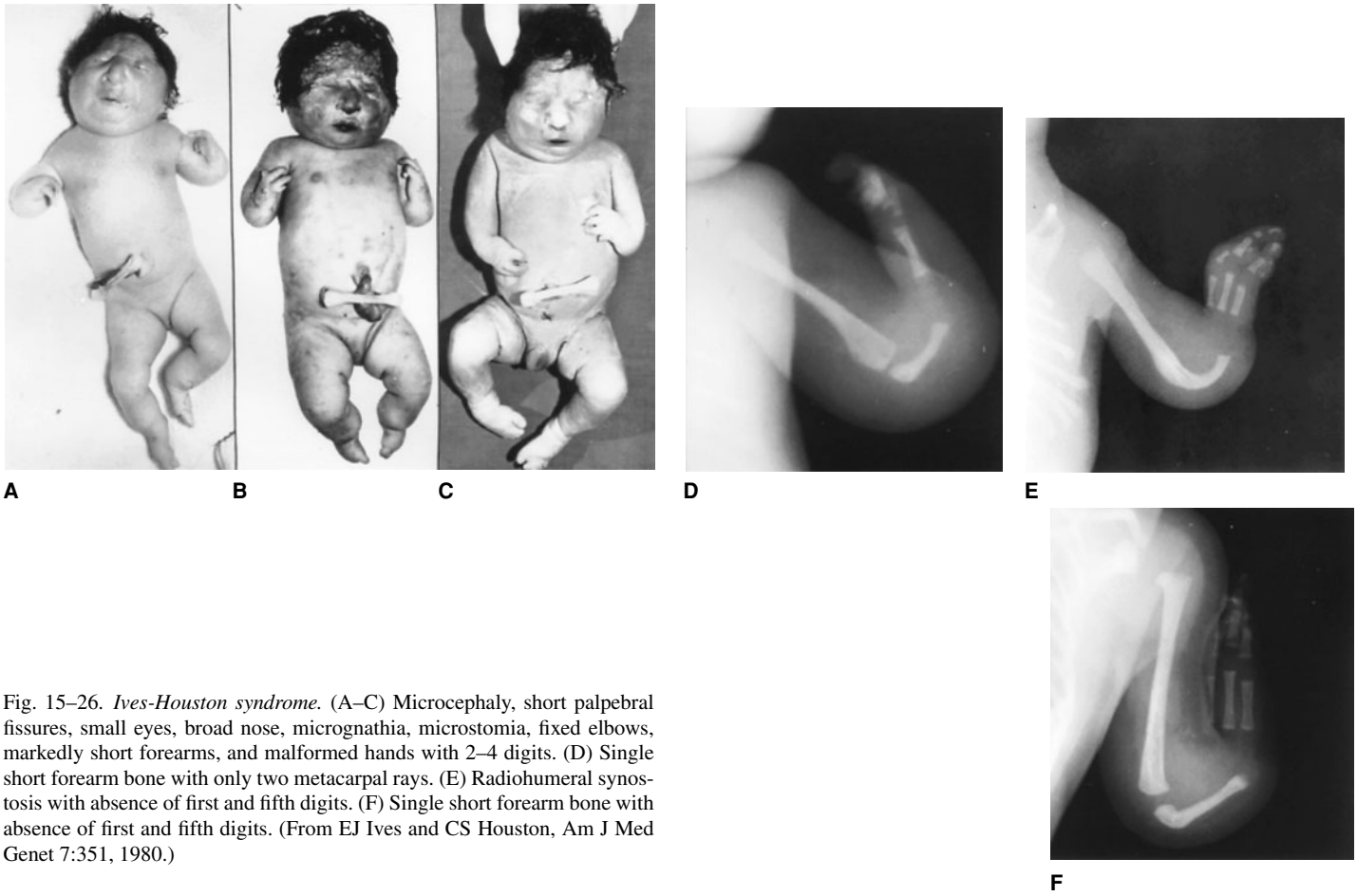


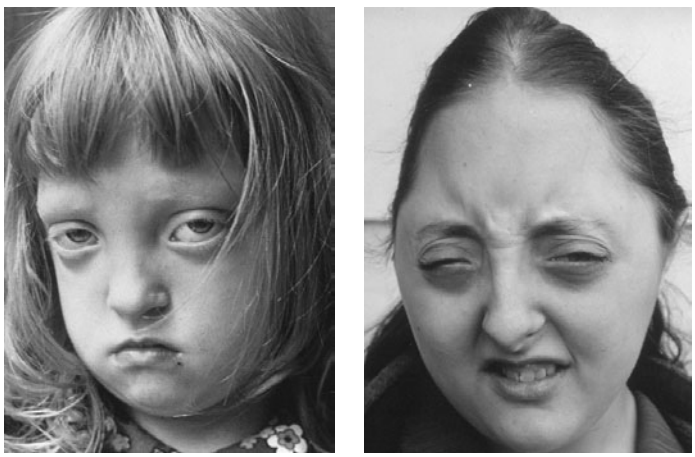
Fig. 15–26. *Ives-Houston syndrome.* (A–C) Microcephaly, short palpebral fissures, small eyes, broad nose, micrognathia, microstomia, fixed elbows, markedly short forearms, and malformed hands with 2–4 digits. (D) Single short forearm bone with only two metacarpal rays. (E) Radiohumeral synostosis with absence of first and fifth digits. (F) Single short forearm bone with absence of first and fifth digits. (From EJ Ives and CS Houston, Am J Med Genet 7:351, 1980.)

well as transitional types . . . occurred . . . Several members of the family . . . [had] . . . a facial resemblance to Crouzon disease." Penetrance was very high.

Jabs et al (132) reported a mutation in the Jackson-Weiss family: Ala344Gly. The same mutation has also been found in a family with Crouzon syndrome (102,165,258). A discussion of the Jackson-Weiss phenotype in a patient with a P252R mutation in FGFR1 has been presented (225a). One family reported as having "Jackson-Weiss syndrome" (4) also called "Adelaide type craniosynostosis" (117) is known to have FGFR3-associated coronal synostosis syndrome (Pro250Arg) (185).

Even though the mutation for the Jackson-Weiss family has also been reported in a Crouzon family, caution is urged in genetic counseling. Most families with *Crouzon syndrome* breed true. Jackson-Weiss syndrome appears to be very uncommon. Perhaps the differences may be explained by modifying genes.

Fig. 15–27. *Jackson-Weiss syndrome*. (A) Hypertelorism, proptosis, and midface deficiency. (B) Severe acrocephaly. (A,B from CE Jackson et al, J Pediatr 88:963, 1976).



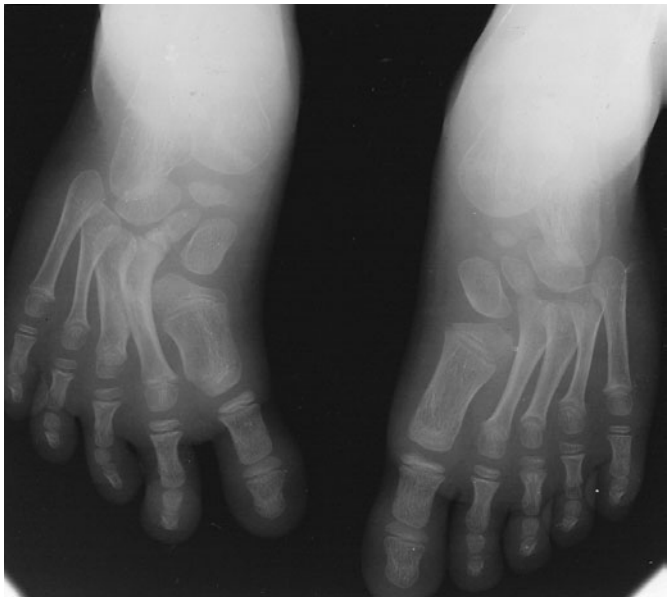
Jones craniosynostosis/Dandy-Walker syndrome

Dandy-Walker malformation and craniosynostosis may each occur as an isolated abnormality or as components of various malformation syndromes. Braddock et al (25) reported an autosomal dominant syndrome of sagittal synostosis and Dandy-Walker malformation.

This distinctive malformation syndrome was discussed with MMC by Kenneth L. Jones, one of the authors, in 1977 (42). Cohen listed the condition as Jones syndrome in a 1979 tabulation of craniosynostosis syndromes (45) and later devoted a one paragraph description to it in 1986 (47). The paper of Braddock et al (25) is the first report of Jones syndrome in detail.

Kozlowski craniosynostosis syndrome

Kozlowski et al (149) reported a 12-year-old girl with short stature, mental deficiency, coronal synostosis, fusion of C_2–C_3, severe Scheuermann-like kyphosis of the upper thoracic spine, hamate-capitate fusion, first rib gaps, and complete duplication of the internal genitalia with a double uterus. Facial dysmorphism was characterized by ocular hypertelorism, ptosis of the eyelids, short downslanting palpebral fissures, low-set ears,



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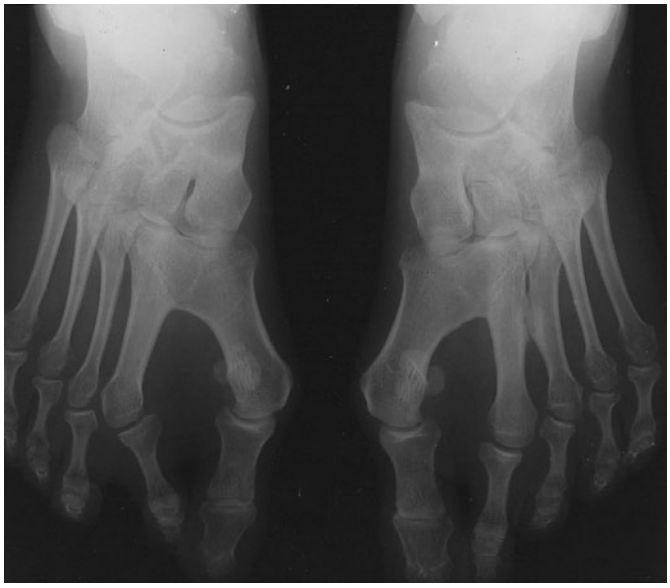


B

Fig. 15–28. *Jackson-Weiss syndrome*. (A) Short, broad first metatarsals and abnormally shaped tarsal bones. Oblique views of patient's feet (not illustrated) showed calcaneocuboid fusion. (B) Short, broad first metatarsals, fused first and second metatarsals, partially fused second and third left metatarsals, abnormally shaped tarsal bones, and fused navicular and first cuneiform bones. Calcaneocuboid coalition is also present, although it cannot be seen on radiograph. In this patient, the face and skull were normal. (A,B from CE Jackson et al, J Pediatr 88:963, 1976).

enlarged tragus, and hypoplastic lobules. The thumbs were proximally placed with fixed flexion. Fifth finger clinodactyly and limited elbow extension were also observed.

Lampert syndrome

Lampert et al (160) reported a sporadic instance of a patient with craniosynostosis, long thin face, midface hypoplasia, mild micrognathia, long tapering fingers, postaxial polydactyly, congenital hip dislocation, hallux valgus, and absent uterus.

Lin-Gettig syndrome

Lin and Gettig (166) reported a syndrome of craniosynostosis, agenesis of the corpus callosum, severe mental deficiency, hypogonadism, and a distinctive facial appearance. Two affected brothers had midline sutural involvement (sagittal in one, metopic in the other), ptosis of eyelids, blepharophimosis, slanted palpebral fissures, epicanthic folds, thin lips, and a long hypoplastic philtrum. Hypertonia, long slender fingers, and contractures were also evident. Third degree hypospadias was striking. Karyotypes were normal. The syndrome may be autosomal recessive, although X-linked inheritance cannot be ruled out. One of the sibs had features suggestive of Opitz C trigonocephaly syndrome, although microcephaly, abnormal palate with midline furrow, oral frenula, loose skin, and digital and limb malformations were absent.

Lowry syndrome

Lowry (170), in 1972, described a syndrome in two male sibs consisting of craniosynostosis and fibular aplasia. Chromosome studies of one sib were normal. A 25-year follow-up of this patient was provided by Lowry in 1993 (171). The other sib died shortly after birth of respiratory distress, and no chromosome studies were carried out. Consanguinity was noted, suggesting an autosomal recessive mode of transmission.

In one patient, both coronal and sagittal sutures were synostosed. In the other, only the coronal suture was involved. The eyes were prominent in both cases, and strabismus was noted in one. A partial cleft of the hard and soft palates was observed in one patient, a highly arched palate in the other (Fig. 15–29A).

The fingers were normal, and single palmar creases were found in both cases. Absent fibulas, talipes equinovarus, and normal toes were also reported in both cases (Fig. 15–29B).

Other findings included cryptorchidism in both sibs; short sternum, pilonidal dimple, and normal intelligence in one sib; and large posterior fontanelle, Wormian bones, low-set ears with pointed helices, short webbed neck, and mild chordee in the other sib.

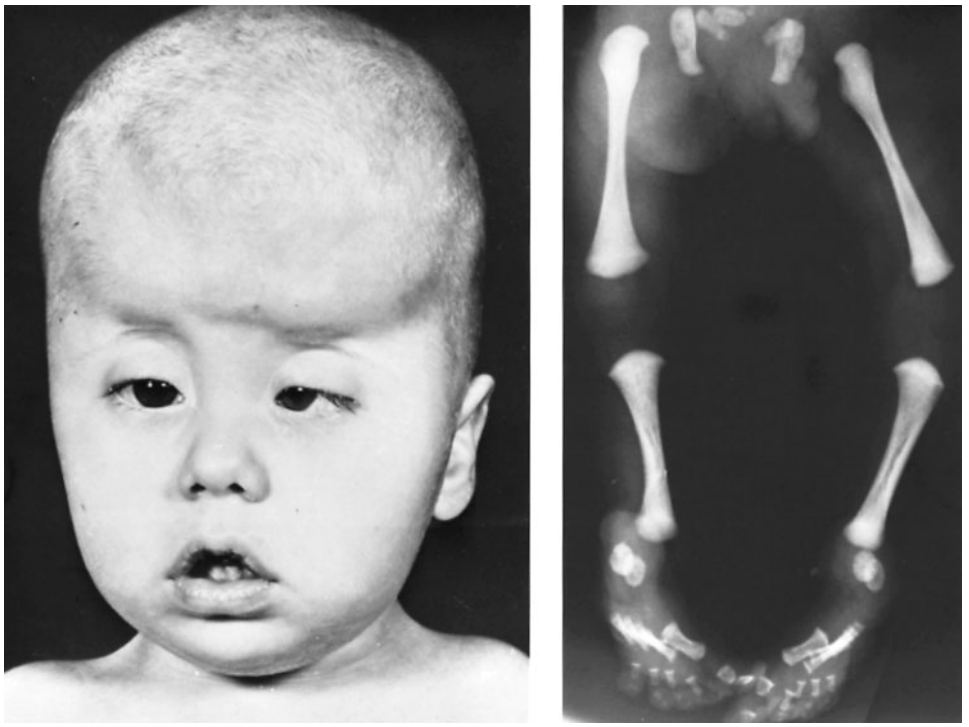
Lowry-MacLean syndrome

In 1977, Lowry and MacLean (172) reported a syndrome characterized by craniosynostosis, microcephaly, facial dysmorphism, ocular proptosis, glaucoma, cleft palate, delayed dentition, preauricular tags and pits, eventration of the diaphragm, congenital heart defect, narrow hyperconvex fingernails, growth failure, and mental deficiency (Fig. 15–30). Other cases have been described by Kousseff and Ranells (148) and Al-Torki et al (8). The name Lowry-MacLean syndrome was introduced by Cohen in 1978 (43) and 1979 (45). Al-Torki et al (8), noting that the father and the sister of their proband also had glaucoma, suggested autosomal dominant inheritance with variable expressivity.

All three reported patients had mental deficiency, but only the patient of Lowry and MacLean (172) had hypoplasia of the corpus callosum, hydrocephalus, and seizures. Congenital heart defects have been variable: ASD, pulmonic stenosis, and bicuspid pulmonic valve in the patient of Lowry and MacLean (172); pulmonic stenosis, PDA, and dysplastic valves in the patient of Kousseff and Ranells (148); and VSD and coarctation of the aorta in the patient of Al-Torki et al (8). One patient had hypospadias, cryptorchidism, and inguinal hernia (148) and one had osteoporosis (8).

Meier-Gorlin (ear-patella-short stature) syndrome

Meier et al (178), in 1959, Gorlin et al (101), in 1975, and others (22,28, 40,89,99,125,168) described an autosomal recessive syndrome of disproportionate short stature, microtia, micrognathia, and absent patellas. There have been several pairs of affected sibs (22,40,89,102a, 125,168,240a). The joints have restricted motion, laxity, or aseptic necrosis. Skeletal alterations include slender long bones, delayed

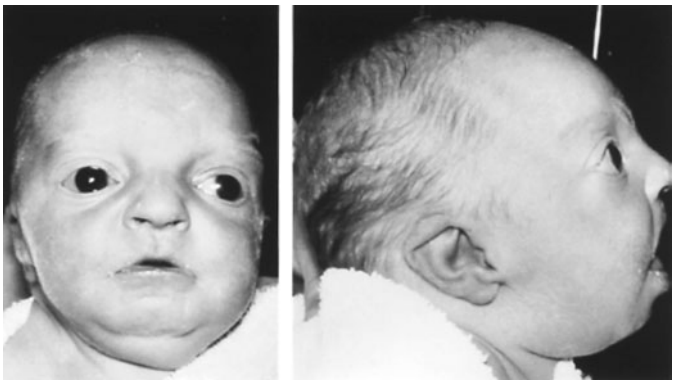


A B

Fig. 15–29. *Lowry syndrome*. (A) Craniosynostosis with tower skull, ptosis of eyelids, and strabismus. (B) Radiograph showing fibular aplasia and talipes equinovarus. (From RB Lowry, J Med Genet 9:227, 1972.)

skeletal maturation, short ribs, hooked clavicles, flat or absent glenoid fossa, absent patellae, and clinodactyly of fifth fingers (22,40,99,125) (Table 15–6). Blount osteochondritis dissecans and bilateral aseptic necrosis of the lateral femoral condyles have been noted (99). Height is below the 3rd centile, but there may be some catch-up growth during adolescence (89). Hearing loss due to Mondini malformation has been documented (168). Craniosynostosis has been noted by Hurst et al (125) and Loeys et al (168). Cryptorchidism and clitoromegaly have been reported. The breasts may be hypoplastic (262a). Lacombe et al (157), postulated that the syndrome is similar to the short ear mouse phenotype, which is an osteochondrodysplasia due to a mutation within the BMP5 gene.

Fig. 15–30. *Lowry-MacLean syndrome*. (A,B) Ocular proptosis, divergent squint, mild downslanting of palpebral fissures, prominent nose, and low-set posteriorly angulated ears with abnormal helix and preauricular fistula. [From RB Lowry and JR MacLean, Birth Defects 13(3B):203, 1977.]



A B

Table 15–6. *Meier-Gorlin (ear-patella-short stature) syndrome*

Features	Frequency (n = 10M, 12F)
Infancy	
Birth length (<3%)	10/15
OFC (<3%)	10/17
Proportionate short stature	11/14
Failure to thrive	10/11
Respiratory problems	7/9
Craniofacial	
Suture closure early	8/15
Microcephaly	12/15
Microtia	22/22
Low-set pinnae	6/7
Dysmorphic pinnae	7/12
Atretic auditory canals	3/4
Small mouth	14/14
Full lips	3/5
Maxillary hypoplasia	6/8
Mandibular hypoplasia	19/21
Cleft palate	3/8
Skeletal features	
Delayed bone age	13/13
Absent patellae	12/17
Hypoplastic patellae	3/17
Slender long bones	12/12
Flat epiphyses	7/9
Abnormal glenoid fossae	5/10
Hook-shaped clavicles	15/10
Rib gaps	2/8
Narrow short ribs	3/4

(EMHF Bongers, personal communication, 2001.)

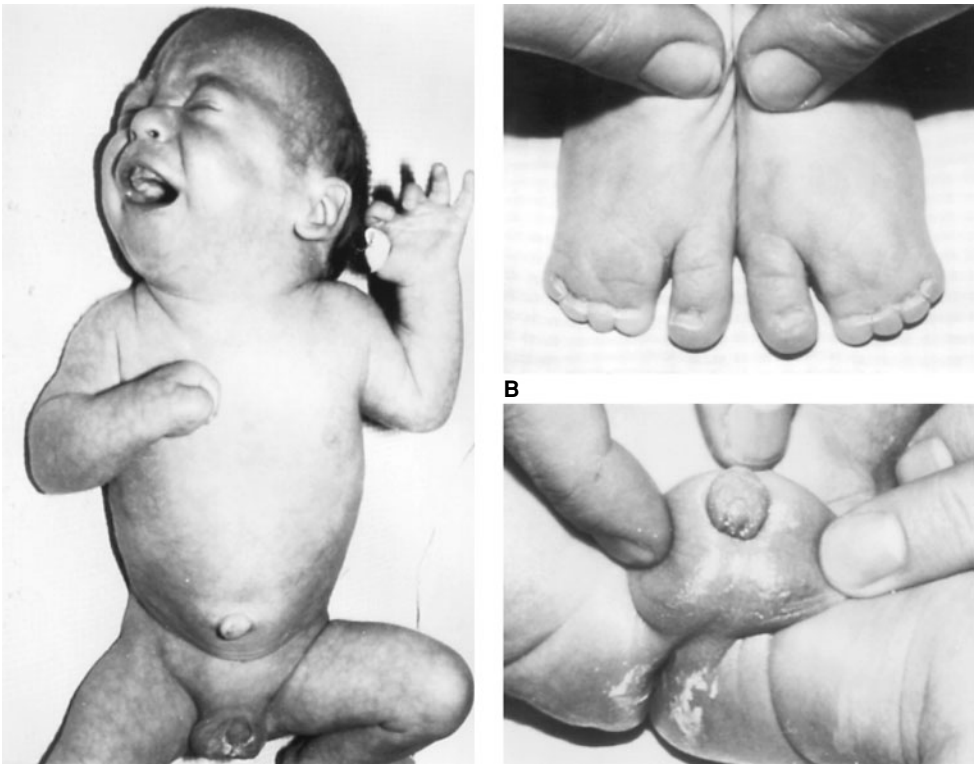


Fig. 15–31. *Pfeiffer type dolichocephalosyndactyly*. (A) Note dolichocephaly, micrognathia, and unilateral ectrodactyly. (B) Note bilateral syndactyly of second, third, fourth, and fifth toes. (C) Note perineoscrotal hypospadias. (From RA Pfeiffer et al, Eur J Pediatr 146:74, 1987.)

Osteocraniostenosis

Verloes et al (272), in 1994, reported a skeletal dysplasia in three unrelated fetuses, calling it osteocraniostenosis. Features included cloverleaf skull, microphthalmia, aniridia, extremely thin diaphyses, flared metaphyses, mild micromelic dwarfism, brachydactyly, and splenic hypoplasia. Whether the cases of "severe Hallermann-Streiff syndrome" reported by Dennis et al (70) really had osteocraniostenosis has been debated (70,270).

Histopathologic examination of the long bones showed abnormal metaphyseal cartilage and adjacent diaphyseal ossification, excessive modeling of the metaphyses, and, in one instance, dysplasia of the epiphyseal cartilage.

Pfeiffer type cardiocranial syndrome

Pfeiffer et al (203), in 1987, reported male and female siblings with sagittal synostosis, facial dysmorphism, and complex cardiovascular malformations. Cohen (68) named the condition Pfeiffer type cardiocranial syndrom in 1988. Other cases have been described by Stratton and Parsons (253), by Williamson-Kruse and Biesecker (279), and by Digilio et al (72), who noted male and female siblings.

Particularly common are growth deficiency, mental retardation, sagittal synostosis, ocular hypertelorism, downturned mouth, dysmorphic low-set ears, congenital heart defects, hypogonadism, and contractures of the large joints and fingers. Cardiovascular defects are both complex and highly variable, e.g., ventricular septal defect, atrial septal defect, and patent ductus arteriosus in one patient and tetralogy of Fallot, peripheral pulmonic stenosis, and atrial septal defect in another.

Anomalies in Pfeiffer type cardiocranial syndrome are facultative rather than obligatory. One of the siblings reported by Digilio et al (72) did not have craniosynostosis and the patient reported by Williamson-Kruse and Biesecker (279) had no cardiovascular defect. Two instances of affected male and female siblings (65,203) support autosomal recessive inheritance.

Pfeiffer type dolichocephalosyndactyly

Pfeiffer et al (204) reported a distinctive, sporadically occurring syndrome consisting of sagittal synostosis, facial dysmorphism, genitourinary anomalies, and limb defects (Fig. 15–31). Craniofacial features included dolichocephaly, upslanting palpebral fissures, inverse epicanthic folds, bilateral iris colobomas, atypical vessels in the fundus, possibly mild optic atrophy, highly arched palate, and micrognathia. Severe mental deficiency was evident. Perineoscrotal hypospadias and bilateral vesicoureteral reflux were also noted. Ectrodactyly of one hand and bilateral 2–5 syndactyly of the toes were observed. The karyotype was normal and the family history noncontributory.

Richieri-Costa overgrowth syndrome

Richieri-Costa et al (221) described two sibs, presenting with craniosynostosis, mental retardation, overgrowth, distal arthrogryposis, sacral dimple, and joint laxity. The fingers were slender. The hallux was long and in valgus position.

The face was long and thin and the skull dolichocephalic. The nasal bridge was broad and the philtrum short.

Inheritance is autosomal recessive.

Sagittal synostosis/auricular anomalies syndrome (Idaho syndrome II)

In 1977, Cohen (42) reported a patient with sagittal synostosis, auricular anomalies, and arachnodactyly. Findings included scaphocephaly, severe mental deficiency, small, low-set, posteriorly angulated ears, preauricular tags, tortuous ear canals, prominent occiput, downslanting palpebral fissures, dystopia canthorum, stellate iris pattern, highly arched palate, and micrognathia (Fig. 15–32). The neck was long. Other features included narrow thorax, pectus carinatum, mild winging of the scapulas, spina bifida at L5 cubitus valgus, mild genua valga, single palmar crease,

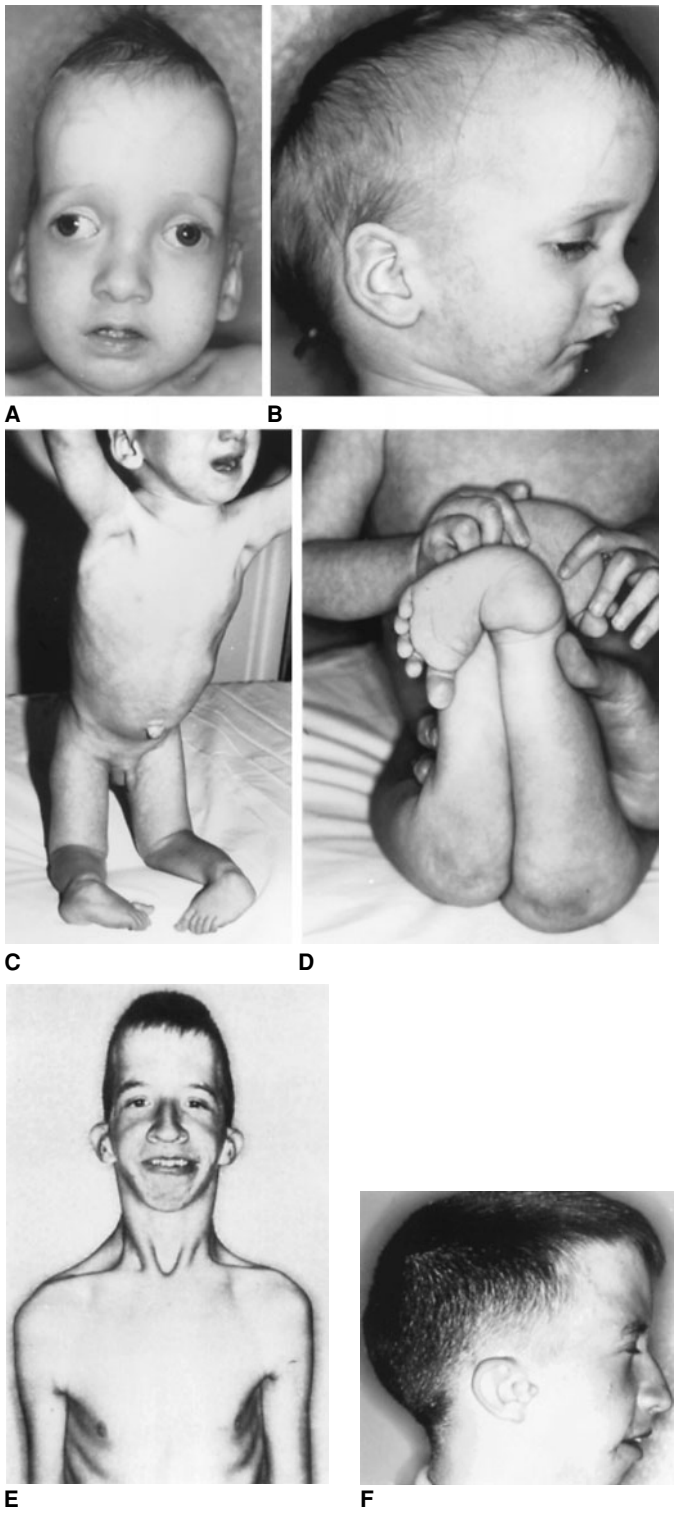


Fig. 15–32. *Sagittal synostosis/auricular anomalies syndrome* (*Idaho syndrome*). (A–D) Craniosynostosis involving sagittal suture, scaphocephaly, prominent veins, strabismus, overfolded helices, micrognathia, umbilical hernia, complete anterior dislocation of tibiae and fibulae with absent patellae allowing the knees to be flexed with the feet against the ventral surface of the body, and foot deformities. (E,F) *Idaho syndrome II*. Craniosynostosis with dolichocephaly, downslanting palpebral fissures, malformed ears, long neck, sloping shoulders, narrow thorax, pectus carinatum, and long arms. Note low-set posteriorly angulated ears with preauricular tags, and micrognathia. (A–D from MM Cohen Jr, The Child With Multiple Defects, Raven Press, New York, 1982. E,F from MM Cohen Jr, J Neurosurg 47:886, 1977.)

arachnodactyly, and bifid renal pelvis. The past history included seizures and bilateral inguinal hernias. The family history was noncontributory.

Sakati syndrome

Sakati et al (229) described a provisionally unique-pattern syndrome consisting of acrocephalopolysyndactyly, short limbs, congenital heart defect, ear anomalies, and skin defects. A chromosome study was normal. The condition should be distinguished from *Carpenter syndrome.*

The calvaria was large and the face was disproportionately small. The orbits were shallow and the eyes prominent. All cranial sutures were synostosed. The ears were dysplastic and low set. A unilateral ear tag was noted. Patches of alopecia with atrophic skin were present above the ears. Linear scar-like lesions were observed in the submental area. The palate was narrow and highly arched. Maxillary hypoplasia and crowding of the upper teeth were reported. The neck was short and the hairline low (Fig. 15–33).

Short arms, cubitus valgus, and short broad hands were evident. Fusion of the proximal interphalangeal joints of the fourth fingers and proximally placed thumbs were observed.

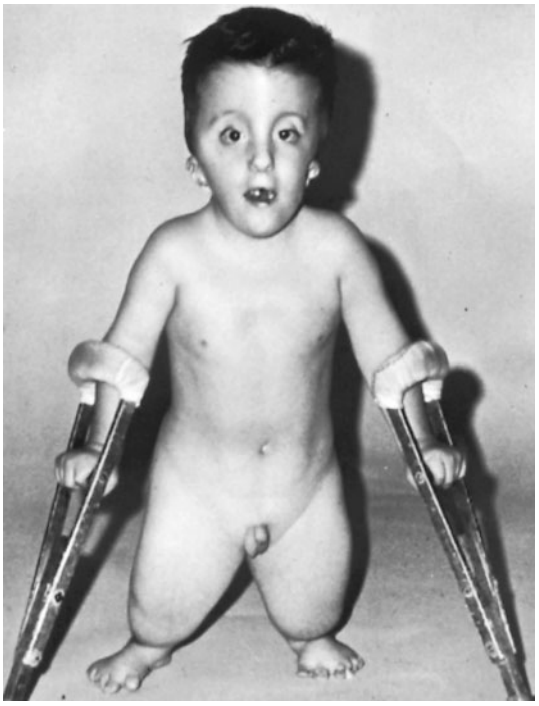
Extreme shortening of the legs and adducted feet were seen together with polysyndactyly (seven toes on one foot and six toes on the other). Radiographic examination showed bilateral coxa valga, lateral bowing of both femurs, hypoplastic tibias, deformity and displacement of the fibulas, and abnormal malposed tarsals and metatarsals. There were six metatarsals in each foot.

Other findings included a congenital heart defect, widely spaced nipples, cryptorchidism, small phallus, and inguinal hernia. Intelligence was normal.

Salinas syndrome

Salinas et al (230) reported a sporadic instance of multiple anomalies confined to the head and face. Features included acrocephaly with a prominent coronal suture thought to be fused, coarse dry hair, malar

Fig. 15–33. *Sakati syndrome*. Acrocephalopolysyndactyly, short limbs, congenital heart defect, ear anomalies, and skin defects. (From N Sakati et al, J Pediatr 79:104, 1971.)



hypoplasia with downslanting palpebral fissures, colobomas of the lower eyelids, small upturned nose, choanal atresia, cleft palate, midline cleft of the lower vermilion, and clefting of the mandibular symphysis.

San Francisco syndrome

In 1978, BD Hall (108) observed a striking syndrome of craniosynostosis, midface hypoplasia, ptosis of eyelids, bulbous nose, and small ears. The disorder followed an autosomal dominant mode of transmission.

Say-Barber syndrome

Say et al (239) reported two brothers with short stature, developmental delay, microcephaly, craniosynostosis in one of them, sloping forehead, beaked nose with high nasal bridge, highly arched palate, micrognathia, large protruding ears, flexion contractures, anal stenosis, hypoplastic patellas, scoliosis, small penis, small testes, and decreased subcutaneous fat (Fig. 15–34). Both brothers developed eczema during infancy and had recurrent infections and transient hypogammaglobulinemia.

Perandones et al (202) reported a third male patient with metopic synostosis, multiple infections, and a marked decrease in leukocyte chemotaxis. At this writing, the genetic basis of Say-Barber syndrome is not clear. However, two affected brothers and a third affected male suggest the possibility of X-linked inheritance.

Say-Meyer trigonocephaly syndrome

In 1981, Say and Meyer (237) described an X-linked recessively inherited syndrome consisting of craniosynostosis especially involving the metopic suture, developmental delay, and short stature. All three patients had vertical ridging of the metopic area together with hypotelorism. In two patients, the lambdoid sutures were also prematurely synostosed, and, in one patient, the sagittal suture was additionally involved. One of the three affected individuals had seizures. Low-frequency findings also included highly arched palate, secondary alveolar ridges, clinodactyly, and VSD. The syndrome needs to be further delineated.

Differential diagnosis includes Frydman trigonocephaly syndrome (this chapter) and Opitz C trigonocephaly syndrome (this chapter). Trigonocephaly may occur with mental deficiency in various chromosomal syndromes, most commonly with *del(9p)* (5) and *del(11q)* (33) and less commonly with *del(13q)* (196) and *dup(13q)* (119).

Say-Poznanski syndrome

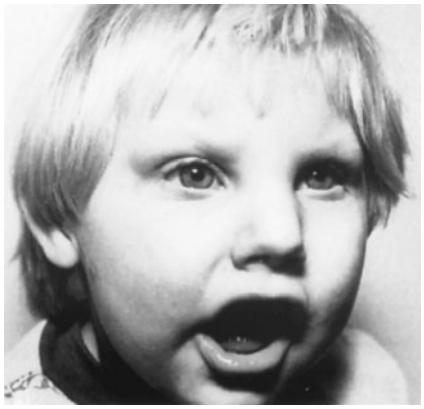
Say and Poznanski (238) reported a distinctive syndrome with cloverleaf skull; polydactyly of the hands and feet; grossly abnormal metacarpals and metatarsals; angular ulnas with fusion to the midportion of the radial bones; short, wide clavicles; winged scapulas; unusually shaped ribs with abnormal spacing between them and with prominent costovertebral junctions; and widely separated ischia (Fig. 15–35).

Other findings included dilated ventricles, agenesis of the corpus callosum, micropenis, small testicular masses with rugae on either side of the penis, anteriorly placed anus, and a sacral dimple.

SCARF syndrome

SCARF is a mnemonic for *S*keletal abnormality, *C*utis laxa, *A*mbiguous genitalia, *R*etardation, and *F*acial abnormalities. The syndrome was reported in two male maternal first cousins, suggesting X-linked recessive inheritance (146).

Both patients had excess nuchal skin. The 7-year-old had a distinctive craniofacial appearance with sparse hair, low anterior and posterior hairlines, epicanthic folds, high nasal bridge, long philtrum, enamel hypoplasia, low-set posteriorly angulated ears, and short neck. Other finding included barrel-shaped chest, hypoplastic nipples, cryptorchidism, and



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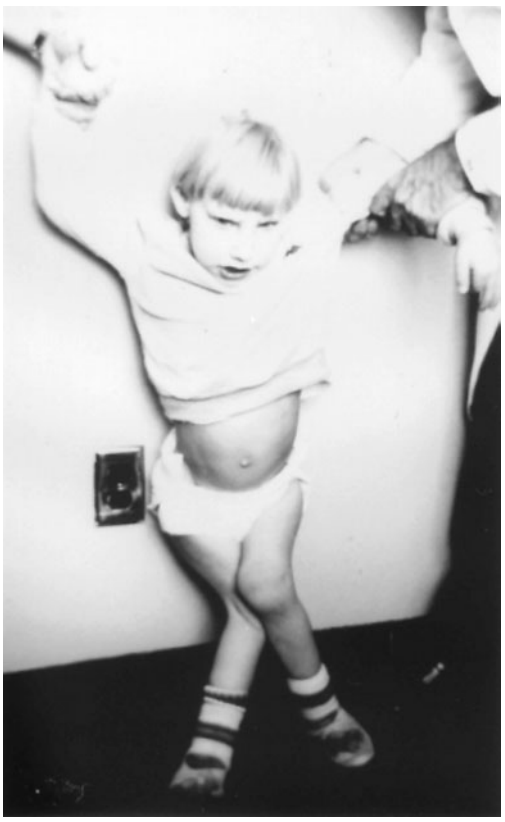
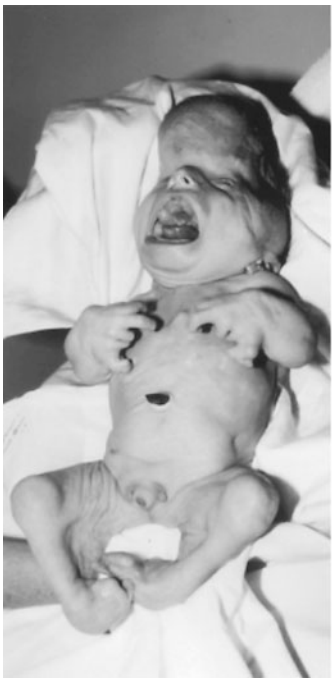


B

Fig. 15–34. *Say-Barber trigonocephaly syndrome.* (A) Age 6.5 years. Note microcephaly, large protruding ears, carp-shaped mouth, and micrognathia. (B) Age 6.5 years. Note elbow contractures, dislocated hips, marked laxity of knees with absent patellae, and inward deviation of lower ends of femora. (From B Say et al, J Med Genet 23:355, 1986.)



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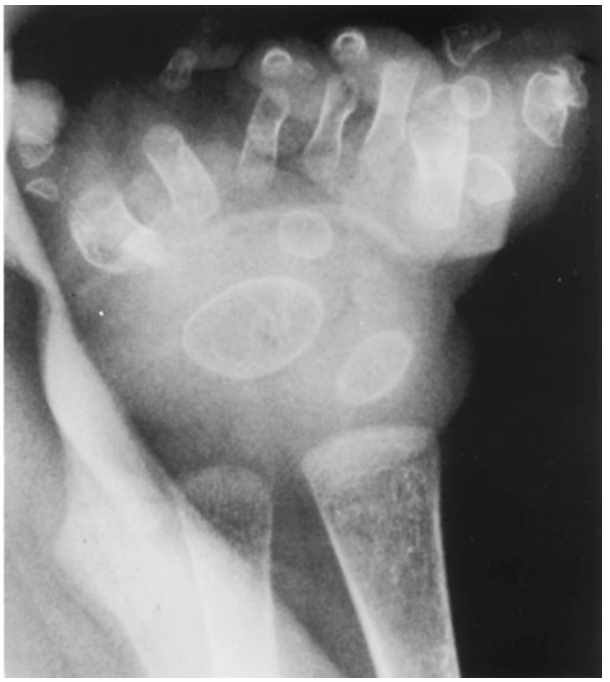


B

Fig. 15–35. *Say-Poznanski syndrome*. (A) Note cloverleaf skull and bizarre polydactyly of hands and feet. (B) Hand radiograph showing polydactyly with many ossicles. (From B Say and AK Poznanski, Pediatr Radiol 17:93, 1987.)

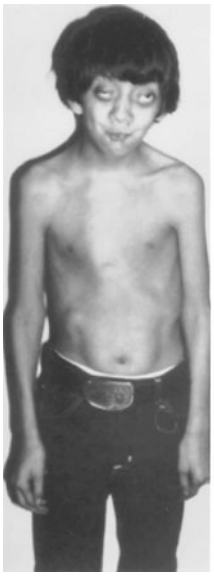
inguinal and umbilical hernias. Multiple nodular liver tumors were discovered by ultrasonography for which no definitive histopathologic diagnosis could be made. The 7-month-old had excess nuchal skin, micropenis, hypospadias, and bifid scrotum.

Shprintzen-Goldberg syndrome

Shprintzen and Goldberg (245), in 1982, described a recurrent-pattern syndrome of craniosynostosis, dolichocephaly, mental deficiency, ocular proptosis, ocular hypertelorism, downslanting palpebral fissures, strabismus, low-set anomalous ears, maxillary hypoplasia, micrognathia, arachnodactyly, hypotonia, camptodactyly, clubfoot, umbilical/inguinal hernia, and other skeletal and connective tissue defects (Fig. 15–36) (Table 15–7). The reader should be aware that this syndrome has nothing to do with *Goldberg-Shprintzen syndrome*. At least 15 cases have been reported (3,103,112,192,227,245,254). The syndrome has been extensively reviewed by Greally et al (103). Adès et al (3) reported four cases and Saal et al (227) noted a patient with cloverleaf skull. Hassed et al (112) observed a patient with cranial asymmetry, osteopenia, and hydrocephalus.

Earlier, in 1979, Cohen (44) used the term Montefiore syndrome to refer to the Shprintzen-Goldberg syndrome because Shprintzen and Goldberg had reviewed their patients with one of us (MMC) during a visit to the Montefiore Hospital. By 1982, Shprintzen and Goldberg (245) had published their paper. In 1986, Cohen (46) coined the term Shprintzen-Goldberg syndrome.

Fig. 15–36. *Shprintzen-Goldberg syndrome.* (A–E) Scaphocephaly, ocular proptosis, strabismus, micrognathia, pectus excavatum, arachnodactyly, camptodactyly of fifth fingers, and enlargement of palatal shelves. (From RJ Shprintzen and RB Goldberg, J Craniofac Genet Dev Biol 2:65, 1982.)



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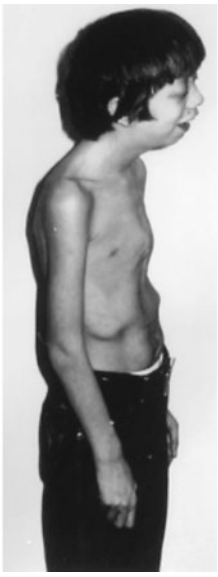

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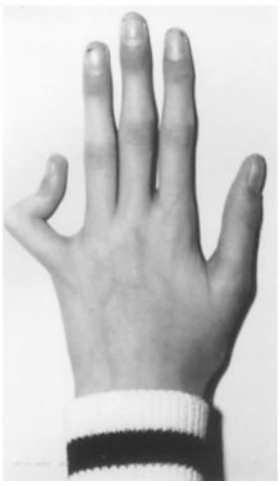
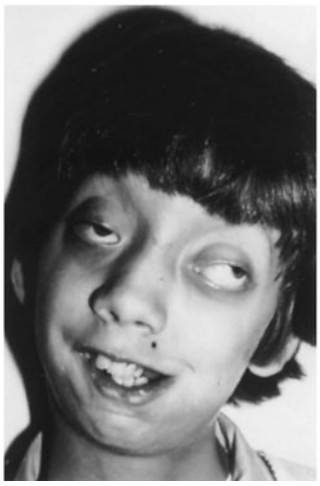
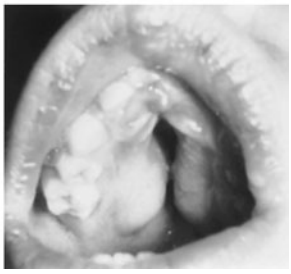


C



D



E

Table 15–7. *Shprintzen-Goldberg syndrome*

Findings	Relative frequency
Performance	
Hypotonia	3/3
Mental deficiency	3/3
Craniofacial	
Craniosynostosis	2/3
Ocular hypertelorism	3/3
Ocular proptosis	3/3
Strabismus	3/3
Downslanting palpebral fissures	2/3
Maxillary hypoplasia	3/3
Obstructive apnea	2/3
Byzantine arch palate	3/3
Micrognathia	3/3
Low-set anomalous ears	3/3
Limbs	
Arachnodactyly	3/3
Camptodactyly	3/3
Talipes equinovarus	3/3
Genua valga	1/3
Hypermobile joints	1/3
Other	
Mitral valve prolapse	1/3
Pectus excavatum	1/3
Pectus carinatum	1/3
Scoliosis	1/3
Hyperelastic skin	1/3
Umbilical hernia	3/3
Inguinal hernia	3/3
Cryptorchidism	1/3
Small external genitalia	1/3

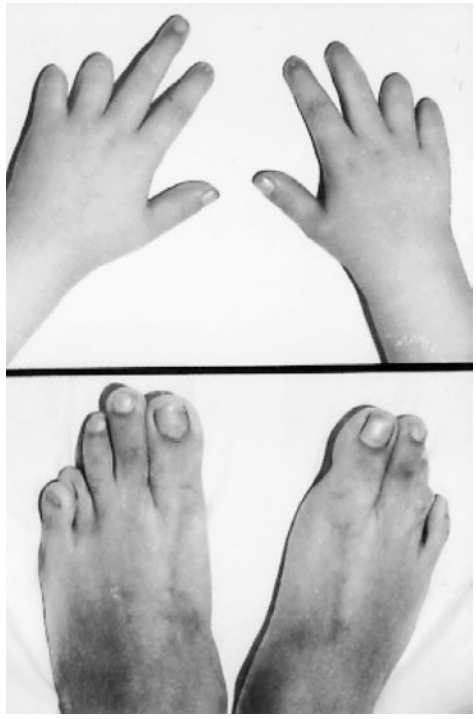
(From MM Cohen Jr, Craniosynostosis: Diagnosis, Evaluation, and Management. Raven Press, New York, 1986.)

At this writing, the etiology is still unknown. Sood et al (248) reported a patient said to have Shprintzen-Goldberg syndrome with a mutation in fibrillin 1 (FBN1): Pro1148Ala. Wang et al (274) and Schrijver et al (242) studied Pro1148Ala and concluded that it was a polymorphic variant rather than a disease-causing mutation.

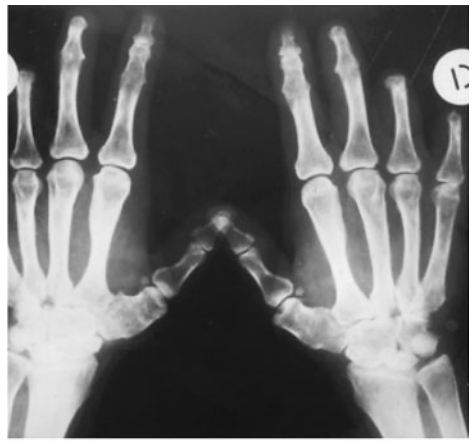
Although there are similarities between Shprintzen-Goldberg syndrome and Marfan syndrome, there are also differences. Part of the problem is that as syndrome delineation has taken place, a widened clinical spectrum of sporadic cases has probably resulted in heterogeneity. Thus, what Shprintzen and Goldberg described originally has been expanded to mean "craniosynostosis with Marfanoid features."

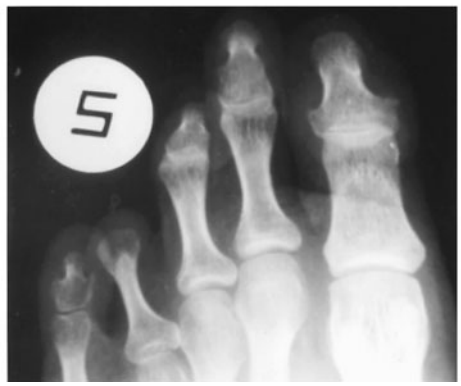
The patients reported by Furlong et al (91), Lacombe and Battin (156), Shah et al (244), and Mégarbané and Hokayem (177) are phenotypically somewhat different from Shprintzen-Goldberg syndrome patients and have normal intelligence. The photographs of Furlong et al (91) show a patient who looks like he has Marfan syndrome, but with accompanying simple synostosis. Greally et al (103) described characteristics that appear to differentiate Shprintzen-Goldberg syndrome from the patients of Furlong et al (91) and Lacombe and Battin (156). These include hypotonia, developmental delay, hydrocephalus, ventriculomegaly, Chiari-I malformation, and C_2–C_3 vertebral anomaly in Shprintzen-Goldberg patients.

Differential diagnosis includes classic *Marfan syndrome* and the syndrome of arachnodactyly, abnormal cranial ossification, protruding eyes, and mental deficiency reported by Kosztolányi et al (147). *Antley-Bixler syndrome* and *sagittal synostosis/auricular anomaly syndrome (Idaho syndrome II)* are discussed elsewhere in this chapter.



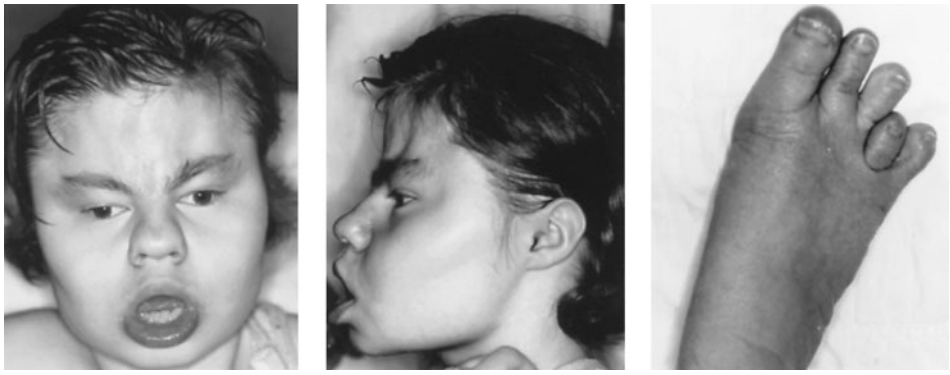
A





B

Fig. 15–37. *Ventruto syndrome.* (A) Hands and feet of affected individuals showing brachydactyly, absence or hypoplasia of middle and distal phalanges, and aplastic or hypoplastic nails. (B) Radiographic changes in hands and feet of affected individuals. Note absence or hypoplasia of middle and distal phalanges and symphalangism. (From V Ventruto et al, J Med Genet 13:394, 1976.)



A B C

Fig. 15–38. *Wisconsin syndrome*. (A,B) Craniosynostosis, sloped forehead, upslanting palpebral fissures, microtia, and hypoplastic helix. (C) Short fourth metatarsal with recessed fourth toe. (A-C courtesy of JM Opitz, Helena, Montana.)

Spear-Mickle syndrome

Spear and Mickle (249) reported a patient with several soft tissue tumors in the left frontal area of the scalp together with unilateral coronal synostosis and plagiocephaly, bifid nose, highly arched palate, lumbar meningomyelocele, cryptorchidism, thoracic kyphoscoliosis, hip dislocation, equinovarus deformity of one foot with calcaneovalgus deformity of the other, and elbow contractures. Chromosomes were normal and there were no other affected individuals in the family. The mother had been a frequent user of alcohol and heroin and the pregnancy had been ectopic.

Spondyloepiphyseal dysplasia/craniosynostosis syndrome

Nishimura et al (193) reported spondyloepiphyseal dysplasia, craniosynostosis, cataracts, micrognathia, cleft palate, and mental deficiency. Most features were present at birth. However, skeletal alterations and cataracts became more pronounced in early childhood. These authors evaluated four affected sibs—a finding consistent with autosomal recessive inheritance.

Coronal synostosis was associated with frontal bossing, bitemporal hollowing, ocular hypertelorism, midface hypoplasia, and short nose. Spondyloepiphyseal dysplasia resulted in mild micromelia during infancy and short trunk with thoracolumbar kyphoscoliosis in late childhood.

Ventruto syndrome

In 1976, Ventruto et al (269) reported a distinctive autosomal dominantly inherited syndrome consisting of brachydactyly, aplastic or hypoplastic nails, symphalangism, carpal and tarsal fusion, dysplastic hip joints, and craniosynostosis (Fig. 15–37). Five affected individuals were reported through three generations. The proband was first seen for acute leukemia.

Craniosynostosis involved the coronal suture. Strabismus was commonly observed. Anomalies of the hands and feet varied in severity and were not symmetric. The thumbs and great toes were not involved. Absence or hypoplasia of the middle and distal phalanges of the fingers was variable in degree and was associated with absence or hypoplasia of the nails. In some instances, both the middle and the distal phalanges were involved. In other instances, only the distal phalanges were affected. Symphalangism, when present, involved the proximal interphalangeal joints. First metacarpals showed brachymetapody. Carpal fusions involved the hamate and capitate or were more complex and involved the trapezium, trapezoid, capitate, hamate, and lunate.

Fusion in the tarsals involved the second and third cuneiform bones and/or other fusions such as between the first cuneiform and scaphoid, the calcaneus and cuboid, or the second cuneiform and second metatarsal. In some affected individuals, one or more cuneiform bones were absent. Brachymetapody involved the first metatarsal in several patients. The pattern of absence or hypoplasia of the middle and distal phalanges of the toes was similar to the pattern observed in the fingers. In the feet, symphalangism also involved the proximal interphalangeal joints. Pelvic radiographs showed osteochondritis or sclerosis involving the acetabular roofs but sparing the femoral necks.

Differential diagnosis includes isolated type-C brachydactyly and type-C brachydactyly with associated abnormalities. Type-C brachydactyly involves the proximal and middle phalanges of the second and third fingers, hypersegmentation of the proximal phalanges, brachymetapody, and symphalangism. Type-C brachydactyly also occurs with Legg-Perthes disease of the hip as a familial syndrome.

Wisconsin syndrome

Wisconsin syndrome consists of craniosynostosis, mental deficiency, upslanting palpebral fissures, microtia, and short fourth metatarsals with recessed fourth toes (Fig. 15–38). Chromosomes were normal and the patient was the only affected member of the family (195).

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Chapter 16
Syndromes of Abnormal Craniofacial Contour

Anencephaly

Anencephaly is a congenital anomaly characterized by an open neural tube in the cephalic region with an exposed mass of degenerate neural tissue on the skull floor. The cranial vault is absent, producing characteristic bulging of the eyes and absence of the neck. Both the membranous neurocranium and the chondrocranium are grossly malformed (Figs. 16–1 and 16–2). Anencephaly is classified anatomically as meroacrania if the defect does not involve the foramen magnum, holoacrania if the defect extends through the foramen magnum, and holoacrania with rachischisis if spina bifida accompanies anencephaly (31).

The reader is referred to the following sources for extensive coverage: general aspects (29–31), classification (28,30,31), anatomy and morphology (10,14,22,30,35,36,41), pathogenesis (11,30), epidemiology (3,5,21, 34,39,46,55,60,63–65,67,75), twin studies (6,11,20,47,52,57,76,77), etiologic factors (9,16,18,25–27,49,56,66,68,70,77), associated anomalies (2,8,12,33,37,40,74), prenatal diagnosis (23,24,43–45), and recurrence risk (7,12,26,38,48,60,79).

Most epidemiologic studies include both anencephaly and spina bifida (ASB) because both arise by nonclosure of the neural tube, the closing of the anterior and posterior neuropores being 24 and 26 days, respectively. Neural tube defects (NTD) in spontaneous abortions is about 10 times higher than NTDs found at term. Of nine specimens in the series of Byrne and Warburton (5), ASB accounted for four of the cases and chromosomal abnormalities were noted in two. Wide divergence in birth prevalence has been recorded. Average prevalence is approximately 1/1000 births in the eastern United States, Denmark, Kenya, Malaysia, India, Taiwan, and South Africa. High prevalence has been observed in Ireland and Wales (3.05–6.79/1000), the remaining British Isles (approximately 2–3/1000), Egypt, and Lebanon. Low prevalence (0.1–0.6/1000) has been noted in France, Norway, Hungary, Czechoslovakia, Japan, and Yugoslavia. Overall, an east–west gradient occurs with higher prevalence in the British Isles followed by eastern North America, then western North America, and finally the Far East (28). Some studies have shown decreasing rates with time (34,55,60,64,66a,75), although the reasons for this are not known. Melnick and Marazita (39) showed that neural tube defects were nearly five times higher in Northern China than in Southern China.

Wide ethnic differences also occur. US whites have a rate of over 1/1000; native Americans, 0.32/1000; and blacks, 0.1–0.4/1000. Striking variation exists in Singapore with the Chinese having a rate of 0.62/1000, Eurasians 1.45/1000, Europeans 2.15/1000, and Sikhs 6.5/1000 (2,3,28).

Most studies show a higher frequency of anencephaly in females than in males, although the sex ratio has been close to 1 : 1 in some studies (28,31). The prevalence in twins is significantly higher than in singletons. The twin female-to-male sex ratio is lower than the singleton female-to-male sex ratio. Among twins, concordance for anencephaly is low (approximately 3.7%) (76,77). Anencephaly appears to occur with higher frequency among monozygotic than among dizygotic twins as same-sexed twins have a higher frequency than opposite-sexed twins. Furthermore, anencephaly seems to be relatively common in conjoined twins (20). It has been concordant among monozygotic (MZ) triplets (59). Concordance between MZ twins is about 7% (19). Neural tube defects are more common in spontaneous abortions (5).

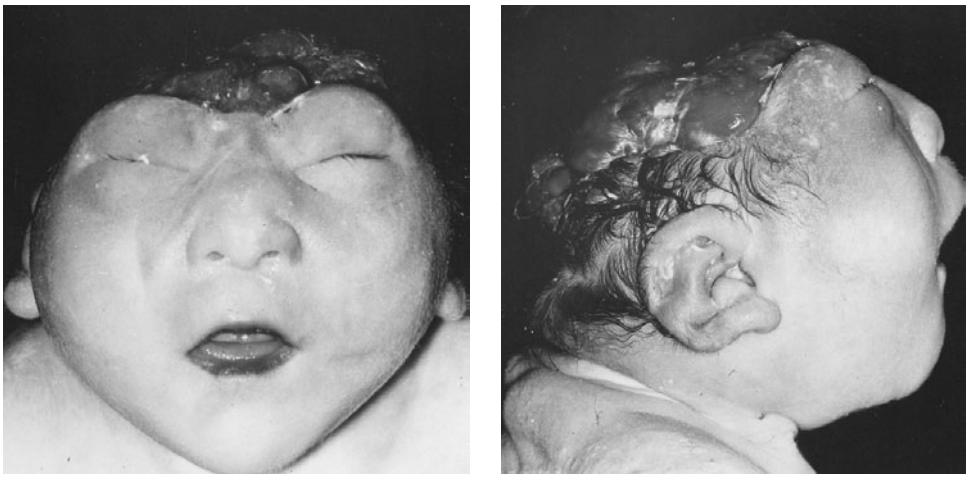
A consistently reported epidemiologic factor has been a higher prevalence of ASB among poorer social classes (28). An epidemiologic study that strongly suggests etiologic heterogeneity is that of Khoury et al (21). After excluding cases of known cause, they divided their sample into two groups, isolated and syndromic (multiple malformations), and found marked differences in the epidemiology of the two groups. The isolated group showed marked predominance of females and whites, geographic variation with an east-to-west gradient, and decreasing rates over time. The group with multiple malformations showed no female predilection and occurred less often in whites, showed no geographical variation, and demonstrated little or no downward trend over time.

The etiology of many cases is unknown, although various factors are known to be responsible for some. The condition is clearly etiologically heterogeneous. Most instances occur sporadically, but a tendency toward familial aggregation of ASB is observed in some pedigrees. In other kindreds, instances of encephalocele or hydrocephaly may also be noted. Most cases appear to be multifactorially determined. Chromosomal, monogenic, and environmental causes have been reviewed by Holmes et al (16), Khoury et al (21), Toriello et al (70), and Farag et al (9). It has been suggested that nongenetic factors fall into two categories: immediate factors related to pregnancy and intergenerational factors related to a woman's growth and development (64). Multi-site closure of the neural tube has been discussed by Nakatsu et al (47a), Van Allen et al (72), and Seller (61).

Autosomal recessive and X-linked families have been recorded (9,70). The Meckel syndrome is most commonly observed with occipital encephalocele, but anencephaly has been noted on rare occasions (16). Holmes et al (16), Khoury et al (21), and van den Maldergem et al (73) have reviewed known chromosomal conditions in which ASB have been reported. Known teratogens include aminopterin (anencephaly or encephalocele in some cases), thalidomide (rarely anencephaly and/or spina bifida), and diabetic pregnancies (16,56). Postulated environmental causes have included influenza A, hyperthermia, alcohol ingestion during pregnancy, water softness, maternal zinc deficiency, organic solvents, dietary factors, and vitamin deficiency (18,25–27,49,66,78). Folic acid given during the first four weeks of pregnancy have been found to prevent about 50% of neural tube defects. Mothers of infants with neural tube defects have increased homocysteine levels (6,11,47,73a).

Theories of pathogenesis have been reviewed by Lemire et al (31). The primary defect is either in the neuroepithelium itself or in the surrounding mesoderm. Some lesions may be caused by reopening of a closed neural tube secondary to either an increase in the intraluminal pressure or to some defect in the neuroepithelium (13). Most experimental evidence favors the concept that anencephaly arises from a neural tube that fails to close (28).

Craniofacial features. Variation in central nervous system pathology is related to the extent of the neural tube defect as well as the gestational age. Generally, the more complete the absence of the cranial vault, the less likely nervous tissue is to be found on the cranial base. The cerebral hemispheres are soft, red-to-purple in color, and formless, being composed of thin-walled vascular channels distended with blood and separated by irregular masses of brain tissue. A thin covering of squamous epithelium and choroid plexus-like tissue may be present in some cases. The cerebellum may be normal or malformed (31). In some instances of meroacrania, brain tissue may bulge out, resembling an encephalocele. As a result, meroacrania has been misdiagnosed on occasion in the literature. Absence of skin covering separates meroacrania



A B

Fig. 16–1. *Anencephaly*.

from encephalocele (28). Anencephaly and holoprosencephaly may occur together (32). Diprosopus and facial clefting may also be associated (15).

The pituitary gland is almost always present, despite the assertion in the literature that it may be absent. The neurohypophysis is almost always hypoplastic, distorted, and frequently found in the craniopharyngeal canal, which usually remains open in anencephaly. The hypothalamus is absent as are the neural connections between the adeno-hypophysis and the central nervous system (31).

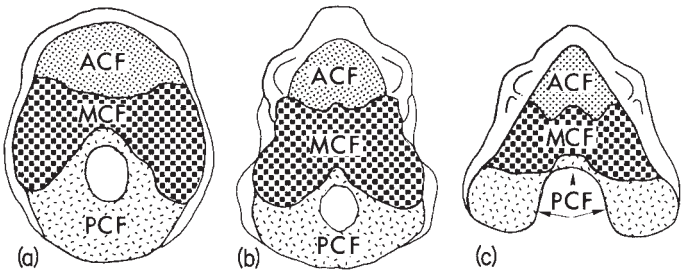
Craniofacial malformations may include hypoplastic and/or low-set ears, anomalous ear folds, absent helices, exotropia, ocular proptosis, small palpebral fissures, microphthalmia, clinical anophthalmia, subcutaneous nasal cleft, absent or incompletely defined philtrum, anomalous palate with midline grooving, cleft lip, cleft palate, bifid uvula, microstomia, prominent maxillary alveolar ridges, and mandibular prognathism (31). Short neck is common. The thyroid gland may be normal, small, or increased in size (31).

The craniofacial skeleton has been studied by a number of authors (10,14,22,35,36,41). In the facial skeleton, the frontal bone is severely affected with a marked increase in angulation. The superior orbital rims are directed posterolaterally. The orbital plate of the frontal bone usually cannot be identified. The zygomatic bones are severely affected and, in lateral view, have a rhomboid shape. Cephalometric study shows the mandible to be prognathic in every case (41).

In large cranial defects, the interparietal portion of the occipital bone is relocated anteriorly to approximate the frontal bone. Occipital components are rotated anterolaterally and inferiorly with lack of fusion of the chondrocranium posterior to the foramen magnum. The squamae of the frontal bone are collapsed horizontally and reduced in size, lying peripheral to the anterior cranial fossa to form most of the orbital roofs (14).

Changes in the cranial floor are caused by alterations in the size, form, or duration of the neural functional matrix. Sphenoid bone alterations result in a reduced cranial floor angle and a more vertically oriented clivus. Schematic drawings of the cranial fossae in meroacrania and holoacrania are compared with normal in Fig. 16–2. In both types, the anterior and middle cranial fossae are constricted laterally and the posterior cranial fossa is increased in lateral extension, but constricted anteroposteriorly. The lesser wings of the sphenoid have an anteroposterior orientation; the greater wings of the sphenoid have a reduced transverse dimension; and the lateral end of the petrous portion of the temporal bone is positioned more anteriorly (10).

Fig. 16–2. *Anencephaly*. Schematic drawing of the bones of the cranial floor in (a) a normal fetus, (b) a fetus with meroacrania, and (c) a fetus with holoacrania. Note the anteroposterior position of the lesser wings of the sphenoid and the reduced transverse dimension of the greater wings of the sphenoid (b and c) relative to the normal (a). The more anterior position of the lateral end of the petrous portion of the temporal bone is also evident in anencephaly. In holoacrania, the supraoccipital components are nonunited and widely divergent (c). ACF, MCF, PCF, anterior, middle, and posterior cranial fossa. (From HW Fields et al, Teratology 17:57, 1978.)



Associated anomalies. David and Nixon (8) in a study of 294 cases of anencephaly found that the most frequent single malformations were hydronephrosis (8%), cleft palate (8%), diaphragmatic hernia (5%), omphalocele (5%), cleft lip (4%), and horseshoe kidney (4%). Lemire et al (31) studied associated malformations in 68 cases and Melnick and Myrianthopoulos (40) reported a series of 36 cases. Especially significant are spinal retroflexion, scoliosis, talipes equinovarus or calcaneovalgus. Increased anteroposterior chest diameter, high diaphragm, eventration of the diaphragm, absent diaphragm, patent foramen ovale, hypoplastic heart, various other cardiac defects, anomalous lobation of lungs, hypoplastic lungs, hydroureter, hydronephrosis, hypertrophy of the bladder wall, hypoplastic ureters and/or bladder, hyperlobulated kidneys, absent ureters or bladder, undescended cecum, omphalocele, short intestines, and Meckel diverticulum (1,8,31,40,73). The adrenals are characteristically small. The frequency of the sternalis muscle may be as high as 50% in some series. In contrast, the frequency varies between 1% and 4% in the general population. The upper limbs are excessively long in relation to the lower limbs. On the average, arm length is about 12% greater than normal and a proximal-to-distal gradient exists, the upper arm being increased by 24%, the forearm by 16%, and the hand by 2% (31). Aganglionosis (37) and possible association with Waardenburg syndrome (33) have been noted as well as sirenomelia (50,51,53,54,58).

Differential diagnosis. Some cases of *amnion rupture sequence* may resemble anencephaly. Since the former is associated with limb amputations, ring constrictions, distal syndactyly, and tissue bands. In practice, little difficulty should be experienced in differentiating the two. Some authors discuss iniencephaly and anencephaly together (8,30). Both share a female preponderance; iniencephaly appears to be more common in areas

where anencephaly is common, and both may be accompanied by spina bifida. However, the time of onset for each of these malformations is different and families have not been observed with affected members of both types. Anencephaly may occur together with *holoprosencephaly* (32) and all such cases to date have been sporadic. Townes et al (71) reported a sibship with anencephalic male twins and a female infant with alobar holoprosencephaly, radial aplasia, and oligodactyly.

Wynne-Davies (78) carried out a family survey of 337 patients with multiple vertebral anomalies without apparent spina bifida. She found that vertebral anomalies were etiologically related to anencephaly and spina bifida, carrying a 5%–10% risk to subsequent sibs. However, some families with spina bifida and/or other vertebral anomalies are known to occur without anencephaly (17,63,69), suggesting further heterogeneity.

Diagnosis and laboratory aids. Diagnosis is based on the overall pattern of anomalies and family history. An attempt should be made to rule out known syndromes and environmental causes. Certainly chromosome study is indicated. Radiographic studies of the vertebral column in relatives of the proband are also indicated. The presence of an NTD in a first degree relative, second degree relative, or third degree relative of a fetus is an indication for amniotic fluid α-fetoprotein determination, although there is little evidence of an increased risk unless the affected relative is a parent or sib. Approximately 60% of newborns with NTDs have anencephaly. The risks for a neural tube defect in relatives of affected persons are as follows: father's siblings, 7%; mother's sister's children 13%; mother's brother's children 3%; father's sister's children 6%; and father's brother's children 4%. The combination of elevated maternal serum α-fetoprotein and low estriol is highly predictive of anencephaly (79). The success of maternal serum α-fetoprotein screening requires a well-organized program with strict adherence to protocol. In pregnancies with elevated amnionic α-fetoprotein level and a nondiagnostic ultrasound, acetylcholinesterase assay of amnionic fluid assumes major importance. In a pregnant woman with a previously affected child or an elevated maternal serum or amnionic fluid α-fetoprotein level, ultrasonography can be made longitudinally and transversely to specifically identify the NTD (23,24,42–45).

It should be borne in mind that elevated α-fetoprotein levels may be due to maltiming of pregnancy, twinning, congenital nephrosis, abdominal wall defects, hygroma colli, atresia of esophagus, and a host of other causes as well as anencephaly (4).

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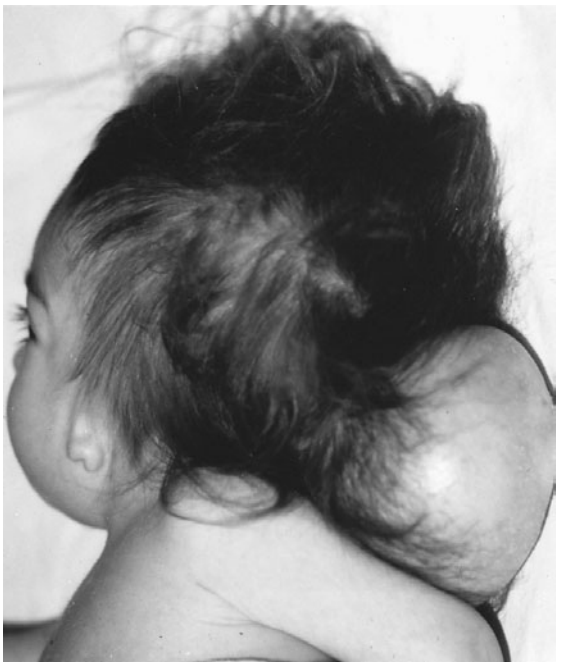

Fig. 16–3. *Encephalocele*. Occipital encephalocele with hemifacial microsomia. [From MM Cohen Jr, Birth Defects 7(7):103, 1971.]

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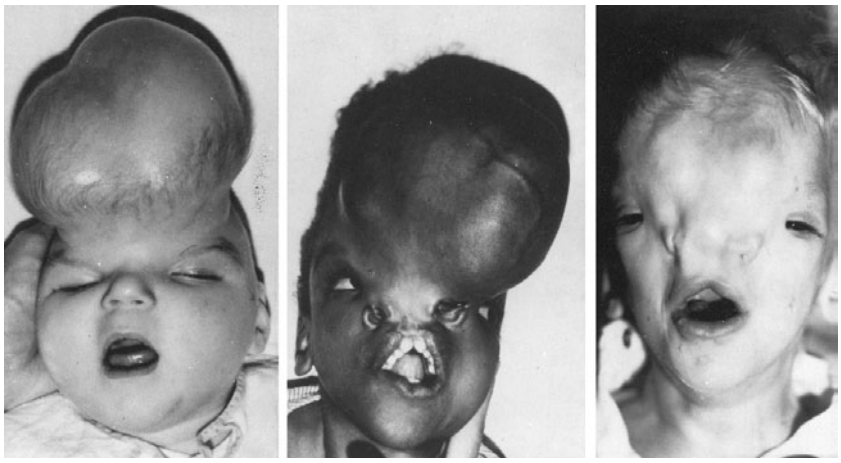
Encephaloceles

Encephaloceles may occur as isolated malformations or in combination with other anomalies making up various syndromes or associations. The literature has been reviewed extensively elsewhere (23,109). Although encephalocele is the most commonly used term for all such lesions, cranium bifidum and cephalocele more properly describe the spectrum of malformations that includes both encephalocele and cranial meningocele (108).

Encephaloceles (Figs. 16–3 to 16–5) can be classified as occipital, parietal, or anterior (Table 16–1). Further subdivision of anterior encephaloceles can be made: visible (sincipital) and not directly visible (basal) (3,102). About 75% of all encephaloceles occur in the occipital region (9,63). Prevalence is said to vary from 1 in 2000 to 1 in 5000 live births. They are more common in African and Asian populations (29,33). Parietal encephaloceles account for approximately 10%–14% of all encephaloceles (9,63,84). Frontal encephaloceles are much less common than occipital encephaloceles in the United States, the ratio being 1 : 6 (33). African studies, however, show a 1 : 1 ratio. Encephaloceles are very common in Thailand, Burma, and India (18), prevalence being about 1/3500 live births (42). The frequency of basal encephalocele appears to be comparatively low, an undocumented prevalence being 1/35,000 live births (106).

At present, it is not possible to know how frequently other anomalies occur with encephaloceles because surveys in the literature have focused primarily on signs and symptoms, natural history, treatment, and treatment outcome (9,17,26,63,77,84,85). Although associated anomalies are mentioned and even tabulated, such data cannot be used for several reasons. First, associated anomalies are not always properly broken



A B C

Fig. 16–4. *Encephalocele*. (A–C) From left to right: frontal encephalocele, frontonasal encephalocele, and frontonasal malformation with flattened encephalocele. (From MM Cohen Jr and RJ Lemire, Teratology 25:161, 1982.)

down. In some series, anomalies that occur with encephalocele and with spina bifida are lumped together. In other surveys that deal only with encephaloceles, associated anomalies cannot always be sorted on the basis of the anatomic location of the encephalocele. Second, associated anomaly categories may be too inclusive. Primary and secondary anomalies are not always separated. Thus, the total number of associated anomalies is confounded in patients with only one anomaly in the total number, and there is no way to break the anomalies down on a per patient basis. Finally, there are a number of problems with ascertainment bias in some surveys and problems with sample size in others (23).

Conditions with encephaloceles are discussed under the following headings: chromosomal syndromes, monogenic syndromes, teratogenic causes, disruptive causes, various associations, and miscellaneous conditions occasionally associated with encephaloceles.

Chromosomal syndromes. Encephalocele has been reported with several chromosomal syndromes, including trisomy 18 on occasion (5,108). It has also been noted with Turner syndrome (14), but this finding can be questioned. With some Turner syndrome abortuses, severe lymphedema of the posterior neck area can mimic cephaloceles and care should be taken not to confuse the two. An encephalocele was said to be present in one patient with dup(1q) karyotype (45), but a photograph of the affected infant shows apparent anencephaly of the meroacrania type. Moeschler et al (89) reported a patient with del(13q) syndrome with a large occipital encephalocele, severe microcephaly, and Type 1 Arnold-Chiari malformation. Schinzel (96) cited a case with meningocele.

Hsia et al (62) reported a sporadic instance of a syndrome with many clinical similarities to the Meckel syndrome but with some differences. The condition was thought to be caused by a chromosomal anomaly. Features of the pseudo-Meckel syndrome included occipital encephalocele, absent olfactory tracts and bulbs, absent corpus callosum, Arnold-Chiari malformation, cleft palate, wide aorta originating from the right ventricle, atretic pulmonary valve, narrow pulmonary artery arising from a blind lumen to the left of the aortic origin, patent ductus arteriosus, ventricular septal defect, single coronary artery, accessory spleen, talipes equinovarus, and hallucal hammertoes. No polydactyly was observed

Fig. 16–5. *Encephalocele*. Transsphenoidal encephalocele with herniation into the posterior nasopharynx. (From JM Lieblich et al, Ann Intern Med 89:910, 1978.)

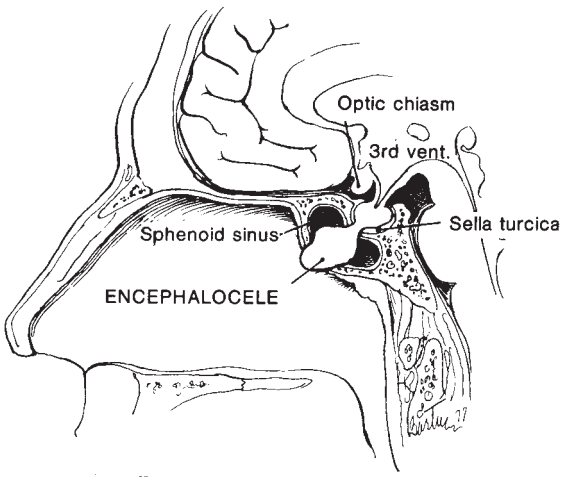


Table 16–1. Classification of sincipital and basal encephaloceles

Location	Boundaries (bones)	Presentation
Sincipital		
Frontoethmoidal		
Nasofrontal	Cribriform plate of ethmoid Nasal process of frontal Frontal process of maxillary	Midline at root of nose
Nasoethmoidal	Ethmoid Frontal Nasal	On one or both sides of nose
Nasoorbital	Lacrimal Frontal	Superior medial angle of orbital cavity; displaces eye laterally; may be bilateral
Interfrontal		
Craniofacial cleft		
Basal		
Sphenoorbital	Superior orbital fissure	Enters orbit, causing exophthalmos
Sphenomaxillary	Superior orbital, then inferior orbital fissure	Pterygopalatine fossa
Transethmoidal	Defect in cribriform plate	Anterior nasal fossae
Sphenoethmoidal	Sphenoethmoidal suture	Posterior nasal fossae
Sphenopharyngeal	Defect in sphenoid	Rhinopharynx, sphenoid sinus

(Adapted from G Avanzini and G Crivelli, Acta Neurochir (Wien) 22:205, 1970; C Suwanwela and N Suwanwela, J Neurosurg 36:201, 1972; J Warkany et al, Mental Retardation and Congenital Malformations of the Central Nervous System, Year Book Publishers, Chicago, 1981.)

and retinal dysplasia, a consistent feature of the Meckel syndrome (81), was conspicuously absent. Lymphocyte study of 15 metaphase spreads showed a karyotype of 46,XX,t(3p+;?). The proximal part of the elongated short arm of chromosome 3 showed the usual banding pattern with quinacrine fluorescence. The origin of the translocated distal portion could not be determined with certainty, although it was thought to have arisen from the long arm of either chromosome 10 or chromosome 6. Karyotype was normal in both parents and in a normal brother of the proband.

Monogenic syndromes. *Meckel syndrome* is the best known malformation syndrome with occipital encephalocele and has been reviewed extensively elsewhere (51,61,81,86,87,91). Features include polydactyly, polycystic kidneys, holoprosencephaly, microphthalmia, retinal dysplasia, various cardiac anomalies, orofacial clefting, ambiguous external genitalia, and various other abnormalities. Occipital encephalocele occurred in 39 of 49 cases tabulated from the literature (86). The syndrome has autosomal recessive inheritance.

Cryptophthalmos syndrome consists of extension of the skin of the forehead covering one or both eyes, unusual hairline, ear anomalies, total or partial soft tissue syndactyly of the fingers and toes, notching of the wings of the nose, and genital anomalies such as micropenis, hypospadias, clitoromegaly, vaginal atresia, and incomplete development of the labia. The syndrome has autosomal recessive inheritance. Approximately 10% of reported cases have been associated with encephalocele. In some instances, osseous defects of the calvaria occur without encephalocele (104).

Dyssegmental dysplasia is etiologically heterogeneous with an autosomal recessive severe form (*type Silverman-Handmaker*) and an autosomal recessive milder form (*type Rolland-Desbuquois*). Both types are usually lethal. Facial features in both consist of mild blepharophimosis, flat nasal bridge, hypoplastic supraorbital ridges, micrognathia, and cleft palate. Occipital encephalocele, occipital bone defect, and hydrocephaly have been noted in some instances. The neck is short. Radiographic findings include short, broad tubular bones with metaphyseal widening, accelerated carpal bone maturation, bowing of the legs as well as the thighs and forearms, short broad pelvis with widely flared iliac wings, vertebral anomalies, and small thorax (1,32,52,55).

Knobloch syndrome in 5 of 10 siblings was reported in 1971 by Knobloch and Layer (72). Features included high myopia, vitreoretinal degeneration, retinal detachment, and occipital encephalocele. Several other sibships have been described (27,94,97,99,115). Inheritance is autosomal recessive and the gene has been mapped to 21q22.3 (99). Encephaloceles tend to be small, commonly with normal cognitive development. Atretic encephalocele, scalp defect, and pigmented hair tuft of the parieto-occipital midline have been noted (27,97,115). Other associated anomalies have included hypoplastic lung, dilated pulmonary lymphatics, dextrocardia, PDA, pyloric stenosis, duplicated renal collecting system with bifid uvula, and spina bifida occulta at L5-S3 (27,72,115).

Roberts syndrome is characterized by growth deficiency, severe hypomelia, cleft lip-palate, prominent eyes with hypertelorism, large phallus, and other anomalies. Inheritance is autosomal recessive, and heterochromatic puffing and centromere separation have been observed cytogenetically. Encephalocele was a feature of one case reported by Freeman et al (44). However, care should be taken not to confuse nuchal cystic hygroma in the fetus, also observed in some cases, with encephalocele.

Walker-Warburg syndrome, also known as Warburg syndrome, HARD±E syndrome, and Chemke syndrome, consists of hydrocephaly, agyria, occipital encephalocele in about 50%, microphthalmia, and/or anterior and posterior chamber abnormalities including corneal opacity, cataract, persistent primary vitreous, and retinal dysplasia. Genitourinary abnormalities are present in some cases. Inheritance is autosomal recessive (4,13,15,23,35,39,93,113). Early demise is characteristic, and recognition of the syndrome is essential for proper genetic counseling of families at risk. Although agyria is a feature of the syndrome, the condition should not be confused with *Miller-Dieker lissencephaly* syndrome (101,105). In the latter disorder, the cerebral cortex is thickened. In Walker-Warburg syndrome, the cortex is atrophic and disorganized. Walker-Warburg syndrome and Meckel syndrome have in common both occipital encephalocele and retinal dysplasia. However, the neuropathologic malformations are entirely different, and polydactyly and polycystic kidneys, which are common in Meckel syndrome, are not features of Walker-Warburg syndrome.

Teratogenic causes. Maternal hyperthermia may be implicated as one cause of occipital encephalocele. Of 17 patients with isolated posterior encephalocele, Fisher and Smith (40) found that four of the mothers gave a history of at least 1.5°C above normal from prolonged fever early during pregnancy. Since Fraser and Skelton (43) implicated maternal hyperthermia as a teratogen that can produce abnormalities from 3 to 14 weeks of gestation, it seems possible that at least some instances of multiple anomalies with encephalocele arising around the same embryonic time may occur on this basis.

Warfarin embryopathy has been associated with a spectrum of malformations, most commonly nasal hypoplasia and bone stippling. The condition has been reviewed elsewhere (95). Various other abnormalities have been observed including limb shortening, low birthweight, optic atrophy, mental deficiency, hypotonia, seizures, and various other defects. Occipital encephalocele has been observed in two instances. Tejani (103) described a patient with nasal hypoplasia, occipital encephalocele, hydrocephaly, microphthalmia, and persistent truncus arteriosus. Warkany and Bofinger (109) reported two affected children with hydrocephaly. One had a huge occipital encephalocele and renal malformations.

Disruptive causes. Features of the *amnionic rupture sequence* have been reviewed elsewhere (9,57,64,69,78). Most instances involve digits or limbs with ring constrictions or amputations. In some cases, an affected newborn will have unusual orofacial clefts, encephaloceles, and other facial anomalies. Amnionic bands become entangled in the oral and nasal orifices and sometimes become attached directly to the face or cranium, producing bizarre disruptions. These encephaloceles are unusual because of their tendency to have (a) irregular surfaces, (b) asymmetric placement with respect to the midsagittal plane, (c) predominantly anterior placement, and (d) multiple sites of involvement. Other anomalies may also occur. Besides disruptions, deformations and malformations have been noted in some instances. Some reported malformations are not secondary to amnionic bands or oligohydramnios. Although the overwhelming majority of cases are sporadic, occasional familial instances have been recorded.

Frontonasal malformation. *Frontonasal malformation* (Fig. 16–4C) or median cleft face syndrome has been reviewed elsewhere (22,24, 31,98). The condition is characterized by a flattened nasofrontal encephalocele, hypertelorism, widow's peak, and wide-set nostrils with lack of elevation of the nasal tip. Occasionally encountered are notching or clefting of the nostrils or an unusual form of median cleft lip. A variety of extracephalic anomalies may be present in some cases. The most extensive review is that of Guion-Almeida et al (53). Most cases are sporadic. Causal genesis includes an autosomal dominant form; dup(2q); autosomal recessive Shanske syndrome; the syndrome of frontonasal malformation, agenesis of the corpus callosum, tibial hypoplasia, and hallucal duplication; and ophthalmofrontonasal dysplasia (53).

von Voss-Cherstvoy syndrome. Cohen (21) called attention to this entity in 1982 and named it von Voss syndrome. It has also been called von Voss-Cherstvoy syndrome (79) and DK phocomelia phenotype. Several cases have been reported (8,16,46a,65,79,107). The disorder is characterized by occipital encephalocele, radial ray defects, and urogenital abnormalities. Other findings have included aplasia or hypoplasia of the corpus callosum and, variably, hypoplastic lung, dextroposition of the heart, and thrombocytopenia. Affected sibs and parental consanguinity have been reported in two cases (3). Lubinsky et al (79) pointed out similarities to

del(13q) syndrome. Bamforth and Lin (8) noted fibroblast mosaicism for del(13)(q12).

Encephalocele/absent corpus callosum association. The association of encephalocele and absent corpus callosum has been observed repeatedly both as a binary combination and together with various other anomalies. McLaurin (84) noted absence of the corpus callosum in four of 13 parietal encephaloceles. Lieblich et al (75) and Avanzini and Crivelli (3) reported agenesis of the corpus callosum with transsphenoidal encephalocele. A posterior orbital encephalocele was observed with agenesis of the corpus callosum and cerebellar atrophy in a patient reported by Fargueta et al (38). Other cases of encephalocele and absent corpus callosum have been described by Mood (90). The combination also has been reported in *frontonasal malformation* and in von Voss-Cherstvoy syndrome (16).

Absent corpus callosum is part of the spectrum of holoprosencephalic disorders in some instances but not in others. The latter is assumed to be the case in the association discussed. The relationship of absent corpus callosum to holoprosencephaly has been discussed extensively by Marburg (82) and Loeser and Alvord (76). Encephalocele and agenesis of the corpus callosum as part of holoprosencephaly may occur in the Meckel syndrome (61,91) and has been observed with cyclopia in a patient with r(18) karyotype (25). Encephalocele and holoprosencephaly can be produced by the same teratogen in animals. DeMyer (30) was able to induce both malformations in rat fetuses with vincristine injected intramuscularly into pregnant rats 8.5 days following mating. The sporadic occurrence of cyclopia and encephalocele has been reported in the goat (67).

Encephalocele/clefting association. The binary combination of encephalocele and orofacial clefting has been reported on a number of occasions and the literature has been reviewed elsewhere (49). In some cases, a sphenopharyngeal encephalocele is associated with cleft palate. In these instances, it is possible to speculate that early encephalocele formation mechanically interfered with closure of the secondary palate. More commonly, sphenopharyngeal encephalocele is associated with cleft lip with or without cleft palate. The association of occipital encephalocele and cleft lip-palate has been noted (26) and the combination of encephalocele and oblique facial clefting has also been observed. Unusual orofacial clefts and encephalocele can be part of the amnionic rupture sequence. Unusual median clefts are observed occasionally with frontonasal dysplasia.

Encephalocele/craniosynostosis association. Craniosynostosis is found as a low-frequency anomaly with encephalocele. Lorber (77) noted two instances of premature sutural fusion in 20 cases of encephalocele. Craniosynostosis has been observed occasionally with the *Meckel syndrome* (91) in which occipital encephalocele is a common feature. Encephalocele has also been noted in acrocephaly (48), *craniotelencephalic dysplasia* (28), and *Apert syndrome* (112).

Three possible theories can be invoked to explain the association of encephalocele with craniostenosis, and each of the three probably has some validity, depending upon the particular case. In some instances, "blow-out" lesions, such as encephaloceles, may result in lack of growth stretch across the sutures producing craniosynostosis on this basis. When hydrocephaly is associated with encephalocele, surgically placed shunts with low-pressure systems may be implicated in which growth stretch at the sutural areas suddenly becomes totally deficient. Finally, in some patients with multiple anomaly syndromes, both encephalocele and craniostenosis may occur on a primary basis (20,23,71).

Encephalocele with Dandy-Walker and Arnold-Chiari malformations. Dandy-Walker defect has been reported in association with parietal encephalocele (84) but also may be observed with occipital encephalocele (92). Arnold-Chiari defect has been noted with occipital encephalocele by several authors (9,92), and several instances of combined Dandy-Walker and Arnold-Chiari defects with occipital encephalocele in the same patient have been noted (92).

Encephalocele/ectrodactyly association. The combination of occipital encephalocele and ectrodactyly has been observed in two sporadic instances (JM Opitz, personal communication). Mental deficiency was present in both cases. No other major anomalies were present and the condition is distinct from von Voss syndrome in which encephalocele and ectrodactyly also may occur.

Encephalocele/hypothalamic-pituitary dysfunction association. Transsphenoidal encephaloceles (Fig. 16–5) herniate through a defect in the floor of the sella turcica and present as epipharyngeal masses. In some instances, they may be small and not always readily appreciated. The encephalocele may occur by itself or together with other craniofacial anomalies. Including additional encephaloceles, optic nerve abnormalities, hypertelorism, and cleft lip-palate. Several patients have been reported with hypothalamic-pituitary dysfunction but with different patterns of involvement. Growth hormone deficiency, hypothyroidism, central hypogonadism, central adrenocortical insufficiency, vasopressin deficiency, and diabetes insipidus have been documented (75).

Encephalocele/Klippel-Feil/iniencephaly association. Occipital encephalocele has been reported in a number of instances of *Klippel-Feil anomaly* (26,77,85), and in iniencephaly apertus it is constant (10,59,74,100). Iniencephaly consists of a defect in the occipital bone around the foramen magnum, spina bifida of considerable degree, and retroflexion of the head on the spine (36). Lewis (74) divided various cases by the presence or absence of occipital encephalocele, calling the former iniencephaly apertus, the latter iniencephaly clausus. Gilmour (46) suggested that iniencephaly and Klippel-Feil anomaly are part of a spectrum. Both conditions seem to have several features in common (73). Further evidence of the association of these defects is found in the experimental work of Warkany and Takacs (110) who produced the lesion in rats with streptonigran.

Encephalocele/myelomeningocele association. Lorber (77) and Mealey and co-workers (85) have observed several instances of occipital encephalocele associated with myelomeningocele. DeMyer (30) was able to produce encephalocele in some rat fetuses and spinal dysraphism in others by administering vincristine to pregnant rats at 8.5 days. The same combination of defects was produced by the administration of salicylates to pregnant rats (47). Wilner (114) described a mother with meningocele who gave birth to a girl with myelomeningocele. Lorber (77) noted that eight siblings of seven infants with occipital encephalocele had myelomeningocele.

Encephalocele/oculo-auriculo-vertebral spectrum. *Oculo-auriculo-vertebral spectrum* is a well-known condition affecting aural, oral, and mandibular growth together with anomalies of the eyes and vertebral column. It has been observed with occipital encephalocele occasionally (Fig. 16–3), and such cases have been reviewed by Cohen (19) and Herrmann and Opitz (56). Minne and Gernez (88) reported occipital encephalocele with absent lung, which is intriguing because hemifacial microsomia has also been observed with absent lung. Frontonasal dysplasia, which occurs with cranium bifidum and flattened encephalocele, has been reported on a number of occasions with dysplastic ears, ear tags, and epibulbar dermoids.

Miscellaneous and/or occasional involvement. A number of miscellaneous conditions have occasionally been associated with encephalocele. Several authors have documented the binary combination of encephalocele with various congenital heart defects (26,41,63,77,85, BD Hall, personal communication). In a case associated with one of the *Ehlers-Danlos syndromes* (34), the encephalocele was not congenital, but acquired. Rarely, occipital encephalocele has been recorded in infants of diabetic mothers (37). Other conditions occasionally reported with encephalocele have included *Marfan syndrome* (83),

neurofibromatosis (58, JW Hanson, personal communication), Poland anomaly (M Bull, personal communication), polysplenia syndrome (KL Jones, personal communication), *rubella syndrome* (11,68), TAR syndrome (RJ Gorlin, personal observation), *lateral nasal proboscis* (2), and *tuberous sclerosis* (12,66). Patients with the combination of encephalocele, ptosis of eyelids, epicanthic folds, and single maxillary central incisor have been observed (MJ Stephan, personal communication). Lateral meningocele syndrome has been reviewed by Gripp et al (50).

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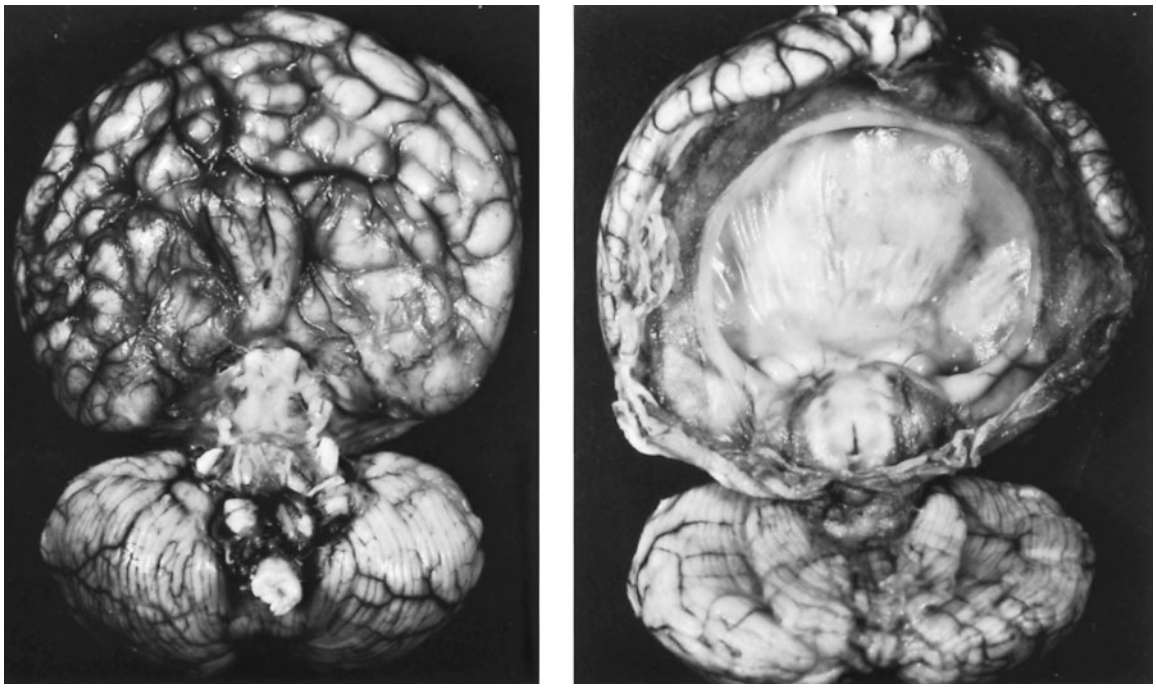
The holoprosencephalic disorders

Holoprosencephaly is a malformation sequence in which impaired midline cleavage of the embryonic forebrain is the basic feature. The prosencephalon fails to cleave sagittally into cerebral hemispheres, transversely into telencephalon and diencephalon, and horizontally into olfactory and optic bulbs (Fig. 16–6). The condition can be graded according to the degree of severity as alobar, semilobar, or lobar holoprosencephaly. Various gradations of facial dysmorphism are commonly associated with holoprosencephaly including cyclopia, ethmocephaly, cebocephaly, median cleft lip, and less severe facial dysmorphism (Fig. 16–7).

Exhaustive reviews and bibliographies are those of Cohen (19,20), Cohen and Gorlin (22), Cohen and Sulik (24), Cohen et al (25), DeMyer (29), DeMyer and Zeman (30), DeMyer et al (31), Ming and Muenke (52), Muenke (57,58), and Siebert et al (78). Central nervous system studies include those of DeMyer (29), DeMyer and Zeman (30), and Probst (67). Coverage for other topics include historical aspects (4,24,77), animal studies (10,24,83), epidemiology (19,28,41,48,49,68), genetic heterogeneity and recurrence risk (8,19,22,62,69,78), and molecular studies (7,34,52–56,60b,71–73,87).

Epidemiology. Croen et al (28) found a birth prevalence of 1.2 per 10,000 (n = 121). Rasmussen et al (68) found an overall birth prevalence of 0.86 per 10,000 (n = 63). The rate increased from 0.58 per 10,000 from 1968 to 1972 to 1.2 per 10,000 from 1988 to 1992. Other estimates have been discussed by Cohen (19). The frequency of holoprosencephalic abortuses is high, being approximately 40 per 10,000 (49).

Birthweights tend to be low except in holoprosencephalic infants of diabetic mothers. The sex ratio in alobar holoprosencephaly has a 3 : 1 female predilection. In contrast, the sex ratio is 1 : 1 in lobar



A B

Fig. 16–6. *The holoprosencephalic disorders*. Holoprosencephalic brain, alobar type. (A) Dorsal view showing pancake-like structure without corpus callosum or septum pellucidum. Diencephalon and telencephalon are uncleft. (B) Ventral view showing absent olfactory bulbs and tracts and no interhemispheric fissure. (From W DeMyer and PT White, Arch Neurol 11:507, 1964.)

holoprosencephaly. Major facial dysmorphism occurs more frequently in females than in males, especially with cyclopia (19). Holoprosencephaly has been described in MZ twins (15).

Molecular studies. A number of mutations in several genes have been identified as causative of holoprosencephaly (86a). About 5% can be explained in this way (60a). The best known of these is *sonic hedgehog* (7,37,53,59,72,73,76). Mutations involve loss of function. Only 23% of autosomal dominant families with holoprosencephaly have sonic hedgehog mutations (7q36). A mutation in a sporadic case is very rare (1 in 184 cases). Other known gene mutations involve *TGIF* (34,63), *SIX3* (64a,86), *ZIC2* (14) and *patched* (54). Several other candidate genes, such as lanosterol synthase (21q22.3), have been discussed by Roessler and Muenke (71). In Smith-Lemli-Opitz syndrome, caused by Δ7-sterol reductase mutations, 2%–4% have holoprosencephaly (42,56). Probably at least 12 genes are involved.

Chromosome abnormalities. There is a plethora of associated chromosome abnormalities. About 40% have an anenploidy, most commonly trisomy 21 (28). However, we have listed in Table 16–2, a number of chromosome findings. A few of these such as del(7q) represent deletion of the *sonic hedgehog* gene, others *patched* mutations at 9q22.3, still others *TGIF* mutations at 18p11.3 (the *TGIF* gene is involved in the retinoic acid pathway), etc. The numerous references in the older literature and in the 1990 edition of this text to association with del(18p) probably refer to *TGIF* mutations. Wallis et al (87) have noted that at least 12 loci and various teratogens can effect holoprosencephaly, among them mutations in the *SIX3* gene on 2p21. Jervine has been used as an experimental teratogen.

Diagnosis and recurrence risk. Conditions with holoprosencephaly or arhinencephaly (19,20,24) are listed in Table 16–2. Diagnosis is based on the overall pattern of abnormalities, chromosome analysis, molecular studies in selected cases, and family history. Careful examination of the proband's family for microforms of holoprosencephaly is essential, especially for anosmia or hyposmia, mild hypotelorism, microcephaly, or single maxillary central incisor (24). Cohen and Gorlin (22) noted that in the presence of a holoprosencephalic proband, sibs with cleft lip-palate but without holoprosencephaly per se should probably be regarded as microforms of the disorder. A family history of short stature, endocrinopathy, or various types of central nervous system anomalies other than holoprosencephaly may be significant (24).

For nonsyndromic cases, if the findings are consistent with autosomal dominant holoprosencephaly and the family is negative for sonic hedgehog mutations, the risk for an obligate carrier is on the order of 16%–21%; the risk for an incomplete form or microform is on the order of 13%–14%; and the overall effect for some risk, either mild or severe, is on the order of 29%–35% (19). Affected sibs in the absence of familial microforms in more than one generation, are consistent with autosomal recessive inheritance (19). A sporadic case with negative family history except for consanguinity certainly suggests that the recurrence risk may be as high as 25% (19). For sporadic, nonchromosomal, nonsyndromic holoprosencephaly, a recurrence risk of approximately 6% may be given. This risk is based on the genetic study of Roach et al (69) of 30 families with holoprosencephalic probands; only two of their pedigrees represented examples of familial holoprosencephaly. A skewed sex ratio exists (males have more mutations in *Sonic Hedgehog* than do females) in familial holoprosencephaly and in those with single maxillary incisor (81).

Central nervous system. In alobar holoprosencephaly (Fig. 16–6), a small monoventricular cerebrum lacking interhemispheric division is present. The thalami and the corpora striata are undivided across the midline. Olfactory tracts and bulbs are always absent as is the corpus callosum, although a few commissural fibers may cross the midline (29). DeMyer (29) further subdivided alobar holoprosencephaly depending upon the degree to which the dorsal lip of the holotelencephalon rolls over

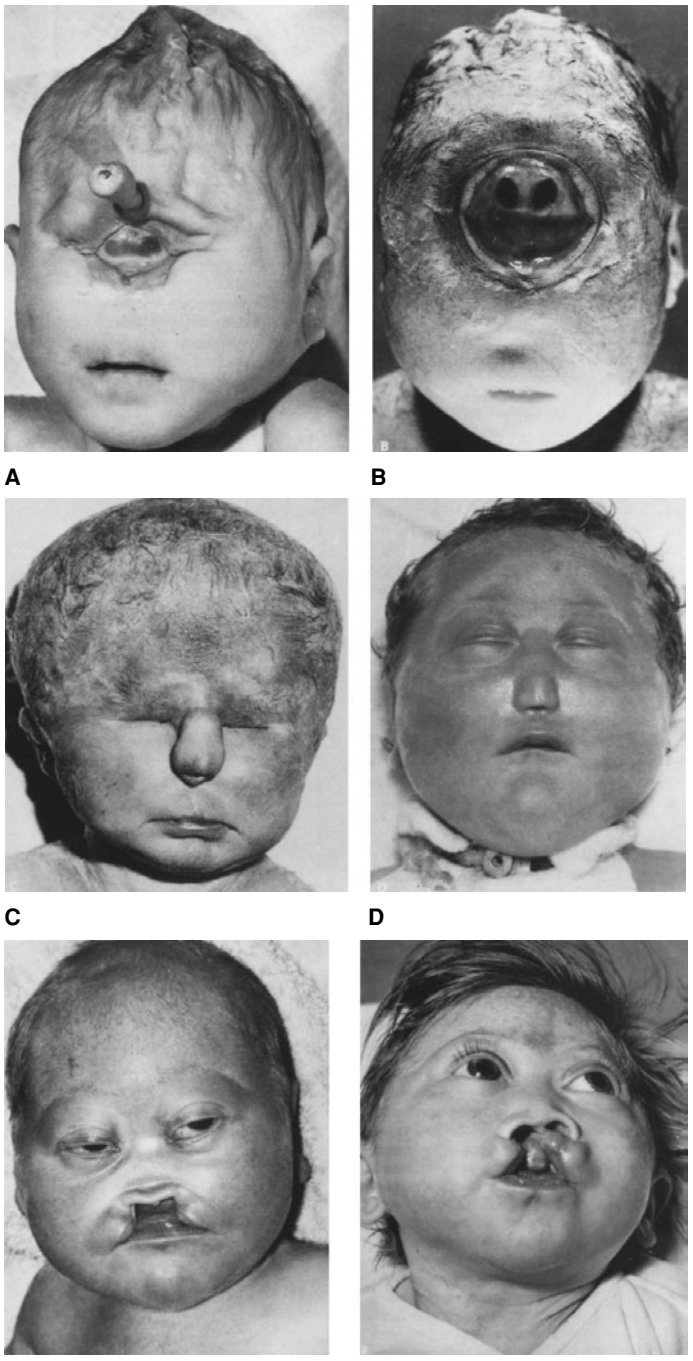


Fig. 16–7. *The holoprosencephalic disorders.* (A) Cyclopia with proboscis. (B) Cyclopia without proboscis. (C) Ethmocephaly; note separate eye sockets. (D) Cebocephaly; note hypotelorism and centrally situated blind-ended nostril. (E) Premaxillary agenesis form. (F) Facies associated with some degree of formation of corpus callosum and septum pellicidum.

to cover the membranous ventricular roof. The three common external configurations of alobar holoprosencephaly are the pancake type, the cup type, and the ball type.

In semilobar holoprosencephaly, rudimentary cerebral lobes are present and although the interhemispheric fissure is never complete, it may be present posteriorly. Commonly, the olfactory tracts and bulbs are absent, but in some instances, they may be hypoplastic. The corpora striata are continuous across the midline. The corpus callosum is

Table 16–2. Conditions with holoprosencephaly (and arhinencephaly)

Condition	References
Chromosomal holoprosencephaly	
Well established types	
Trisomy 13	19,24
del(13q)	19,24,35
Trisomy 19	19,24
Triploidy	19,24
dup(3p)	16,19,24,32
Uncommon and less consistent types	
del(1q)	19,24
del(2p)	88
trisomy 4	82
dup(5q), del(5p)	19,24
r(6)	19,24
dup(9p), dup(11q)	19,24
del(11q)	19,24
dup(11q)	19,24
dup14(pter→q24)	19,24
Trisomy 20	19,24
Trisomy 21	19,24
r(21) or del(21q)	19,24
Trisomy 22	19,24
dup(22q)	19,24
46,XX/46,X,del(X)(p11)	19,24
47,XXX	19,24,55
Chromosomal arhinencephaly	
dup(1q)	19,24
dup(6p)	19,24
dup(6q)	19,24
i(12p)	19,24
dup(16q)	19,24
49,XXXXY	19,24
Monogenic (map location or inheritance pattern) and unknown	
SIX3 mutations (2p21)	88
Sonic hedgehog (SHH) mutations (7q36)	7,37,53,59,72,73,76
Autosomal dominant (non-hedgehog) (7q36)	73
Holoprosencephaly with sacral agenesis(7q36)	73
Holoprosencephaly with limb defect (7q36)	1,73
Holoprosencephaly and sirenomelia	18,41,48
Patched (PTCH) mutations (9q22.3)	54
Smith-Lemli-Opitz syndrome, Δ7-sterol reductase mutations (11q13)	42,56
TGIF mutations (19p11.3)	34,63,84
Z1C2 mutations (13q32)	14
Lanosterol synthase mutations? (21q22.3)	60,73
Deletion 22q11 syndrome	24
Autosomal recessive holoprosencephaly	19,23,24
Meckel syndrome (AR)	19,24
Pseudotrisomy 13 syndrome (AR)	11,24
XK aprosencephaly syndrome (AR)	32
Aprosencephaly (sporadic)	19,24
Heterotaxy and holoprosencephaly (AR)	13
Holoprosencephaly-fetal hypokinesia syndrome (XR)	19,24
Genoa syndrome (AR)	16
Martin syndrome (AD)	19,24
Grote syndrome (AR?)	19,24
Steinfeld syndrome (AD?)	19,24,61
Lambotte syndrome (AR)	19,24,86
Hall-Pallister syndrome (AD)	19,24
Hartsfield syndrome	19,24,39,90
Holoprosencephaly, ectopia cordis, and embryonal neoplasms	24

(*cont.*)

Table 16–2. (*cont.*)

Condition	References
Agnathia-holoprosencephaly (AR?)	66
Agnathia-holoprosencephaly-situs inversus	50
Agnathia-holoprosencephaly (sporadic, 42 cases)	19,24
Monogenic arhinencephaly	
Kallmann syndrome, type I, mutations in KAL1 gene (Xp22.3) (XL)	27,64
Kallmann syndrome 2, KAL2 (AD)	19,24
Kallmann syndrome 3, KAL3 (AR)	19,24
Isolated anosmia, type I (XL)	19,24
Isolated anosmia, type II (AD)	19,24
Perrin syndrome	19,24
Johnson syndrome	19,24
Oral-facial-digital syndrome VI	19,24
Aicardi syndrome (Xp22)	19,24
Majewski short rib-polydactyly syndrome	19,24
Campomelic dysplasia	19,24
Fitch syndrome	19,24
Anosmia/radiohumeral synostosis/cleft palate syndrome	19,24
COH syndrome	19,24
Teratogenic	
Infants of diabetic mothers	5,70
Fetal alcohol effects	75
Low calorie weight-reducing diet?	74
Associations	
Holoprosencephaly/neural tube defect association	22,44
Holoprosencephaly/frontonasal dysplasia association	12,19,24
Arhinencephaly/DiGeorge anomaly association	19,24
Arhinencephaly/Goldenhar spectrum association	19,24
Arhinencephaly/CHARGE association	19,24

not a distinct bundle, although some commissural fibers may cross the midline (29).

In lobar holoprosencephaly, the brain has well-formed lobes that may be of normal size. Although a distinct interhemispheric fissure is present, there may be some midline continuity of the cingulate gyrus. The olfactory tracts and bulbs may be absent or hypoplastic and the corpus callosum may be absent, hypoplastic, or normal. Midline cleavage of the thalami and the corpora striata may be incomplete (29).

At the mild end of the holoprosencephalic spectrum are malformations such as absence of the corpus callosum and arhinencephaly (absence of the olfactory tracts and bulbs) (28). Defects of the corpus callosum result from a variety of different mechanisms (24,29). In some instances, absence of the corpus callosum clearly represents the holoprosencephalic spectrum. In other instances, isolated absence of the corpus callosum is not related to the holoprosencephalic spectrum (24,29). Robin et al (70) described syntelencephaly as a distinct variant of the holoprosencephalic spectrum of midline brain anomalies.

Other central nervous system anomalies may sometimes be present. Although the hindbrain usually develops normally, it may be hypoplastic since the descending fiber tracts fail to develop. Absence of the inferior vermis has also been observed in a number of cases (20).

In alobar holoprosencephaly, electroencephalography shows various abnormal waves, ranging from asynchrony between the right and left sides of the head to synchronous and asynchronous spikes. In lobar holoprosencephaly, multifocal spikes are common (29).

Patients with alobar holoprosencephaly may be completely amented. However, evidence of vision, hearing, and social smiling has been observed in some cases with median cleft lip, lateral cleft lip, or less severe facial dysmorphism. Length of survival is correlated with facial type. With cyclopia, ethmocephaly, and cebocephaly, 50% may survive for 1 to 2 days. With median cleft lip, 50% survive for 4 to 5 months. Of infants with less severely malformed or normal faces, 50% may survive as long as 12 to 18 months (5).

In general, patients with semilobar or lobar holoprosencephaly tend to have better survival rates than do patients with alobar holoprosencephaly. At the less severe end of the holoprosencephalic spectrum, patients may be mildly or moderately retarded and may have sufficient intelligence to live freely in society (29).

Face. In a classic article, DeMyer et al (31) discussed a graded series of facial anomalies that occur with holoprosencephaly (Fig. 16–7). The face predicts the brain approximately 80% of the time. The other 20% of the time, the facial features are nondiagnostic (20,29). In cyclopia, the most extreme variant, a single median eye with varying degrees of doubling of the intrinsic ocular structures is associated with arhinia and usually with proboscis formation above the eye. In ethmocephaly, two separate hypoteloric eyes are associated with arhinia and supraocular proboscis formation. In cebocephaly, hypotelorism is associated with a blind-ended, single-nostril nose, located in normal position. With median cleft lip, hypotelorism is associated with a flat nose and a median cleft due to agenesis of the primary palate. Less severe facial dysmorphism may include hypotelorism or hypertelorism, lateral cleft lip and/or iris coloboma (24).

Agnathia holoprosencephaly differs from classic holoprosencephaly in that there is no lower jaw. This is discussed under *agnathia*. A proboscis seems to occur less often than in the usual severe forms of holoprosencephaly.

A number of minor anomalies have been found with holoprosencephaly (3,9,24,38,45,46). Single maxillary central incisor (9,20,26) and, much less commonly, absence of the nasal septal cartilage (38) can be useful markers in autosomal dominant holoprosencephaly. Other identified defects have included stenosis of the pyriform aperture (2,3), absence of the upper labial frenum (45), and absence of the philtral ridges (46).

Kjaer et al (43) demonstrated that the palate differs among the various forms of holoprosencephaly. In all forms, the premaxillary area is highly malformed. A fan-shaped area behind the premaxilla is broadest in cyclopia and lessens as the severity of the condition lessens.

Differential diagnosis. Hypotelorism may be observed with metopic synostosis. Isolated median cleft lip can occur with normal brain development (24,83). Cohen (21) and Verloes and Koulischer (85) described an oroacral syndrome with absent anterior maxillary teeth without cleft lip or palate but with reduction defects of the fingers and toes. Martínez-Frías et al (47) classified four general types of proboscis formation: holoprosencephalic, lateral nasal, accessory, and disruptive. Stelnicki et al (80) described a craniofacial malformation with prosencephalic duplication. In *Binder phenotype*, hypoplasia of the anterior nasal spine occurs with normal intelligence; the facial appearance may appear "arhinencephaloid." Agenesis of the corpus callosum may occur as an isolated anomaly independent of holoprosencephaly or may occur as a component in a variety of nonholoprosencephalic syndromes. The relationship between holoprosencephaly and septo-optic dysplasia or with *Rieger syndrome* remains speculative. Unilateral arhinencephaly has been noted in a patient with *oculo-auriculo-vertebral spectrum*. Single maxillary central incisor may occur as an isolated defect, with hypothalamic hamartoma and sexual precocity, and also with coloboma and hypomelanosis of Ito. Isolated *agnathia* can occur independently of holoprosencephaly (20,24). Jespers et al (40) described two sibs with hypoplasia of

the corpus callosum and/or cerebellar hypoplasia, Robin sequence, Hirschsprung disease, and other anomalies.

Laboratory aids. Any patient suspected of having holoprosencephaly by physical examination and neurologic observation and testing is a candidate for computed tomography (CT) scanning (24). Patients with holoprosencephaly should have a banded chromosome study and molecular studies in selected cases. Antenatal diagnosis with ultrasound during the third trimester has been reported. The diagnosis of alobar holoprosencephaly is virtually certain when hypotelorism is found in association with absence of the midline echo. Sonographic demonstration of orofacial clefting may be helpful. In semilobar and lobar holoprosencephaly, sonographic diagnosis is difficult or impossible (24).

Some syndromes with holoprosencephaly or arhinencephaly not discussed further in the text but cited in Table 16–2 include:

- *Aprosencephaly*—Facial features of anencephaly but intact cranium.
- *Hartsfield syndrome*—Premature synostosis of coronal and metopic sutures, hypertelorism, cleft lip-palate and ectrodactyly.
- *Genoa syndrome*—Holoprosencephaly and primary craniosynostosis involving the coronal and lambdoid sutures.
- *Martin syndrome*—Holoprosencephaly, median cleft upper lip, microcephaly, mental retardation, hypertelorism, downslanting palpebral tissues, large pinnae, club foot, spinal anomalies, chronic constipation.
- *Grote syndrome*—Holoprosencephaly, hydrocephaly, octodactyly, absent tibial bones, cardiac malformations.
- *XK aprosencephaly*—Aprosencephaly and cerebral dysgenesis, digital and genital anomalies.
- *Steinfeld syndrome*—Holoprosencephaly with median cleft upper lip, short forearms, absent thumb, cardiac defects, renal anomalies, absent gallbladder.
- *Lambotte syndrome*—Intrauterine growth retardation, semilobar holoprosencephaly (25%), mental retardation, microcephaly, large pinnae, hypertelorism, flat face, hooked nose, narrow mouth, retrognathia.
- *Perrin syndrome*—Anosmia, hypogonadotrophic hypogonadism, mental deficiency, congenital ichthyosis.
- *Johnson syndrome*—Anosmia, hypogonadotrophic hypogonadism, alopecia, conductive deafness, protruding dysplastic pinnae.
- *Fitch syndrome*—Arhinencephaly, absent corpus callosum, hydrocephaly, absent left diaphragm, VSD, absent fifth fingernails.
- *COH syndrome*—Arhinencephaly, polymicrogyria, hydrocephaly, cloverleaf skull, duplication of thumb, micropenis, bifid scrotum.
- *Aicardi syndrome*—Chorioretinal lacunae, agenesis of corpus callosum, mental deficiency, arhinencephaly, flexion spasms, rarely holoprosencephaly and/or cleft lip.

References (The holoprosencephalic disorders)

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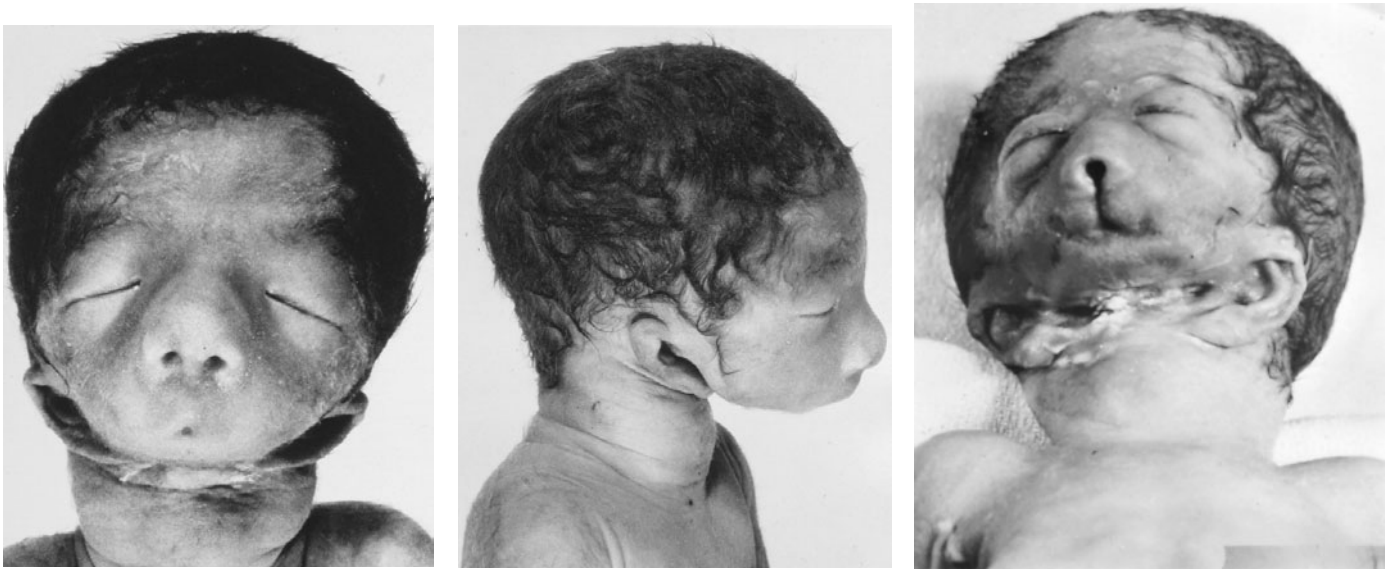
Otocephaly (agnathia)

The primary malformation in otocephaly is agnathia, with malplacement of the external ears with or without fusion, microstomia, and persistence of the buccopharyngeal membrane likely being secondary effects of absence or hypoplasia of the mandibular arch (Fig. 16–8). The condition is lethal since oropharyngeal abnormalities result in an impatent or poorly functioning airway. Many cases have been recorded (1,2,9,11,14–18,23, 25,28–32). Possibly the first case was described by Kerckring in 1717 (see 23). An excellent anatomic study was carried out by Lawrence and Bersu (14). The maximal prevalence is almost certainly less than 1/70,000 births (23). The terms agnathia, synotia, and otocephaly, for all practical



A B C

Fig. 16–8. *Otocephaly.* (A–C). Note tendency of ears to fuse in midline, absence of mandible. Note separate but tiny mouth in A. Note unified nose and mouth in C. (C courtesy of HW Emonds, Washington, DC.)

purposes have approximately equivalent meanings, even though the first term specifically refers to absent mandible, the second term to fused ears. To date, all cases of isolated agnathia have been sporadic. It has been suggested that otocephaly may be caused by mutations in FGF8 (28a). Pauli et al (23) reported a recurrent-pattern syndrome in two nonrelated infants who had agnathia, situs inversus, unilateral renal agenesis, renal ectopia, absent ribs, and vertebral anomalies.

With isolated agnathia, the average gestation is 32.7 weeks and birthweights are commonly below the tenth centile. Polyhydramnios has been a feature of most pregnancies (2). Prenatal diagnosis has been achieved (9a). Most affected infants die within the first few hours or days of life (23). There have been less affected examples that have lived and transmitted the condition to a child (5a).

Craniofacial features. The mandible is either absent or hypoplastic. Although some authors have claimed that the mandible is never completely absent (11), radiography and dissection have failed to reveal any evidence of a mandible in a number of cases (3,23,28,31).The oral aperture may be absent (astomia), but more often is a minute opening 2–3 mm in diameter with its long axis usually rotated 90°. The buccopharyngeal membrane may persist, and microglossia of extreme degree may be present low in the pharynx. The external ears are malformed, ventrally placed, and approach each other or fuse in the midline (Fig. 16–8). Ear canals may be atretic and middle ear anomalies may occur in some cases. Rarely, the external ears may be absent. The palate may be cleft. The palpebral fissures slant downward (2,23).

Other craniofacial features have been reported including hypertelorism, proptosis, blepharophimosis, epibulbar dermoid, microphthalmia, synophrys, cleft lip, choanal atresia, abnormal inner ear and vestibular apparatus, bilobed epiglottis, and rudimentary vocal cords (23,25).

Other abnormalities. Miscellaneous anomalies have included cerebellar hypoplasia, septum pellucidum cavum, agenesis of the left calcar avis (20,23), situs inversus totalis, unilateral renal agenesis, renal ectopia, cystic kidney, Müllerian duct agenesis, cryptorchidism, vertebral anomalies, absent ribs, Sprengel deformity, talipes equinovarus, VSD, pulmonic stenosis, PDA, patent foramen ovale, and unlobated lungs (2,8,9,23).

Differential diagnosis. Isolated agnathia should be distinguished from *agnathia-holoprosencephaly* (3,4,6,7,10,12,13,21,22,24,26). The most extreme example is otocephaly-cyclopia (4). As in cyclopia, there is alobar holoprosencephaly. A defect in prechordal mesoderm is thought to be responsible (2). Agnathia-holoprosencephaly-situs inversus has been described by several authors (16,23,26–27a). Porteous et al (26) described affected sibs with agnathia–holoprosencephaly.

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Nasal aplasia (arhinia), heminasal aplasia with or without proboscis, and their associations

The nose begins its development by the appearance bilaterally of the nasal or olfactory placodes on the lower outer portion of the fronto-nasal prominence around the 28th day (53). Proliferation of ectomesenchyme around the placodes and programmed cell death result in the formation of primitive nostrils (nasal pits) that ultimately extend in a funnellike (choanal) tube to the stomodeum. Migration of neural crest cells causes horseshoe-shaped ridges to appear on either side of the nostrils, becoming the medial and lateral nasal prominences. The cartilaginous septum is formed by neural crest cells that persist between the two nasal sacs, i.e., posterior extension of the nasal pits. At the deepest portion of the sacs, there is the oronasal membrane that normally ruptures during the second month. Rupture is necessary for patency of the nostrils; otherwise choanal atresia results. Due to selective growth of the facial prominences, the medial nasal prominences move toward one another, finally forming the nasal bridge, philtrum, primary palate, and columellar area. The lateral nasal prominences form the lateral sides of the nose. The primitive nostrils fill with epithelial plugs. If there is agenesis of both nasal placodes or sacs or failure of the plugs to resorb, nasal aplasia results; if one placode is missing or if only one plug resorbs, heminasal aplasia results (40).

The reader is referred to Rontal and Duritz (47) and Leperchey et al (29) for discussion of the pathoembryology. This subject is discussed thoroughly by Gorlin and Cohen (20).

Complete aplasia of the nose (*arhinia*) has been recorded on several occasions (3,5,6,10,11,15,16,19,30,33,43,49,51,52) (Fig. 16–9). In some there is no nose, in others a blind-ended pit is present (19). Hypoplasia of the midface is often present (15,19,27,30,37,54). In complete nasal aplasia, ipsilaterally displaced eye, colobomata, microphthalmia, anophthalmia, congenital cataract, Peters anomaly, absence of olfactory bulbs and tracts, and absence of nasolacrimal duct have been noted (19,28,38,50,51,54,59). A few patients have associated cleft palate (30,49). A duplicated thumb has been reported. Intelligence has been normal.

It has been reported in sisters (49) and as an autosomal dominant condition by Thiele et al (54). All other examples have been isolated cases. Arhinia has been seen in association with mandibulofacial dysostosis (6). Prenatal diagnosis has been made (17a).

Aplasia of half the nose (*heminasal aplasia, hemirhinia*) may be found without a nasal proboscis (Fig. 16–9D) (7,14,24,27,50,51,55,60) or, more often, found in association with other anomalies of the facial region. All have been isolated cases. Frequently there is a blind-ended lateral nasal proboscis (Fig. 16–9) (1,4,7–12,14,17,18,26,27,31–37,39,41,42,55,57–61). For examples not cited here, the reader is referred to two publications (12,33). The proboscis, about 2–4 cm in length and 0.5–1 cm extends from an area just lateral to the nasal root. Rarely, a proboscis may be located in the midline with a normal nose (18), attached to an eyelid (4), or lateral to the eye (2). There are examples of bilateral proboscides (48) (Fig. 16–9).

Bony abnormalities in the involved area(s) lack the cribriform plate, nasal septum deviated to unaffected side, loss of structures of the lateral wall of the nasal chamber on the affected side, absence or hypoplasia of the paranasal sinuses on the affected side, absent nasal bone, and disrupted lacrimal bone (16,47,54).

In addition to cleft lip and/or palate or submucous cleft palate (4,6,39,50,52), also discussed in Chapter 23, anomalies of the eye region are common with nasal aplasia but especially with heminasal aplasia. The ipsilateral eye is nearly always laterally displaced. Other eye anomalies include coloboma of the lower lid (1,8,17,32,36,42,45–47), coloboma of the upper eyelid (45,55), coloboma of the iris, choroid, and optic nerve (4,18,19,31,35,49,50,55), microphthalmia and anophthalmia (4,19,36,39,48–50), nystagmus (4,30,50), Peters anomaly (49), cataract (18,50,51), and doubling of lens or globe (31,34). The nasolacrimal canal is disturbed in its formation and epiphora or dacryocystitis is common.

Intelligence is normal with rare exceptions (34).

Hodgson and Saunders (23) reported that the homozygous state for mutation of the aniridia gene results in absence of nose, eyes, and adrenal glands. We wonder whether the sisters described by Ruprecht and Majewski (49) and the family described by Thiele et al (54) may represent a mutation in the *PAX6* gene. However, other genes such as *MSX1* and *2*, *SIX3*, *BMP4* and *7*, *SOX6*, and *GFG8* should also be investigated (21). Trisomy 9 mosaicism, we suspect, is aleatory (25).

Bosma syndrome refers to hypoplasia of the nose, eyes, hyposmia, hypogeusia, inguinal hernia, and hypogonadotrophic hypogonadism with normal intelligence (13,21,22).

References [Nasal aplasia (arhinia), heminasal aplasia with or without proboscis, and their associations]

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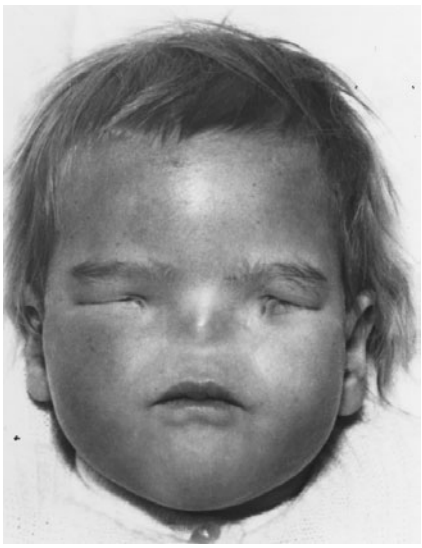

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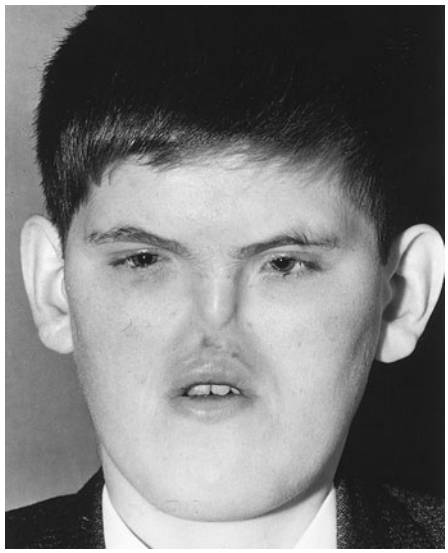

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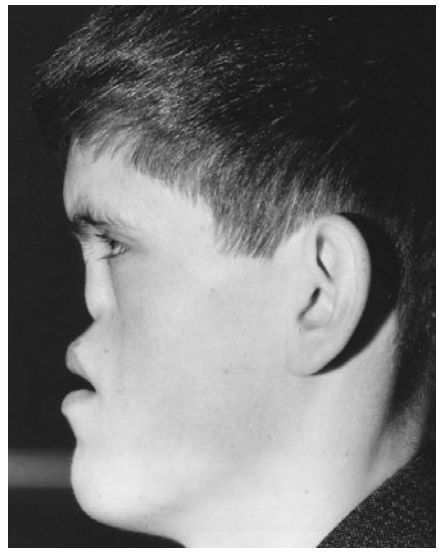

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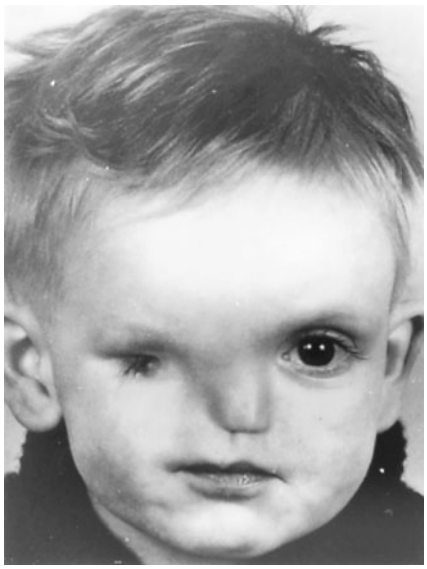

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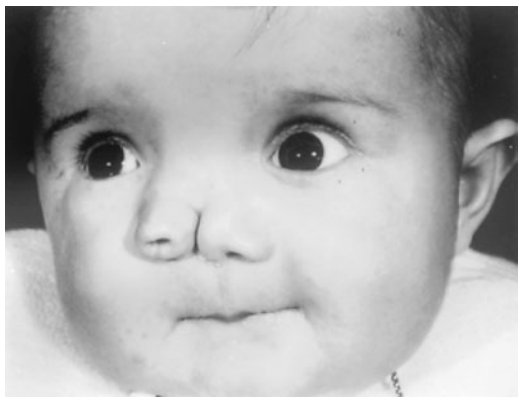

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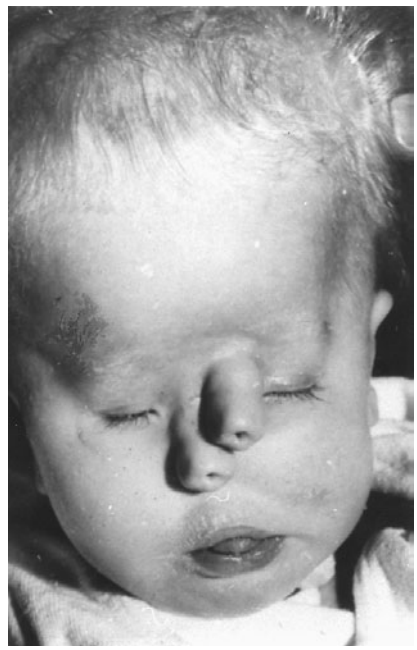

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Fig. 16–9. *Nasal aplasia* (arhinia). (A) Essentially total absence of nose. (B,C) Nasal aplasia. Some formation of nose, hypoplastic midface. (D) Heminasal aplasia. Note absence of half of nose, anophthalmus on ipsilateral side. (E) Unilateral proboscis. Observe ipsilateral location of proboscis. (F) Bilateral nasal proboscides. (B,C from V Lütolf, J Maxillofac Surg 4:245, 1976. E courtesy of P Tessier, Paris, France. F courtesy of AJ Cassini, Cincinnati, Ohio.)

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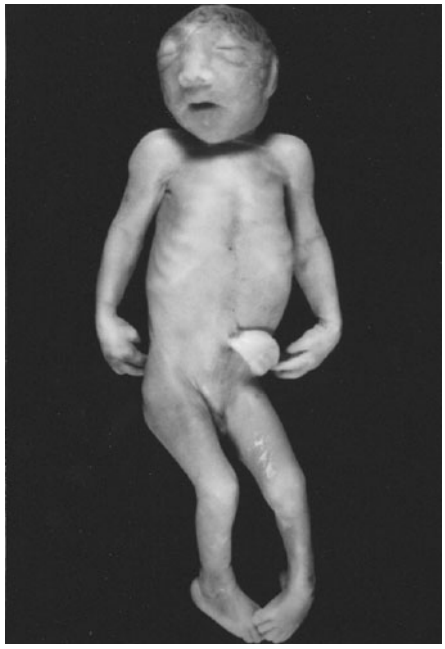
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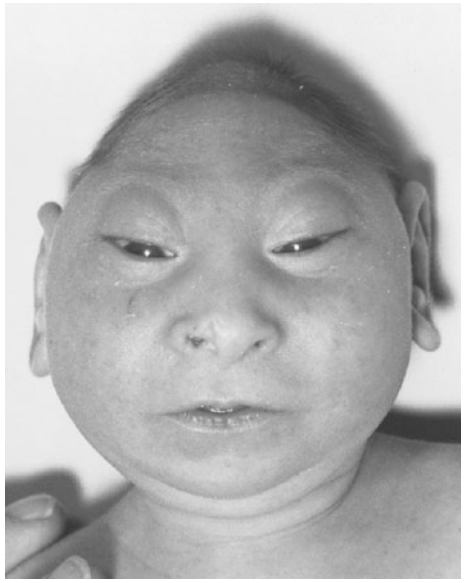
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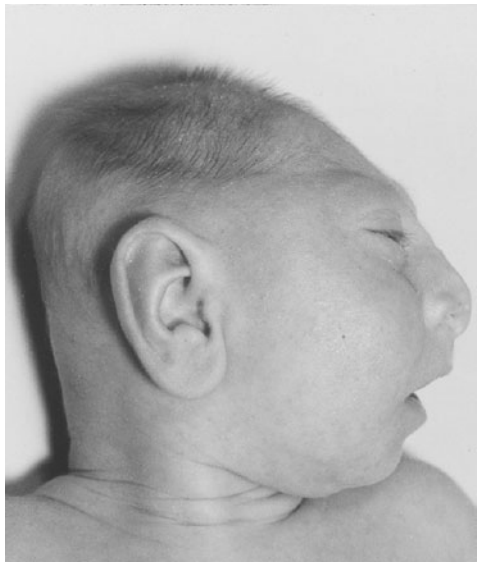
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Fig. 16–10. *Aprosencephaly.* (A) Diminished head size, sloping forehead, talipes equinovarus. (B,C) Microcephaly, sloping forehead, broad nasal bridge. (A from SR Florell et al, Am J Med Genet 63:542, 1996. B,C from J Towfighi et al, Arch Pathol Lab Med 111:146, 1987.)

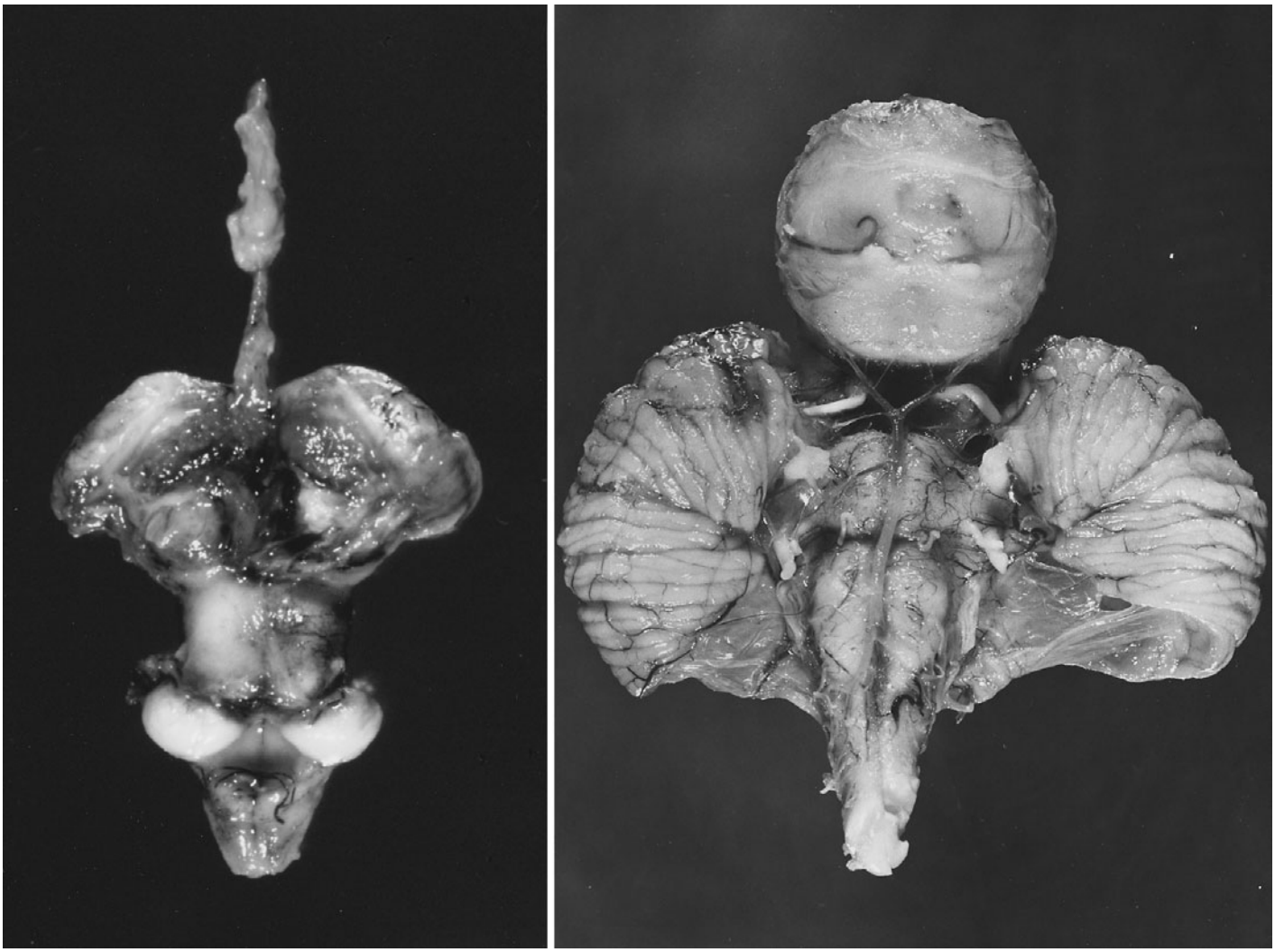

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Fig. 16–11. *Aprosencephaly.* (A) Absence of cerebral fissures. (B) Ventral view of brain showing small globular forebrain, absence of olfactory tracts. Other cranial nerves present. (A from SR Florell et aI, Am J Med Genet 63:542, 1996. B from J Towfighi et al, Arch Pathol Lab Med 111:146, 1987.)

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Aprosencephaly

Aprosencephaly is a rare, lethal malformation sequence of the central nervous system. It resembles anencephaly, but the scalp and cranium are intact with fused sutures. Head circumference is greatly reduced. The eyes protrude (1–8) (Fig. 16–10).

There is absence of the telencephalon and pyramidal tracts, lateral and third ventricles, rudimentary diencephalic and mesencephalic structures, primitive cerebellar hemispheres, posterolateral clusters of premature neural cells in the medulla, normally formed spinal cord and retinal dysplasia within normally formed globes (Fig. 16–11). There is a perivascular mesenchymal proliferation seen only in the central nervous system.

If genitalia and limb abnormalities are present, the term *syndrome aprosencephaly* or *XK aprosencephaly* is used (6,7). Limb anomalies include absent or hypoplastic thumbs and halluces, clinodactyly, and clubfoot.

Anogenital/urinary anomalies comprise hypoplastic penis, cryptorchidism, atresia ani, and agenesis of the kidney, ureter, and bladder.

Cardiac anomalies are ASD, VSD.

Oral anomalies although rare, include cleft palate, bifid uvula, and wide gingiva.

Inheritance may possibly be autosomal recessive (1). However, del(13q) has also been reported (2,8).

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Chapter 17
Syndromes Affecting the Central Nervous System

Myotonic dystrophy (Steinert syndrome)

Myotonic dystrophy is characterized by myotonia, progressive muscle wasting, cataracts, and variable mental deficiency. The diverse progressive clinical manifestations relate to multiple system involvement that includes the eye, heart, endocrine system, gastrointestinal tract, skeleton, and skin. An excellent comprehensive and historically interesting monograph on myotonic dystrophy has been written by Harper (24). A cogent editorial on molecular diagnosis is that of Suthers et al (58).

Early reports of myotonic dystrophy date from Hoffmann (26), in 1896, and from Rossolimo (48), in 1902, but delineation of myotonic dystrophy as a condition clearly distinct from myotonia congenita (Thomsen's disease) was first made by Steinert (55) and Batten and Gibb (3) in 1909.

Myotonic dystrophy has autosomal dominant inheritance with greatly variable penetrance and clinical presentation and course. The prevalence is estimated at 4–15/100,000 population (53). This may be an underestimate because of the high frequency of stillbirth and neonatal death in families with this disorder. There may be a higher frequency among the French Canadian population (35). In genetic counseling of a heterozygous female, the risk for an affected child is approximately 10% but after having one, it increases to 20%–35% (32). There is no evidence that the homozygotic state is more severe than the heterozygotic state (68).

Molecular genetic studies have mapped the gene to band 19q13.2–q13.3, and a large number of flanking markers have been found (22,52,58). The mutation identified to be the cause of myotonic dystrophy consists of a trinucleotide (CTG) repeat that undergoes expansion in female, and less often male, meiosis. Severity varies with the number of repeats. Unaffected individuals have between 5 and 30 copies. Patients with mild symptoms have 50–80 repeats, while more severely affected patients have expansion up to 2000 or more copies (19). The number of repeats increases with transmission from an affected mother to child, thus explaining the phenomenon of anticipation (increase in severity in successive generations) (12,22,23,25,28,63). This is correlated with hypermethylation (54). Also there has been a report on the decrease in size of the repeat (29). There are a few examples of the congenital form having been transmitted from a mildly affected male (4,9,38). The CTG repeat segment is transcribed and is located in the 3′ untranslated region of a protein kinase gene (8). There is some evidence that there is mitotic instability of the repeat throughout life, resulting in expansion (34). There is a second gene that maps to 3q in which triplet repeats do not play a role. The calves are enlarged like those with Duchenne muscular dystrophy (44,60).

Congenital myotonic dystrophy was first described by Vanier (65) in 1960 and has subsequently been delineated in several clinical reports (41,61). Infants with the neonatal form vary widely in clinical presentation. Problems vary from mild hypotonia, feeding problems, and talipes to severe respiratory insufficiency, leading to death. There is reduced fetal movement. Other findings may include hydramnios, decreased fetal activity, facial diplegia, cleft palate, cryptorchidism, hip dislocations, and thin ribs on chest radiograph (37,56). Several infants have pleural effusion and hydrops fetalis (16,51). In those who survive, mental retardation (IQ less than 65) and language delay are found in all. Myotonia is rarely elicited in the newborn period, and electromyogram (EMG) and muscle biopsy changes are inconsistent in this age group (46). However, follow-up reveals hypotonia and delayed motor development (47). The reader is referred to a 2000 review of pathogenesis (58a).

Infants with the neonatal form are almost exclusively born to mothers with myotonic dystrophy who may manifest few or no symptoms of their disorder at the time of their infant's birth, hence, the importance of the use of trinucleotide repeats to estimate the degree of expansion of the gene (vide supra).

The disorder has multiple and variable manifestations affecting every organ system. The usual age of onset is approximately 20–25 years, but isolated symptoms may precede definitive diagnosis by several years. At least 80% are affected by age 50 (6). These estimates do not reflect those with neonatal presentation and those whose symptoms are so mild as to escape detection. Average age of death has been estimated at between 45 and 50 years. Death generally results from respiratory illness or cardiac failure.

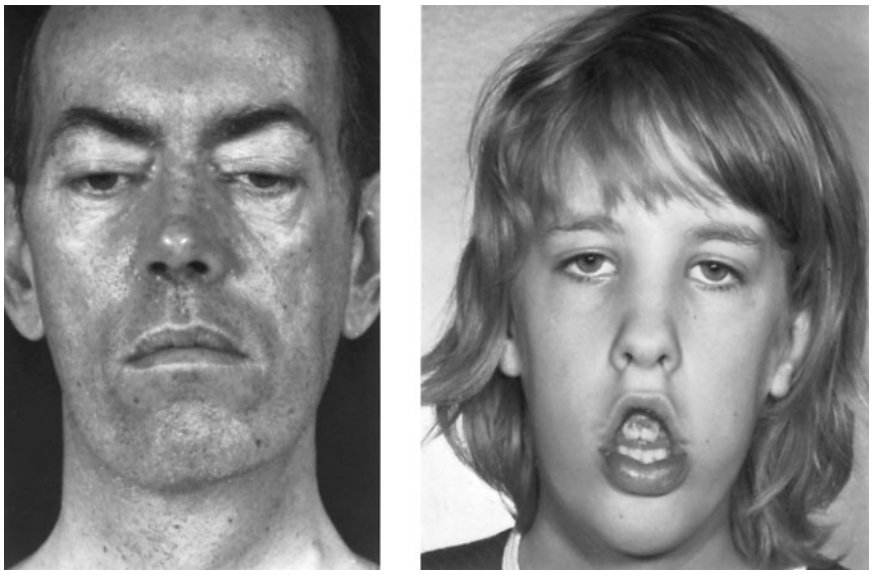
Facies. Facial weakness is an early and consistent recognizable feature of myotonic dystrophy. The face changes with time, becoming narrow, expressionless, and masklike with progressive muscle wasting. There is bitemporal hollowing and the eyes appear sunken. Premature baldness is striking. There is diminished ability to close the eyes, inability to wrinkle the forehead, whistle, or puff out the cheeks with air. The face in congenital myotonic dystrophy is particularly notable with a triangular open mouth due to jaw muscle weakness (Fig. 17–1). Gazit et al (18) discussed the cephalometric aspects of myotonic dystrophy.

Eyes. Cataracts are observed in over 85% of older individuals with myotonic dystrophy. Slit lamp examinations in younger individuals may reveal bilateral iridescent or multihued dust-like lens opacities and posterior subcapsular zones. This is very useful in presymptomatic detection, being seen in all (2,46). Cataracts are rare in congenital myotonic dystrophy. Retinal abnormalities of peripheral pigmentary changes, macular degeneration, and abnormal dark adaptation are quite common (50). Electroretinographic changes may be noted in presymptomatic patients (16). Ptosis is extremely common, but not invariable, even in severely affected patients. Other less common eye abnormalities include strabismus, blepharospasm, extraocular muscle weakness, keratoconjunctivitis, blepharitis, and decreased intraocular pressure.

Auditory system. Hearing loss has not been widely recognized but appears to be common. Wright et al (67) reported moderate to severe, usually sensorineural, hearing loss in 17 of 25 patients. It is more frequent in older individuals (59,66).

Hair and skin. Early frontal balding, as noted above, is very common in males, the extent appearing to parallel the severity of the muscle disease (23). A very unusual benign skin tumor, calcifying epithelioma of Malherbe or pilomatrixoma, has been observed to segregate with myotonic dystrophy in approximately 3% of reported families (17,24,33). These examples are multiple in approximately 70% of those cases. The nature of this association is unclear but unlikely to be coincidental.

Central nervous system. Apathy, inertia, reluctance to seek medical advice, and social decline are common, and efforts to help may not be welcomed. Hypersomnia is very common and has been observed even after correction of alveolar hypoventilation, suggesting a central cause. Probably all patients with the congenital form and some with childhood



A B

Fig. 17–1. *Myotonic dystrophy.* (A) Characteristic expressionless face, ptosis of eyelids, temporal and buccal hollows, and slack mandible. (B) Compare facies in 12-year-old. (A from HH Thayer and J Crenshaw, J Am Dent Assoc 72:1405, 1966.)

onset have mild to moderate mental retardation (43). Thus, mental retardation correlates with onset of neuromuscular symptoms, and size of CTG expansion, but not with severity of weakness or sex. MRI scans in mentally retarded individuals may show generalized or focal cerebral atrophy, focal white matter abnormalities, especially in the anterior temporal lobe, and increased skull thickness (14,27).

Cardiovascular system. Cardiac involvement is common and not confined to severely disabled patients. Most patients have cardiac conduction defects, and sudden death has been reported frequently (31). Approximately 50% exhibit first-degree heart block or other arrhythmias such as atrial flutter (10,62). Hypotension is common. Few patients have signs of cardiac failure, despite histopathological changes of cardiomyopathy. In one family, 30% exhibit mitral valve prolapse (57,62).

Respiratory system. Involvement of the diaphragm, shown by elevation on X-rays and functional studies, results from both weakness and myotonia. Alveolar hypoventilation, frequent in patients with either mild or severe disease, may have a central component. Aspiration pneumonia is due to weakened chest wall and diaphragmatic musculature as well as to possible central nervous system factors. Moderate restriction and lung volume with mild hypoxemia can be observed in myotonic dystrophy patients without clinical dyspnea (30).

Hypersomnia has been a frequently noted clinical symptom, occasionally attributed to alveolar hypoventilation. Sleep apnea can be a serious complication and may be worsened by procedures such as a pharyngeal flap designed to reduce velopharyngeal insufficiency, which is also common (13). Anesthesia, which may pose special risks in the infant, pregnant patient, and adult with myotonic dystrophy, has been the topic of several reviews (1,7,37).

Gastrointestinal system. Multiple dysfunctional aspects of gastrointestinal motility have been observed repeatedly with a resultant wide array of symptoms including esophageal reflux, gastric retention, megacolon, cholelithiasis, malabsorption, and constipation in 80% (31). Manometric studies of intestinal motility have confirmed abnormal motility patterns (20,39). Infants with neonatal presentation may exhibit poor sucking and swallowing, delayed gastric emptying, and recurrent vomiting (6). Intestinal pseudoobstruction has been reported (10).

Musculoskeletal system. The age of onset is difficult to determine because of the long asymptomatic period. Median age of onset is 20–25 years, and at least 80% are affected by age 50 (6). The striking and severe clinical variant, known as congenital myotonic dystrophy, which occurs in approximately 20% of patients born to affected mothers, is due to anticipation.

In most patients, the earliest neuromuscular symptoms are weakness and wasting of facial and jaw muscles. Extraocular muscles produced ptosis, weakness of lip closure, and limited extraocular movements. Jaw weakness due to atrophy of masseters results in sagging jaw and temporomandibular joint dislocation. Sternocleidomastoid weakness and wasting are prominent, while posterior neck and shoulder girdle muscles are less affected. Limb involvement early in the course is usually mild and first noticed in the small muscles of the hands and feet, wrist extensors, and foot dorsiflexors. Proximal limb weakness occurs much later, allowing most patients to remain ambulatory throughout their lives. It is unusual for patients to be confined to a wheelchair, even when affected severely otherwise.

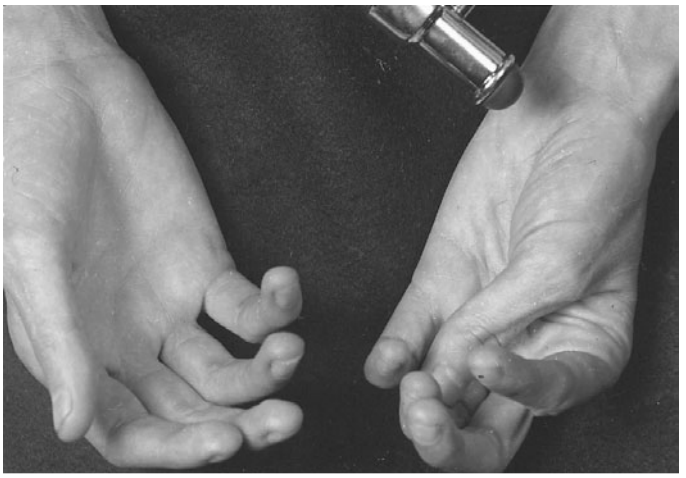
The other striking neuromuscular abnormality observed is myotonia, which consists of a delay in relaxation of normal muscle contractions (Fig. 17–2). It is best elicited in the hand or with percussion of the tongue, as generalized myotonia is rare. Many patients seem unaware of the myotonia, even if obvious on exam. Those who are aware of it usually described it as stiffness, which is often aggravated by cold.

In congenital myotonic dystrophy, the disease begins before birth and results in much more severe manifestations. This severe form is nearly always inherited from the affected mother. During pregnancy, diminished fetal movements and polyhydramnios are common. At birth, respiratory distress is frequent and is the major cause of mortality. Facial and jaw muscle weakness and wasting are severe, resulting in a tented upper lip and contributing to severe feeding problems. Generalized hypotonia is present and usually severe. Other abnormalities may include talipes, gracile ribs, congenital hip dislocation, undescended testes, and hernias. The weakness and hypotonia slowly improve during infancy, and virtually all surviving children learn to walk. Speech and swallowing difficulties usually improve, but residual problems persist.

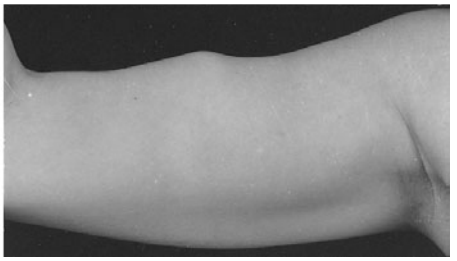
Electromyogram changes are striking, and consist of excessive insertional activity, other signs of electrical irritability, and myotonic potentials. The latter are repetitive potentials that wax and wane in frequency and amplitude, resulting in the so-called dive-bomber sound.

There is no single muscle pathologic change that is diagnostic, but the overall pattern is distinctive. The most characteristic changes on muscle biopsy include increased central nuclei, nuclear chains, ringed fibers, sarcoplasmic masses, type 1 fiber atrophy, increased fiber splitting in muscle spindles, and increased arborization of nerve endings. Less prominent changes include small angular fibers, moth-eaten fibers, type 2 fiber hypertrophy, and increased fibrosis.

Radiographic changes include calvarial hyperostosis and large paranasal sinuses, small sella turcica, prognathism, or micrognathia.



A



B

Fig. 17–2. *Myotonic dystrophy*. (A,B) Myotonic response to percussion of thenar eminence and biceps muscle.

Other changes such as thin ribs in infancy, kyphoscoliosis, and talipes are probably secondary to inactivity and muscle weakness (Fig. 17–3).

Endocrine system. Multiple endocrine abnormalities have been noted with testicular atrophy, infertility, and hypogonadism observed in 60%–80% of affected males. Females may have dysmenorrhea and symptoms of ovarian dysfunction. Postprandial hyperinsulinemia is a common finding, probably being secondary to total body insulin resistance. The risk for diabetes mellitus had been estimated to be approximately 5%. Colloid goiter and hypothyroidism are occasional associated findings. *Klinefelter syndrome* is associated with higher frequency than chance (11).

Oral manifestations. Lingual myotonia and/or velopharyngeal incompetence resulting in slow nasal and indistinct speech may be the initial sign (49). Retention of saliva in the oral cavity and a high rate of dental caries are common. Gazit et al (18) studied a series of patients cephalometrically and found increased interocclusal distance, increased face height, increased height of the palatal vault, narrow maxillary arch, increased crossbite, open bite, tongue thrust, and mouth breathing (Fig. 17–4). Recurrent jaw dislocation is common (31).

Differential diagnosis. Congenital myotonia is rare in myotonic dystrophy as in other myotonic syndromes but can be seen occasionally in myotonia congenita, a heterogeneous phenotype with both dominant and recessive modes of inheritance. The differential diagnosis of the neonatal presentation of myotonic dystrophy may include congenital myasthenia gravis, *Moebius syndrome*, and *Prader-Willi syndrome*. In the older patients, differential diagnosis includes various myotonia congenita syndromes, paramyotonia congenita, *Schwartz-Jampel syndrome*, different forms of periodic paralysis, and other types of muscular dystrophy (5). Patients with *facioscapulohumeral muscular dystrophy* have similar weakness and wasting of the face and sternocleidomastoids, but the posterior neck and shoulder girdle muscles are more severely affected. Distribution of the weakness is proximal rather than distal. They also have retinal vascular abnormalities that differ from the retinal dystrophy and cataracts observed in myotonic dystrophy, and lack involvement of other systems.

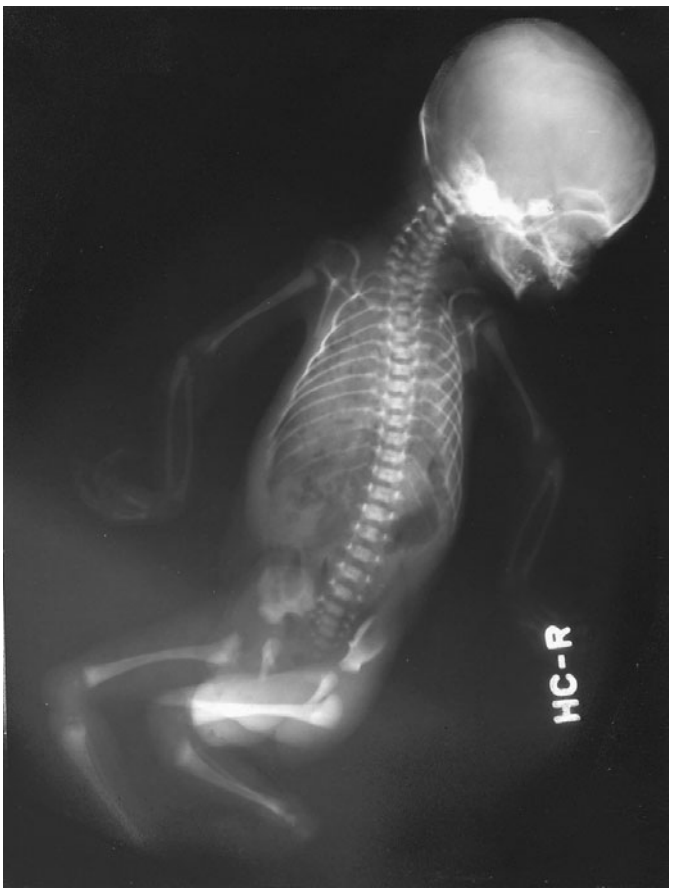
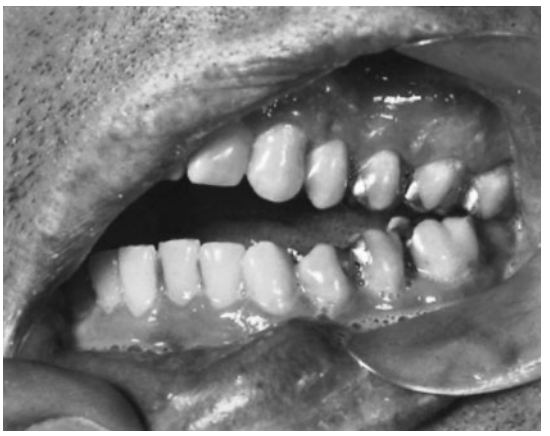


Fig. 17–3. *Myotonic dystrophy.* Radiograph of newborn of affected mother. Note remarkably thin or gracile ribs.

Laboratory aids. Diagnosis is aided by electromyographic studies, particularly of forearm and hand musculature. Occasionally muscle biopsy may be helpful. Slit-lamp evaluation of the eyes is valuable in the diagnosis of at-risk family members, and electroretinogram abnormalities may be even more sensitive in the detection of asymptomatic affected individuals.

Fig. 17–4. *Myotonic dystrophy.* Pronounced anterior open bite. (From HH Thayer and J Crenshaw, J Am Dent Assoc 72:1405, 1966.)



Direct estimation of the size of CTG repeats can be done by Southern blotting. Normal individuals have up to 37 repeats, while affected have 50 to several thousand in peripheral leukocytes (42).

Both prenatal and presymptomatic diagnosis are possible using flanking markers or by determining the size of the CTG repeat (45).

Although no specific microscopic feature is pathognomic for myotonic dystrophy, combined histologic changes on muscle biopsies are characteristic in myotonic dystrophy. Biopsy is rarely necessary for the diagnosis of this disorder, but may be helpful in patients with minimal myotonia and progressive muscle wasting, in those with minimal weakness and a negative family history, and in children in whom the differential diagnosis of congenital hypotonia may be extensive. Microscopic features include increased central nuclei, nuclear chaining, ringed fibers, type 1 fiber atrophy, terminal innervation, sarcoplasmic masses, and muscle spindle abnormalities.

An abnormal electroretinogram has proven useful in distinguishing asymptomatic gene carriers.

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Isolated lissencephaly sequence (classical lissencephaly)

Isolated lissencephaly sequence (ILS) consists of classical lissencephaly (smooth brain) and subtle facial abnormalities and was first delineated by Dobyns (3,5). Children with the same brain anomaly with more severe craniofacial abnormalities are classified as having either Miller-Dieker syndrome (4), Baraitser-Winter syndrome (14), or any of 10 syndromes (8) (Table 17–1). An especially helpful paper is that of Allanson et al (1).

At least two types have been described, an autosomal dominant disorder mapping to 17p13.3 (*LIS1*) (1b) and an X-linked form mapping to Xq22.3–q23 (*XLIS* or double cortin). Patients with ILS associated with mutations of *LIS1* are designated as having ILS17, and those with mutations of *XLIS* as having ILSX. A large majority of patients are sporadic, and the empiric recurrence risk is less than 5% (the 7% risk cited by Dobyns et al (5) included two sibs with probable polymicrogyria). However, X-linked inheritance has been observed in several families, which makes genetic counseling more complicated. A three-generation family with X-linked mental retardation and Dandy-Walker complex has been described (N. Philip, personal communication, 2000). All were tall with macrocephaly, deep-set eyes, and prominent chin. An X-linked lissencephaly family with absent corpus callosum and ambiguous genitalia has been noted (T. Annick, personal communication, 2000). Currently available laboratory testing is able to detect the mutation in approximately 75% of patients (vide infra) (12,13). Among patients with mutations of *LIS1*, none of the parents have been carriers and no recurrence has yet been observed. Among boys in whom mutations of *XLIS* were detected but not found in their mothers, no recurrence has yet been observed. This suggests that the rate of parental germinal mosaicism is low, and such families may be given a recurrence risk of less than 1%. When mutation analysis is negative or has not been performed, the standard recurrence risk of 5% should be modified based on sex of the proband. In families with a female proband, no recurrence in sibs has been reported, so the recurrence risk is probably significantly less than 5%. In families with a male proband, the possibility of X-linked inheritance may be further evaluated using MRI scan. Carrier mothers with mutations of *XLIS* have so far always had a mild form of lissencephaly known as subcortical band heterotopia, which can be identified by a high quality brain MRI scan. When a band is detected, the mother is a carrier and counseling for X-linked inheritance should be given. When no band is detected on a high-quality brain MRI, the mother is unlikely to be a carrier. The quality of the MRI and experience of the reviewer are important because the subcortical band heterotopia may be subtle in these women.

An autosomal recessive lissencephaly with cerebellar hypoplasia mapping to 7q22 is due to mutations in the *RELN* gene (9).

Table 17–1. Lissencephaly sequence

Features	Manifestations
Frequent	
Brain	Classical lissencephaly and associated anomalies
Brain function	Severe or profound mental retardation, decreased spontaneous activity, early hypotonia, subsequent hypertonia, seizures, poor feeding
Craniofacial	Microcephaly, bitemporal hollowing, micrognathia
Occasional	
Brain	Somewhat small cerebellar vermis with cortical dysplasia, hypoplasia of corpus callosum
Brain function	Infantile spasms
Prenatal	Polyhydramnios, decreased fetal movements
Perinatal	May require resuscitation, contractures

(Modified from WB Dobyns, Birth Defects 23(1):225, 1987.)

Craniofacial features. The facial features are subtle and consist of prominent forehead, bitemporal hollowing, and somewhat small jaw (3,4) (Fig. 17–5A). The head circumference is usually normal at birth, but head growth is slow so most become microcephalic. Some have a few subtle features reminiscent of Miller-Dieker syndrome, but not sufficient for diagnosis. Cleft palate has been described (10).

Central nervous system. All patients have classical lissencephaly and associated malformations (Fig. 17–5B). The malformation consists of diffuse agyria-pachygyria with an abnormally thick cortex containing

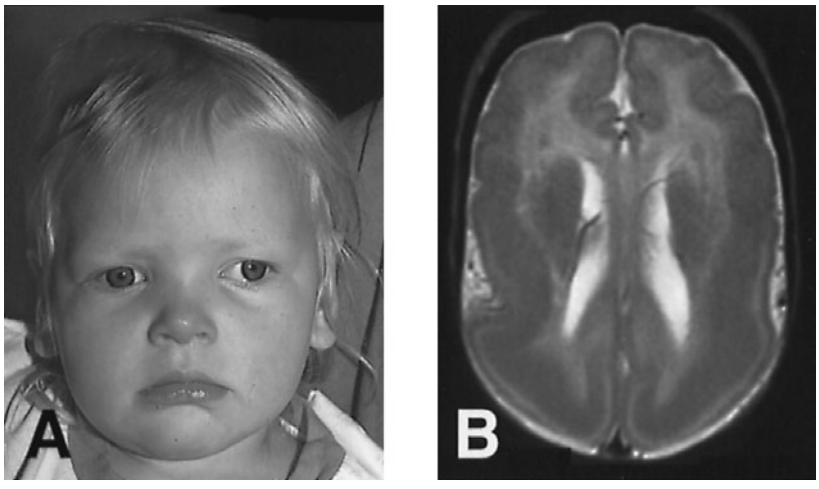

Fig. 17–5. *Isolated lissencephaly sequence.* (A) Essentially normal facial appearance, although with subtle prominence of forehead. (B) Cranial MRI of same patient shows grade 3a lissencephaly with frontal pachygyria and posterior agyria and thus a greater posterior than anterior gradient.

many heterotopic neurons deep to the normal cortex, thus comprising a malformation of neuronal migration (2,3). The severity varies more than in Miller-Dieker syndrome, varying from complete agyria (grade 1) to complete pachygyria (grade 4) (5,8,13). An anterior to posterior gradient is usually apparent (8). Patients with mutations of the *XLIS* gene usually have more severe gyral malformation anteriorly, whereas those with *LIS1* mutations usually have more severe malformation posteriorly. Associated abnormalities consist of enlarged body and posterior horn of the lateral ventricles, mild hypoplasia of the corpus callosum, and frequent cavum septi pellucidi et vergae. Pathological studies also demonstrate involvement of the cerebellum and inferior olives, but this is rarely apparent by imaging studies.

Other anomalies. Other abnormalities include transverse palmar creases, clinodactyly, mild distal contractures, prominent sacral dimples, cryptorchidism, and small penis (5). An X-linked form has been noted with ambiguous genitalia (11). Lissencephaly III, a recessive disorder, has stippled epiphyses and loose thick skin (1a).

Clinical course. Pregnancy may be complicated by diminished fetal movements and polyhydramnios, presumably secondary to poor fetal swallowing movements. Growth parameters including head circumference are most often normal but may be at or just below the 2nd centile. Some newborns appear normal, but many have some clinical evidence of the syndrome, such as hypotonia, feeding problems, and apneic spells with cyanosis. Only a few have seizures during the neonatal period (5).

The major clinical manifestations observed in all affected children consist of profound mental retardation, intractable epilepsy including frequent infantile spasms, and feeding problems that predispose to recurrent aspiration and pneumonia (5,6). During infancy, most affected children have moderate hypotonia with frequent arching spasms or opisthotonus, which gradually disappears over the first two years of life. Almost all children are subject to recurrent seizures that often prove difficult to control. They most commonly begin at 3–4 months of age, but may start anytime during the first year of life, or rarely, even later. The seizures often include infantile spasms, which are observed in more than two-thirds of affected children during the first year. True infantile spasms have rarely been observed in children up to age 3 years, which is very unusual.

Differential diagnosis. The classical form of lissencephaly also occurs in *Miller-Dieker syndrome (MDS)* and *Baraitser-Winter syndrome*. The differential diagnosis is discussed in more detail in the section on MDS. Kerner et al (10) described lissencephaly in sibs with cleft palate and severe cerebellar hypoplasia.

Laboratory aids. The brain malformation may be detected by obvious MRI or CT scan, although the former is more accurate, especially for subcortical band heterotopia. Chromosome analysis has always been normal except for two patients with balanced translocations, one disrupting *LIS1* and the other disrupting *XLIS* (1,5). However, currently available laboratory testing is able to detect the mutation in approximately 75% of patients (12,13). Heterozygous submicroscopic deletions of *LIS1* are detected in only approximately 20% of patients using the fluorescence in situ hybridization (FISH) with probe D17S379 that is approximately 150 kb telomeric to the gene. However, this increases substantially to approximately 40% of patients using FISH with a *LIS1*-gene specific probe. At this time, FISH studies using a LIS1-specific probe should be carried out in all patients with lissencephaly. Point mutations of *LIS1* are detected in approximately 24% and point mutations of *XLIS* in approximately 12% of ILS patients by direct sequencing and Southern blots. Currently, these studies are available only in a few research labs.

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Miller-Dieker syndrome

Miller-Dieker syndrome (MDS) consists of classical lissencephaly (smooth brain) and a group of characteristic facial abnormalities associated with deletions of a large region in the short arm of chromosome 17. This syndrome was first described by Miller (15) and Dieker et al (2) and the eponym was first used by Jones et al (12). Children with the same brain anomaly who lack the striking facial changes are classified as having isolated lissencephaly sequence (ILS), which is discussed in the prior section (Table 17–2). The facies is discussed by Allanson et al (1).

Genetics. Miller-Dieker syndrome is caused by large visible or submicroscopic deletions of 17p13.3 that include the *LIS1* gene and other loci at least 150 kb telomeric to *LIS1* (1a,4,6,8,14,17,18). Smaller deletions or intragenic point mutations of *LIS1* cause ILS. It has recently been renamed *PAFAH1B1* as it appears to function as the β subunit of platelet activating factor acetylhydrolase brain isoform (11).

In families in which one parent carries a balanced rearrangement of 17p13.3, the risk of recurrence is relatively high. In a study of 12 families in which there was a reciprocal translocation involving the MDS critical region in 17p13.3, the overall risk for abnormal pregnancy outcome was 29%, or 38% when unexplained pregnancy losses were not considered in the total (16). This is within the upper range of the reported risk for unbalanced offspring of carrier parents assessed through liveborn aneuploid offspring. The miscarriage rate (22%) was higher but not significantly higher than the population frequency of approximately 15%. Only two families with pericentric inversions of chromosome 17 have been reported, with recurrence observed in one of the two families (10).

Pregnancy is often complicated by diminished fetal movements and polyhydramnios, presumably secondary to poor fetal swallowing movements. Growth parameters, including head circumference, are most often normal but may be at or just below the 2nd centile. Some newborns appear normal except for the craniofacial anomalies, but most have some clinical evidence of the syndrome, such as hypotonia, feeding problems that predispose to hyperbilirubinemia, and apneic spells with cyanosis. Only a few have seizures during the neonatal period.

The major clinical manifestations observed in all affected children consist of profound mental retardation, intractable epilepsy including frequent infantile spasms, and feeding problems that predispose to recurrent

Table 17–2. Features of Miller-Dieker syndrome

Features	Manifestations
Frequent	
Brain	Type I (grade 1–3) lissencephaly, lissencephaly sequence, midline calcification
Brain function	Lissencephaly sequence
Craniofacial	Lissencephaly sequence, relatively high forehead. Low nasal bridge, telecanthus, epicanthal folds, upturned nares. Long, thin upper lip, prominent alveolar ridges
Body	Abnormal palmar creases, clinodactyly, camptodactyly. Cryptorchidism, sacral dimples
Growth	Small at birth, severe postnatal growth deficiency
Occasional	
Brain and brain function	Lissencephaly sequence
Prenatal, perinatal	Lissencephaly sequence, prolonged neonatal jaundice
Craniofacial	Vertical wrinkling of forehead
Body	Congenital heart defect, polydactyly, visceral anomalies, sacral tail
Cause	
Chromosomes	Visible rearrangement of (17)(p13.3) in 60%

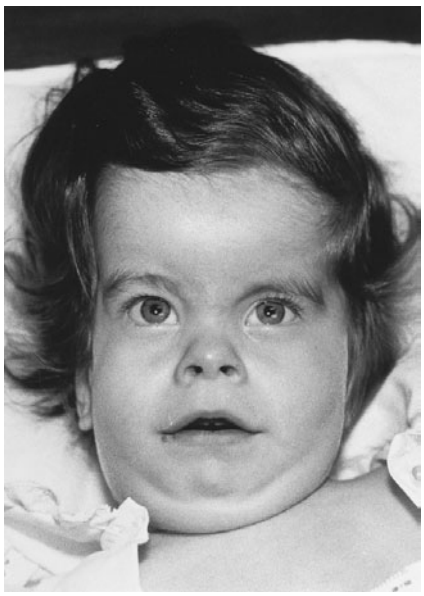
(Modified from WB Dobyns, Birth Defects 23(1):225, 1987.)

aspiration and pneumonia (7,8). During infancy, most affected children have moderate hypotonia with frequent arching spasms or opisthotonus, which gradually disappear over the first two years of life. Almost all children are subject to recurrent seizures that often prove difficult to control. They most commonly begin at 3–4 months of age, but may start at anytime during the first year of life or rarely even later. The seizures often include infantile spasms, which are observed in more than two-thirds of affected children during the first year. True infantile spasms have rarely been observed in children up to age 3 years, which is very unusual.

Craniofacial features. The defining facial features consist of prominent forehead, bitemporal hollowing, short nose with upturned nares, low nasal bridge with prominent skin folds leading down and outward to the cheeks, flat midface, thick upper lip with downturned vermilion border, and small jaw (Fig. 17–6A) (5,6). The head circumference is usually normal at birth, but head growth is slow so many become microcephalic. They often have a prominent occiput and large anterior fontanelle in infancy. The skin over the mid-forehead is vertically furrowed in many children during infancy, although this feature is lost with growth. Less constant abnormalities include telecanthus, epicanthal folds, low-set and posteriorly rotated ears with abnormal helices, high and narrow palate, and late eruption of teeth.

Central nervous system. All patients have severe classical lissencephaly and associated malformations (Fig. 17–6B). The malformation consists of diffuse agyria and pachygyria with abnormally thick cortex containing many heterotopic neurons deep to the normal cortex, thus comprising a malformation of neuronal migration (3,5). The severity may differ somewhat among patients, who may have complete (grade 1) or nearly complete (grade 2) agyria, or mixed agyria and pachygyria (grade 3) (9). Less severe grades do not occur in MDS. An anterior to posterior gradient is apparent with the lissencephaly either more severe posteriorly than anteriorly or equally. Associated abnormalities consist of enlarged body and posterior horn of the lateral ventricles, mild hypoplasia of the corpus callosum, and frequent cavum septi pellucidi et vergae. Pathological studies also demonstrate involvement of the cerebellum and inferior olives, but this is rarely apparent by imaging studies. A few patients have small midline calcifications in the region of the septum pellucidum or genu of the corpus callosum.

Other anomalies. Limb anomalies are relatively common and include transverse palmar creases, clinodactyly and mild distal contractures, with camptodactyly and polydactyly observed rarely. Congenital heart defects occur in approximately 65%, with patent ductus arteriosus and ventricular septal defects being the most frequent. Urogenital anomalies have included prominent sacral dimples, cryptorchidism, and small penis. Severe anomalies such as unilateral renal agenesis, bilateral collecting system and hydronephrosis are observed much less frequently. A few have had omphaloceles. In general, more severe anomalies involving regions other than the face and brain, especially more severe congenital heart malformations, are much more frequent in patients with large chromosome deletions or unbalanced derivative chromosomes (5,6).



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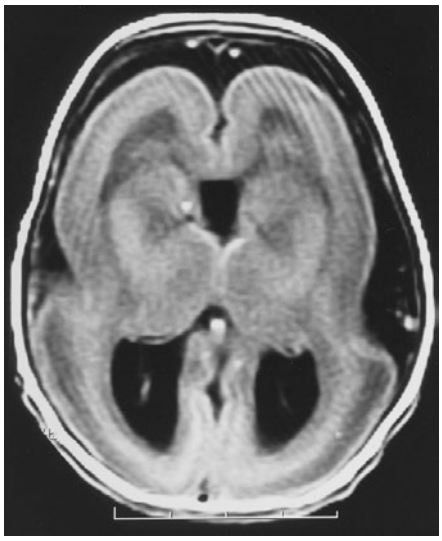

B

Fig. 17–6. *Miller-Dieker syndrome.* (A) Prominent forehead, bitemporal hollowing, short nose with anteverted nares, prominent upper lip with downturned vermilion border especially toward the corners, and mildly small jaw. (B) MRI shows classical lissencephaly with diffuse agyria. On this image, no gradient can be seen although, in most cases, patients with Miller-Dieker have a posterior to anterior gradient. (A from WB Dobyns et al, J Pediatr 102:552, 1983. B courtesy of WB Dobyns, Chicago, Illinois.)

Differential diagnosis. The classical form of lissencephaly may occur without other major anomalies. This is known as *isolated lissencephaly sequence* (ILS). It has also been observed in children with the Baraitser-Winter syndrome, which consists of trigonocephaly, shallow orbits, ptosis, and colobomas with variable lissencephaly. The cobblestone type of lissencephaly occurs in Fukuyama congenital muscular dystrophy, muscle-eye-brain disease and *Walker-Warburg syndrome*. Several different types of microlissencephaly (smooth brain surface with head circumference at birth less than −3 standard deviations) have been observed including microlissencephaly with a thick cortex (probably the same as Norman-Roberts syndrome), "lissencephaly with extreme neopallial hypoplasia," microlissencephaly with thin cortex (one type the same as the "radial microbrain"), and in *Neu-Laxova syndrome*. Several other types have also been described including lissencephaly with cleft palate, simian creases, long distal thumbs and halluces and cerebellar hypoplasia (13), lissencephaly with ambiguous genitalia, and the Winter-Tsukuhara syndrome.

Laboratory aids. The brain malformation may be detected by magnetic resonance imaging or computerized tomographic scan. Chromosome analysis has shown visible deletions of 17p13.3 in approximately two-thirds of the cases, with deletions of the same region demonstrable by fluorescence in situ hybridization (FISH) in the remainder (6,8). Children with ILS never have visible deletions, but may have deletions detected by FISH. For those with an inherited chromosomal abnormality, prenatal diagnosis is possible.

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Walker-Warburg syndrome (HARD±E syndrome, Warburg syndrome, cobblestone lissencephaly)

Walker-Warburg syndrome (WWS) is the most severe of a small group of "muscle-eye-brain" syndromes that also includes Fukuyama congenital muscular dystrophy (FCMD) and muscle-eye-brain disease (MEB). It is observed worldwide, whereas FCMD has been documented in only Japan and Korea, and MEB has been seen predominantly in Finland. Milestones in delineation of the syndrome include the first known description by Walker (18), the first detailed eye studies (9), the association of retinal nonattachment and hydrocephalus (19), the first notation of multiple affected sibs suggesting autosomal recessive inheritance (1), the first general delineation of the syndrome (11,13), and the recognition that WWS was often associated with congenital muscular dystrophy (3,4,17). The term HARD±E syndrome for hydrocephalus, agyria, retinal dysplasia with or without encephalocele was introduced by Pagon et al (12), then changed to Warburg syndrome (11) and finally to Walker-Warburg syndrome (5,20).

Inheritance is clearly autosomal recessive based on many observations of parental consanguinity and multiple affected sibs with normal parents. Walker-Warburg syndrome and related syndromes all have autosomal recessive inheritance. The gene for FCMD has been mapped to chromosome 9q31 (16), whereas the MEB gene has been excluded from this region, indicating that at least two genes must cause the muscle-eye-brain syndromes (14). In addition, a few patients with congenital muscular dystrophy due to laminin $\alpha 2$ (merosin) deficiency have had small patches of agyria in the occipital regions. Prenatal diagnosis has been accomplished by ultrasound, although no series of patients has been reported to determine the success of this approach (2).

Walker-Warburg syndrome consists of cobblestone lissencephaly, retinal dysplasia or other retinal abnormalities, frequent anterior chamber anomalies, and congenital muscular dystrophy (4) (Figs. 17–7 to 17–9). The current diagnostic criteria for WWS and related syndromes were established at several workshops on congenital muscular dystrophy, and are summarized in Table 17–1 (6–8).

Most children with WWS have profound mental retardation and hypotonia, mild distal spasticity and poor vision. Some present with macrocephaly and severe progressive hydrocephalus, whereas others have microcephaly and sometimes occipital cephaloceles. Children with less severe brain involvement still have moderate to severe mental retardation. The median survival is only four months, although some patients may live more than five years. Those with longer survival have seizures, feeding problems and susceptibility to pneumonia (4).

Craniofacial features. Many have a dysmorphic facial appearance but none of the anomalies is specific except for visible abnormalities of the eyes. Typical facial abnormalities include macrocephaly or microcephaly, puffy face, low-set and malformed ears, epicanthal folds and small jaw (Fig. 17–7A). Some have cleft palate and dysmorphic pinnae.

Central nervous system. The brain abnormality, called cobblestone lissencephaly, is pathognomonic for the muscle–eye–brain group of syndromes. This consists of (*a*) "cobblestone cortex" consisting of atypical agyria-pachygyria and polymicrogyria with a pebbled texture due to fibroglial tissue covering the surface and obstructing the subarachnoid space, (*b*) white matter dysmyelination and cystic changes that are more severe in WWS than in FCMD or MEB, (*c*) enlarged lateral and third ventricles, sometime with hydrocephalus, (*d*) brainstem hypoplasia, and (*e*) cerebellar (especially vermis) hypoplasia, which may be associated with Dandy-Walker malformation and usually small occipital cephaloceles (approximately 25%). All of these are apparent on cranial MR imaging (Figs. 17–7B,C and 17–8) (4). On microscopic exam, the cortex is thick and totally disorganized with no discernible horizontal layers, neurons that lie at irregular angles, and abnormal vascular channels and fibroglial bands that divide the cortex into sheets that again lie at irregular angles (3,4,17,18,20).

Eyes. Eye anomalies often involve both the anterior and posterior chambers. These include unilateral or bilateral microphthalmia, angle

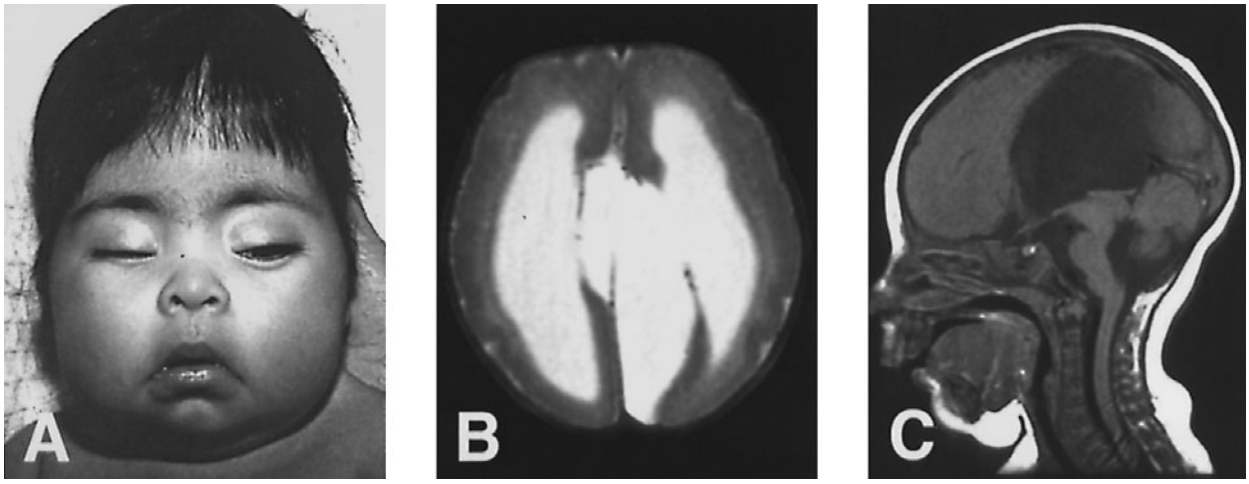
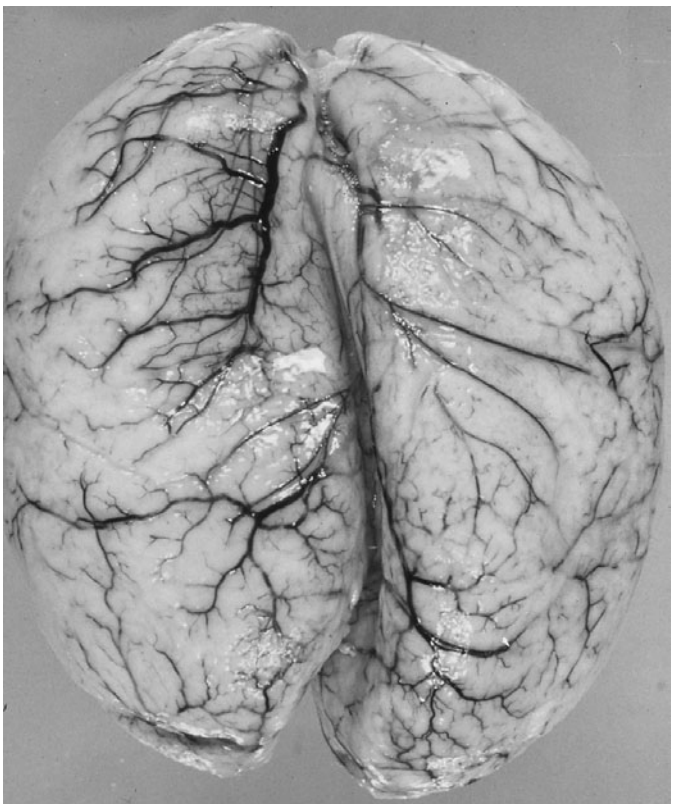


Fig. 17–7. *Walker-Warburg syndrome.* (A) Round face with puffy cheeks, ptosis, subtle prominence of left eye suggesting that it is larger than right, low nasal bridge, short nose with upturned nares, downturned corners of the mouth and slightly small jaw. (B) Cranial MRI of different patient shows cobblestone dysplasia (lissencephaly) with very irregular pebbled brain surface and irregular cortical white matter border, hydrocephalus with a large midline cyst. (C) Hypoplastic brainstem and cerebellum with upward rotation of the cerebellar vermis and small retrocerebellar cyst consistent with a mild Dandy-Walker malformation. (Courtesy of WB Dobyns, Chicago, Illinois.)

anomalies causing congenital glaucoma and sometimes buphthalmos, iris hypoplasia, corneal opacity due to abnormal adhesions to the iris or lens such as observed in Peters anomaly, cataracts, persistent pupillary membrane, persistent posterior hyaloid artery, persistent hyperplastic primary vitreous, retinal nonattachment or detachment, retinal dysplasia, optic nerve hypoplasia, and other less severe retinal and optic nerve abnormalities (4) (Fig. 17–9).

Fig. 17–8. *Walker-Warburg syndrome.* Agyria-smooth lateral surfaces of cerebral cortex with absence of normal convolutions. Only narrow Sylvian fissure is identified.



Neuromuscular system. Most, although perhaps not all, patients have congenital muscular dystrophy or a less specific myopathy (4). This may not become apparent until after the first year of life in children with the related MEB, and the same is probably true for WWS (15). The simplest way to document this is with serum creatine kinase, which may be elevated 5–10 times the upper limit of normal. Otherwise, muscle biopsy is required.

Other findings. The puffy appearance is most common in severely affected children, and may involve the entire body, especially the dorsa of the hands and feet. Some male patients have had genitourinary anomalies such as micropenis and cryptorchidism. Many other anomalies have been observed in occasional patients such as omphalocele.

Differential diagnosis. Differential diagnosis includes other syndromes with lissencephaly, polymicrogyria or hydrocephalus, Aicardi syndrome, and intrauterine infections such as toxoplasmosis or cytomegalovirus that cause hydrocephalus and eye abnormalities (4). Dandy-Walker malformation has been observed in association with many different types of anomalies (10).

Laboratory aids. The brain abnormalities are best delineated by MRI although CT scans usually show these well enough to establish diagnosis. Abnormalities of the eyes may be investigated further by electroretinograms that usually demonstrate attenuated responses, visual evoked potentials that show unusual giant potentials and orbital ultrasound that may demonstrate major posterior pole abnormalities such as persistent hyperplastic primary vitreous, retinal nonattachment and colobomas in patients in whom severe anterior chamber anomalies prevent adequate visual inspection. The muscle changes may be investigated by serum creatine kinase levels that are often greatly elevated, electromyography, and muscle biopsy (4). However, there are no molecular anomalies detected prenatally (8a.)

References [Walker-Warburg syndrome (HARD±E syndrome, Warburg syndrome, cobblestone lissencephaly)]

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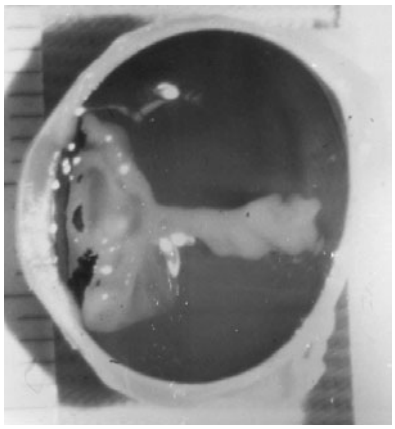

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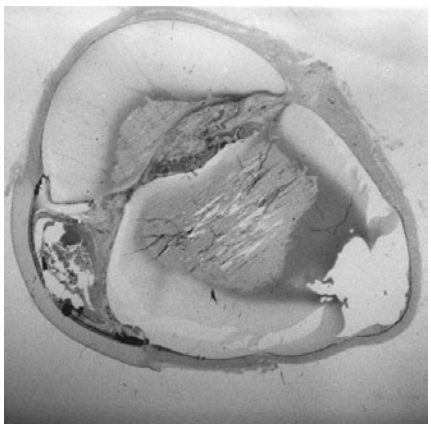

B

Fig. 17–9. *Walker-Warburg syndrome.* (A) Section of eye showing retinal detachment. (B) Sagittal section of eye showing anterior and posterior chamber anomalies (corneal opacity, cataract, persistent primary vitreous) and retinal dysplasia. (A from J Chemke et al, Clin Genet 7:1, 1975. B from D Donnai and PA Farndon, J Med Genet 23:200, 1986.)

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Familial dysautonomia (Riley-Day syndrome, hereditary sensory and autonomic neuropathy type III)

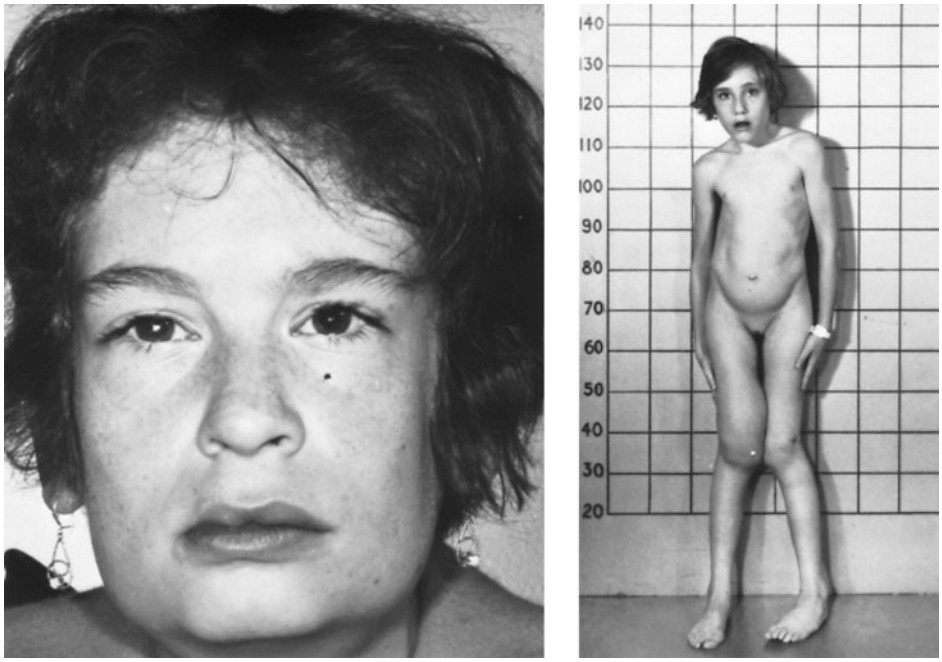
Riley et al (39), in 1949, described a syndrome involving autonomic, sensory, and motor dysfunctions: absence of overflow tears, vasomotor instability, hypoactive deep-tendon reflexes, relative indifference to pain, feeding difficulties, and absence of lingual fungiform papillae. Subsequently, Riley et al (37,38) and others (3,7,8,17,28) presented thorough reviews of its clinical picture. An earlier report is that of Aring and Engel (1).

The syndrome has autosomal recessive inheritance (19). Nearly all patients have Ashkenazic Jewish ancestry, the great majority stemming from eastern Europe (Galicia, Bukovina, Ukraine, Romania, and parts of Austro-Hungary) (7). In Israel, the frequency of the disorder is approximately 1/3700, heterozygotes in this population being 1:30 (19). Cases in non-Jews are rare, but well documented (18,26,27,30). Parental consanguinity has been noted in at least 5%. The syndrome maps to 9q31–q33 and prenatal diagnosis has been established (5,11). Mutations in *ICAP* cause the disorder (40a).

Approximately 30% have breech presentation in contrast to 3%–8% of normal infants (4). Premature rupture of membranes occurs in approximately 30% (4). Meconium staining (35%) is approximately three-fold normal (4). Stature is small even at birth (3). Approximately 25% die of pulmonary infection by the age of 20 years. Recurrent bronchopneumonia is common, probably because food is frequently aspirated (12). Respiratory arrest during sleep is more common during adolescence (2). Diagnosis is extremely difficult in the neonate, especially in the premature infant (34).

Facies. A fixed, sad, empty or frightened expression with a slit-like mouth (grimace) and a peculiar lingual rolling movement are typical (3,38) (Figs. 17–10 and 17–11). The face is thin, frequently asymmetric, with a pale to grayish color except during excitement. External strabismus is common.

Nervous system. In the newborn, approximately 60% have poor or no suck with 25%–30% exhibiting hypotonia and/or hypothermia. Regurgitation and difficulty in swallowing appear soon after birth, and the infant fails to produce overflow tears with the usual stimuli (20). Especially marked are lethargy, somnolence, and unresponsiveness. Other virtually constant signs are absent to diminished deep-tendon reflexes, motor retardation and/or motor incoordination, hypotonia, breath-holding spells, hypersalivation, dizziness or ataxia on change in position, postural hypotension, paroxysmal hypertension, emotional lability, and relative indifference to pain (38). However, many of these children do not like their feet or scalp to be touched (dysesthesia). The indifference to pain may result in Charcot joints as the child ages. Older patients tend to have increased dysfunction in pain sensation, proprioception, and vibratory sense due to neuron depletion (4,33). There is relative insensitivity to hypercapnia and hypoxia (8). Many manifest alternate bouts of diarrhea and constipation. Skin blotching, abnormal sweating, erratic temperature control, and cyclic vomiting are seen frequently (20). Approximately 80% exhibit growth retardation. Severe progressive scoliosis, found in 55%, appears around the eighth or ninth year of life (28,38). Intelligence is normal (3,44). Speech is often monotonous, slurred, and dysarthric with an unusual nasal quality (7).



A B

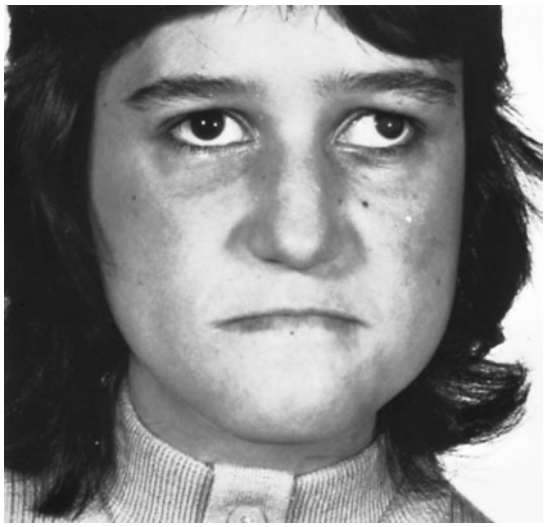
Fig. 17–10. *Familial dysautonomia.* (A, B) Fixed expression, asymmetric thorax, scoliosis, genu valgum due to Charcot joint-like changes. (B courtesy of VA McKusick, Baltimore, Maryland.)

Defective nerve condition (6) and a reduction in the number of unmyelinated nerve fibres, no myelinated nerve fibers greater than 12 μm in a diameter, and abnormally short internodal length of small myelinted nerves have been demonstrated in the sural nerve (4,32). Sensory neurons in the spinal ganglia are decreased (33). There is paucity of cells in the geniculate and scarpa ganglia (43).

Skin. A macular erythema, varying in color from pink to bright orange and located principally on the trunk and limbs, especially during periods of emotional excitement or eating, is common. Cold hands and feet, verging on acrocyanosis, and excessive sweating after the first month of life are constant features (4,28). Severe burns have resulted from indifference to pain in some patients.

Eyes. Constant features are decreased tearing, absent corneal reflex, and immediate papillary constriction in response to subconjunctival instillation of methacholine (3,34,38). Neuroparalytic keratitis sicca or corneal ulceration has been noted in at least 30%. The eye changes can be so severe that blindness may result (9). Myopia and retinal vascular tortuosity are also frequently observed (7,17). Optic atrophy has been reported (40).

Fig. 17–11. *Familial dysautonomia.* Characteristic slitlike mouth. (Courtesy of AA Reitman, Garden City, New York.)



Oral manifestations. Quite characteristically, the mouth is transversely elongated into a horizontal slit (Fig. 17–11). Smith et al (41) reported absence of fungiform papillae on the tongue (Fig. 17–12). Rarely, some are present but are atrophic (13). Circumvallate papillae are also absent or greatly reduced in number (15,28). Sensitivity to sweet and salty taste is diminished (14). Pearson et al (31) were unable to find nerve fibers traveling to the rudimentary papillae. The parents of some patients may have decreased numbers of fungiform papillae (31,38).

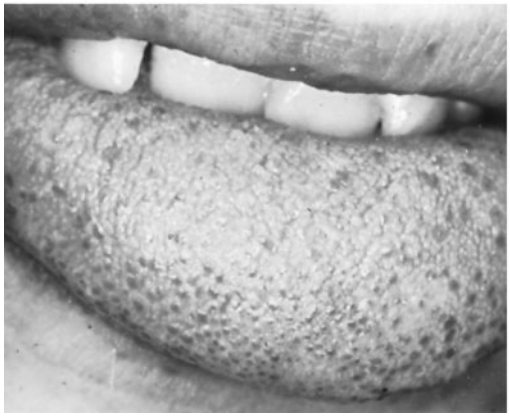
Excessive drooling and diminished gag reflex or swallowing disturbance occur in approximately 80% (28). However, excess saliva is produced because of denervation supersensitivity (23). Dental caries is infrequent, perhaps because of ample saliva, reduced taste sensibility, and a consequent lowered desire for sweets (23,26). However, plaque accumulation, periodontal disease, anterior dental trauma, and small jaws are common (7,22,25). The teeth have been shown to be somewhat smaller than normal (24). Orodental self-mutilation has been found in 35% (21,22). These may take the form of ulcers of the lips, buccal mucosa, or tongue (21) as in Riga-Fede disease (10,21,35,36).

Differential diagnosis. No disorder exactly mimics familial dysautonomia, but many progressive sensory neuropathies have similar features (7) (Table 17–3). Absence of fungiform and circumvallate papillae is an important specific clinical finding. Fungiform papillae may also be absent in Behçet syndrome.

There is some resemblance to congenital *sensory neuropathy with anhidrosis*, a disorder characterized by sensory deficit (diminished knee jerks, deficient taste discrimination, failure of axon flare after histamine injection) but differing from familial dysautonomia in that there are normal tear secretion and failure to produce miosis or to alter taste thresholds after methacholine administration. Suzuki et al (42) summarized cases of dysautonomia in non-Jewish infants. Most were atypical examples, probably representing other disorders.

Laboratory aids. Patients show a wheal but little to no pain or axon flare on intracutaneous injection of 0.01 ml of 1:10,000 histamine phosphate and a strong reaction to norepinephrine and related drugs (3,16). Some affected children fail to respond to a pinprick. There is immediate pupillary constriction with 0.0625% pilocarpine eyedrops. This test is

A



B

Fig. 17–12. *Familial dysautonomia.* (A) Tongue in familial dysautonomia. Note absence of fungiform papillae. (B) Normal tongue for comparison. Observe presence of fungiform papillae. (Courtesy of AA Smith, New York.)

helpful but not pathognomonic and there are 5%–15% false positive responses. Taste acuity for salty and sweet foods is absent in familial dysautonomia (15). An increased homovanillic acid to vanilmandelic acid (HVA/VMA) ratio has been reported in the urine of affected patients (15,36). Heterozygotes have normal ratios (10). Prenatal diagnosis, using linked genetic markers, has been used successfully (11,29).

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Table 17–3. Features of the five types of hereditary sensory neuropathy

Feature	Hereditary sensory radicular neuropathy HSN 1	Congenital sensory neuropathy HSN 2	Familial dysautonomia HSN 3	Congenital sensory neuropathy with anhidrosis HSN 4	Congenital indifference to pain HSN 5
Transmission	AD	AR	AR	AR	AR
Intelligence quotient	Normal	Normal	Normal	Mental retardation	Normal
Sensitivity to pain	Reduced on extremities	Absent	Absent	Absent	Absent
Tactile sensitivity	Absent	Absent	Normal	Normal	Normal
Heat sensitivity	Absent	Absent	Reduced	Reduced	Normal
Osteotendinous reflexes	Absent	Absent	Absent	Normal or reduced	Normal
Self-mutilation	Present	Present	Present	Present	Present
Other symptoms	Vertigo, deafness	Hypotonia	Absence of fungiform papillae	Recurrent fever	
Neuropathologic findings	Segmental degeneration of the dorsal root ganglia	Absence of myelinated fibers, unmyelinated fibers normal or reduced	Absence of unmyelinated fibers	Absence of unmyelinated fibers, small myelinated fibers reduced	Small myelinated fibers absent, unmyelinated fibers ± reduced
Autonomic nervous system	Normal	Normal	Hyperhidrosis, disorders of body temperature, postural hypotension, decreased tearing	Anhidrosis, disorders of body temperature	Normal

(From JC Domingues et al, Pediatr Dermatol 11:234, 1994.)

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Lesch-Nyhan syndrome [hypoxanthine-guanine phosphoribosyltransferase (HGPRT) deficiency]

Lesch-Nyhan syndrome is an X-linked disorder, largely limited to males, resulting from deficiency of the enzyme hypoxanthine phosphoribosyltransferase (HPRT). The syndrome is characterized by hyperuricemia, uric acid stones, spasticity, choreoathetosis, mental retardation, and compulsive, aggressive and self-mutilating behavior (30). Although the disorder has been noted earlier (5,34), Lesch and Nyhan (21) first described the complete syndrome in 1964 and Hoefnagel et al (16) soon after demonstrated X-linkage. Female heterozygotes have two cell populations but always exhibit normal enzyme activity in the blood. Carriers must be identified by deficient enzyme activity in hair root lysates. However, fully affected females have been described (2,31, 46,51), some possibly explained by extreme lyonization, others possibly by uniparental disomy.

More than 250 patients have been reported (28,29), and several multiple case series have been published (6,47,49).

Genetics and biochemistry. The human HPRT gene has been mapped to the distal end of the long arm of the X chromosome (Xq26–Xq27). Using cloned DNA probes, molecular analysis has shown that the gene is present as a single copy of approximately 44 kb in length with 9 exons (19,24,43,49). Mutations are quite heterogeneous and may affect enzyme expression, catalytic activity, or protein stability in vivo (39). Gibbs and co-workers (11,12) described HPRT mutation detection by ribonuclease A cleavage and by direct DNA sequencing of in vitro amplified cDNA. Davidson et al (7) used polymerase chain reaction (PCR) to identify mutations in HPRT in RNA from B-lymphoblasts. Heteroduplex detection has also been used to screen for mutations (4).

Hypoxanthine phosphoribosyltransferase catalyzes the transfer of the phosphoribosyl moiety of 5-phosphoribosyl-1-pyrophosphate (PRPP) to either hypoxanthine or guanine to form inosine monophosphate or guanosine monophosphate. These reactions are considered to be *salvage pathways* or alternate metabolic routes for hypoxanthine and guanine that lead to formation of uric acid-the end product of purine catabolism, which is subsequently excreted unchanged in the urine (41). Substrates and products of the reactions are regulators of other purine metabolizing enzymes; hence, HPRT influences multiple steps in purine metabolism (43).

Complete deficiency of HPRT activity is the usual finding in males expressing the Lesch-Nyhan phenotype, although some neurological deficits are present in approximately 20% of patients with significant partial HPRT deficiency (6,14,23,33). In other individuals with partial deficiency (Kelley-Seegmiller syndrome), hyperuricemia and gout may be the only manifestations (1).

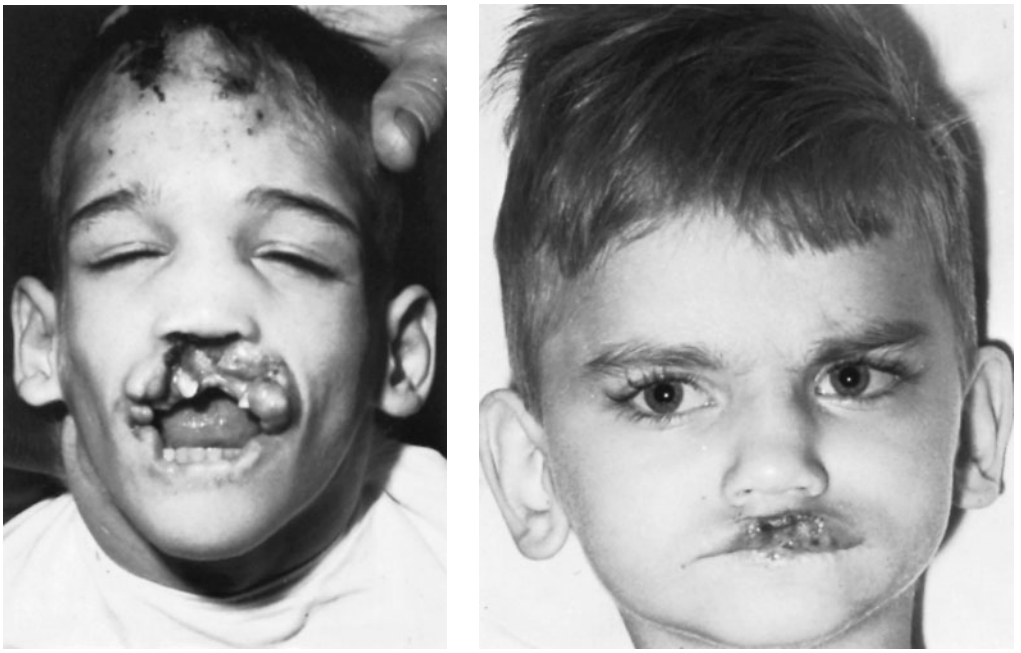
Pathogenesis. Neurochemical studies suggest that dopamine is reduced to one-half their normal levels (17,50). This specific deficit in the basal ganglion dopamine system may be instrumental in the development of behavioral changes (9,38,46a). This area of the brain is highly dependent on HPRT activity to maintain purine pools, and synaptic function is regulated by purine nucleotides (22,43).

Patients with HPRT deficiency also develop gout. This is directly related to increased de novo purine synthesis that arises from lack of feedback inhibition from the products of the HPRT reaction. The excess purines are converted to uric acid which, being of limited solubility, crystallize in situ. Tissues with high urate concentrations, particularly the kidney and joints, are prone to crystal-induced damage.

There is a partial defect in the adrenocortical 11β-hydroxylation of steroids (48).

Growth. Patients are normal at birth but growth failure is evident at the time neurological changes appears—after the second year of life (48). The height and weight of older patients are usually below the third centile. Delayed osseous maturation may occur, but is usually less severe than delay in linear growth. The onset of puberty may also be delayed. Christie et al (6) found microcephaly in only 6 of 16 patients (39%) for whom head circumferences were reported.

Neurological features. Patients are usually not identified clinically until neurological symptoms are noted. Some delay in motor development and hypotonicity becomes significant at approximately 4–6 months of age. Some infants cannot support their head. Others may have dislocated hips. Dysphagia is not rare. Choreoathetosis develops in all patients, but other nonspecific neurological features are also found, including opisthotonus (89%), scissoring (63%), upgoing toes (58%), and, less frequently, pure dystonia (21%) (6,37,42). Although self-mutilation is said to be present in all cases, exceptions have been reported (21,47). The average age of onset for self-mutilating behaviors is approximately



A B

Fig. 17–13. *Lesch-Nyhan syndrome.* (A) Self-mutilation of lips. (B) This boy and his brother have Lesch-Nyhan syndrome. Brother is more severely affected neurologically. (A courtesy of D Hoefnagel, Hanover, New Hampshire. B courtesy of B ter Haar, Nijmegen, The Netherlands.)

2 years but varies widely (4 months to 4 years) and has been delayed until the second decade in some instances (6,20,40,44). Self-mutilation most often involves biting, the lips and tongue being the most common targets, followed by fingers and shoulders (Fig. 17–13). Pain is perceived, but mutilation can only be inhibited by physical restraint. Other destructive behaviors include head-banging or chin-banging, which may lead to mutilations of the ears or nose, and aggressive behavior toward other people (biting, hitting, kicking, pinching, verbal aggression). Mental deficit varies widely and normal intelligence has been recorded. Most children will talk but speech is always dysarthric, presumably on the basis of choreoathetosis (6). Severely affected children are never capable of ambulation.

Hyperuricemia and gout. Urinary uric acid concentrations are always increased. Retrospectively, most parents (95%) have reported that orange sand or orange crystals were present in their infants' diapers even before the onset of neurological problems (6). If untreated, hyperuricosuria may progress to symptomatic nephrolithiasis (hematuria), obstructive uropathy, and permanent renal damage (18). This has been described as the most common cause of death in untreated patients in the first decade of life. Gouty arthritis is uncommon, but other features of gout including auricular tophi (28,36) and subcutaneous nodules (38) have been described.

Other features. Megaloblastic anemia observed in some patients has been associated with low serum folate (37,42). An increased rate of infection has also occurred, but this may be more a consequence of the neurological handicap than of the biochemical defect (6,37,42). Testicular atrophy is common (6).

Differential diagnosis. If self-mutilation occurs, there should be little difficulty recognizing *Lesch-Nyhan syndrome*. Among the mentally handicapped, however, some degree of self-mutilation is not that uncommon, particularly if autism is also present (47). Self-mutilation has been associated with *de Lange syndrome* and is seen in those with *congenital indifference to pain syndromes*. Individuals with conditions related to Lesch-Nyhan syndrome with similar clinical findings but without an enzymatic defect have been described (25,35,37,42). Conversely, in ostensibly normal patients with hematuria, episodes of oliguria and azotemia, a variant of HPRT has been found (45). An unusual variant with mild mental retardation, spastic gait, pyramidal tract signs, short stature, proximally placed thumbs, and clinodactyly of the fifth fingers has been reported (32). Self-mutilation can result from many causes (15).

Laboratory aids. Assay of HPRT enzyme in skin fibroblast, hair root lysates, or lymphocyte cloning may be used to identify heterozygous or hemizygous states. Similarly, assays of amniocytes, chorionic villus tissue, or even 8-cell preimplantation embryos provide a reliable basis for prenatal diagnosis (3,8,10,13,27,52).

The elevated morning urinary uric acid/creatinine ratio (often 2–5 times normal) is a useful screening test to detect individuals with undifferentiated neurological signs. Although the normal ratio (usually 0.2–0.6) varies with age and individual, results must be compared with those of age-matched controls, the urinary ratio reliably identifies Lesch-Nyhan patients and other hyperuricemic conditions (26). Serum urates are elevated, but may not be, in up to 10% during infancy.

Preimplantation genetic diagnosis has been carried out (32a).

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Hereditary sensory syndromes with oral mutilation

There are many varieties of hereditary sensory and autonomic neuropathy that present as inability to perceive pain with subsequent trauma to and/or infection of both soft and hard tissues. The patient may receive extensive burns or fractures or osteomyelitis and perceive no discomfiture. Some patients destroy their own eyes or bite off their lips, tongue, or fingers.

Dyck (10) and Dyck et al (11) proposed a classification of these conditions based on mode of inheritance, natural history, and population of neurons or axons affected, under the name *hereditary sensory and autonomic neuropathy* (HSAN). These disorders were divided into five forms. HSAN type I, autosomal dominantly inherited, was previously reported under a large variety of names, among them hereditary perforating ulcers of the feet and hereditary sensory radicular neuropathy. Symptoms start between the second and fourth decades. The main manifestations are in feet and legs and particularly with variable degree of peroneal muscular atrophy. The gene maps to 9q22.1–q22.3 (34). Biopsy of peripheral nerves demonstrates diminished numbers of both myelinated fibers (MF) and unmyelinated fibers (UF), especially of cutaneous nerves. Hereditary sensory and autonomic neuropathy types II, III, IV, and V are congenital and all have autosomal recessive inheritance. Type II is characterized by pansensory neuropathy mostly manifested in the limbs, with less tendency to affect the face and trunk. It is an abnormality of cutaneous rather than deep nerves, which are small and formed mostly of unmyelinated fibers that are atrophic and decreased in number. In these patients, MF tend to be absent from cutaneous nerves. Consanguinity among the parents of these patients (31) as well as affected sibs (31,44) has been reported. Type III is *familial dysautonomia* associated with various degrees of pansensory disturbance. The gene maps to 9q31–q33 (3). In familial dysautonomia, biopsy demonstrates altered afferent neurons and gamma motor neurons with great reduction in UF and an absence of MF greater than 12 μm in diameter.

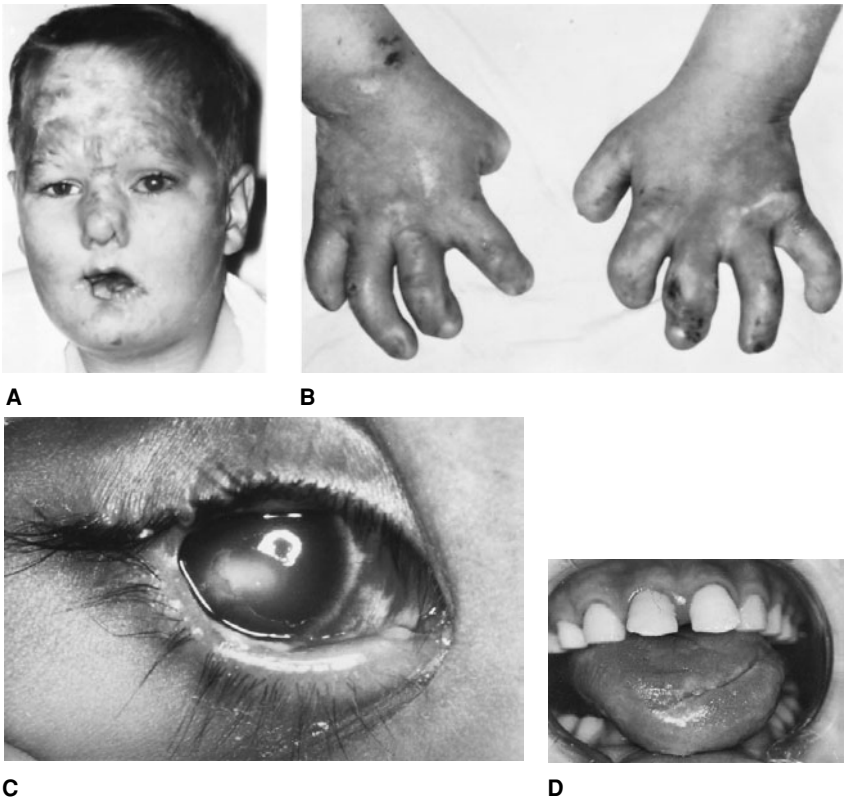

Fig. 17–14. *Hereditary sensory syndromes with oral mutilation.* (A) Five-year-old male chewed off anterior tongue and lower lip. Repeatedly traumatized nose, eye, forehead. Parents were first cousins. (B) Hands of same child. (C) Active corneal ulcer. Patient had tarsorrhaphy. (D) Deep scar, disappearance of lingual papillae. (C from R Yagev, Am J Ophthalmol 127:322, 1999. D from A Amano, Oral Surg Oral Med Oral Pathol Oral Radiol Endod 86:425, 1998.)

Type IV has been described as congenital insensitivity to pain with anhidrosis, unexplained fever, failure to thrive, and mild mental retardation (Fig. 17–14). At least 40 cases have been described (2). In this type, biopsy of peripheral nerves demonstrates complete absence of UF but normal or near normal large MF. Autopsy, performed in one patient, demonstrated the brain to be normal, but small neurons in the dorsal root ganglia were absent as well as the dorsolateral fascicular tract. The spinothalamic tract in the spinal core was absent (43). Consanguinity (4,21,22,24,47) as well as affected sibs [4,29,37(cases 2 and 3),42,45,48] have been found. The gene maps to 1q21–q22 (20). The gene, *TRKA*, encodes a high-affinity receptor for nerve growth factor (14a,29). Surely, over 100 patients have been reported (1). There seem to be many cases in Japan. Type V is similar to type IV, but without mental retardation (Table 17–4). Histology demonstrates marked decrease in A delta fibers and minimal decrease of C fibers. Good reviews are those of Donaghy et al (8), Gwathmey and House (16), Rosemberg et al (40), and Amano et al (1).

Earlier examples have been cited in the third edition of this text.

The usage of the terms indifference and insensitivity to pain should be discouraged because neither reflects the true nature of the conditions being discussed. For the purpose of clarification, we will use the term *hereditary nonneuropathic analgia* (HNNA) to refer to the condition characterized by universal lack of pain sensation but with perception of nociceptive stimulation, and with no alterations in sweating or other autonomic functions. Additionally, nerve biopsy should demonstrate normal peripheral nerve histology. Consanguinity (12,28) and affected sibs (19) have been reported in HNNA.

Type I does not present oral manifestations and type III is discussed in this chapter. Types II, IV, V, and HNNA are discussed here because they present variable degrees of oral and/or paraoral mutilation. Table 17–4 shows a schematic differentiation among the entities discussed.

Facies and general appearance. Frequent scarring of the face and corneas, with mutilation of the lips, arms, and legs, as well as phalangeal amputation due to self-mutilation have been noted in type II HSAN (11,32,45,48), type IV HSAN (24,27,37,42), type V HSAN (10), and HNNA (39) (Fig. 17–14). Corneal ulceration is especially common in type IV HSAN (49).

Anhidrosis. Anhidrosis is limited to type IV HSAN. The resultant hyperpyrexia may result in death in approximately 20% (40).

Musculoskeletal system. Osteomyelitis, aseptic necrosis, fracture, Charcot joint, and distal necrosis with spontaneous resorption of toes and fingers are virtually constant features in all these conditions (9,10,11,13, 15,17,18,23,33,35,38,41,42,44–48). The complications have been ascribed to lack of pain sensation—the patient failing to recognize trauma and then healing poorly (46). Several patients have exhibited loose joints.

Nervous system. In type II HSAN there is absence of reaction to painful stimuli most marked in the extremities. In some patients the lack of sensation may affect almost the entire body but present islands of normal sensation (10,11,48). Patients may have occasional seizures. Temperature sensation is reduced and touch sensation is markedly decreased. There is also lack of sweating over arms and legs (48). Anosmia has also been reported (45).

In type IV HSAN patients present with various degrees of mental retardation. Lack of pain sensation is almost universal but islands of normal sensation can be found. Temperature and touch sensation are slightly reduced. Hypohidrosis, but with variable degree, is typical (4,7,11,14,26, 27,30,42,48). Horner syndrome has been occasionally documented (37), as well as absence of Lissauer's tract and of small dorsal root ganglion cells and axons (21,43).

Type V HSAN has been described in only a few patients (11,25,36). These patients have universal lack of pain sensation, markedly reduced temperature sensation, moderate reduction in touch sensation, and peripheral hypohidrosis. The main difference with the other types of HSAN and HNNA is found in the abnormal histology of peripheral nerves (11).

In HNNA there is total absence of reaction to painful stimuli over the entire body. Deep-tendon reflexes are intact. The corneal and gag reflexes are often absent or diminished (28); taste, touch, sweat, temperature sensation, joint position sense, tickling, itching, and vibration are generally normal (11,28).

Intelligence has ranged from dull to normal. Patients with mental retardation generally represent examples of type IV HSAN (IQ-range 40–80)

Table 17–4. Hereditary sensory syndromes

Condition	Inheritance	Mental retardation	Oral lesions	Deep tendon reflexes	Touch sensation	Temperature sensation	Axon reflex	Tears	Sweat	Abnormal histology	Childhood manifestations	Other manifestations
HSAN Type I, hereditary radicular neuropathy	AD	No	No	±	Reduced+	Reduced++	No	Normal	Distal loss	Yes	No	Feet and legs peroneal atrophy
HSAN Type II, congenital sensory neuropathy	AR	No	Yes	Absent or reduced	Reduced++	Reduced+	No	Diminished	Distal loss	Yes	Yes	Mostly arms and legs
HSAN Type III, familial dysautonomia (Riley–Day)	AR	Could be retarded	Yes	Decreased	Normal	Reduced±	Yes	Absent	Erratic	Yes	Birth	Yes
HSAN Type IV, congenital sensory neuropathy + anhidrosis	AR	Could be retarded	Yes	Decreased	Reduced±, some normal	Reduced±	Yes	Normal	Absent or reduced	Yes	Birth	Yes
HSAN Type V	AR	No	Yes	Normal	Reduced++	Reduced±	Yes	Normal	Absent peripheral	Yes	Birth	Yes
HNNA	AR	Normal or reduced	Yes	Normal	Normal	Normal	Yes	Normal	Normal	No	Birth	Yes

(see Table 17–4). However, one can have normal intelligence with HSAN type IV (5). Recent studies (12) tend to support the theory that HNNA is not due to neuropathic alterations but possibly to an endogenous analgesic peptide disorder in which the patient produces abnormally high levels of opiate and nonopiate analgesic substances.

Oral manifestations. Lack of pain sensation results in severe oral mutilation (Fig. 17–14A). In nearly all, the tongue and lips are especially subject to injury, with resultant scarring. This has been seen in type II HSAN (11,32,45,48), type IV HSAN [14 (case 1),24,33,37–39,42 (case 1),44,46 (case 1, same as 29),47,48 (case 2, same as 44)], type V HSAN [11 (case 1)] and in HNNA.

Oral involvement becomes apparent as soon as the teeth appear and may lead to early diagnosis (44). Bruxism is present in approximately 50%. Extensive decay is not accompanied by toothache, and teeth may be lost early on this account (39). In approximately 80%, patients have painlessly extracted their own teeth (1,44). Oral burns are noted in 25%. Thrush (45) described a fibrous cord buccal to the teeth in each of his type II HSAN patients.

Differential diagnosis. Lack of pain sensation also occurs in leprosy, oligophrenia, hysteria, multiple sclerosis, postleukotomy state, and asymbolia (45). Asymbolia for pain is a form of aplasia associated with lesions of the supramarginal gyrus of the parietal lobe, usually due to trauma, tumor, or infection. Analgia may also be seen in syringobulbia and syringomyelia, but in these conditions temperature sense is also lost. Proper classification of patients presenting with congenital absence of pain sensation can be achieved only by careful clinical and neurological study, including testing of sensory and autonomic functions, as well as by histologic studies of peripheral nerves (sural nerve biopsy). The reader interested in a detailed differentiation of these entities is referred to the excellent work of Dyck et al (10,11).

Patients with *Lesch-Nyhan syndrome* also show signs of self-mutilation, especially of lips and hands, but they usually have severe mental retardation, choreoathetosis, and hyperuricemia. Critchley et al (6) described an autosomal recessively inherited syndrome characterized by acanthocytosis and neurologic disorder without lipoproteinemia. Tongue, lip, and buccal mucosal biting leading to severe mutilation resulted from uncontrollable, jerky movements that generally occurred at night. Patients responded normally to pain stimulation, but deep-tendon reflexes were absent. Self-mutilation is also seen in Tourette syndrome and *Brachmann-de Lange syndrome* (1).

Decreased sweating may also be seen in *hypohidrotic ectodermal dysplasia* and *Fabry syndrome*.

Laboratory aids. Histaminic flare is normal in HNNA, but is diminished or absent in HSAN types II, IV, and V (11,46). Fabbri et al (12) have found high levels of analgesic peptides such as opioid and calcitonin in the cerebrospinal fluid of a patient with HNNA. Injection of this lyophilized fluid in the lateral cerebral ventricles of rats induced deep analgesia.

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Cranial nerve syndromes involving III, IV, V, VI

These arise from areas in which cranial nerves are geographically located in close approximation. Lesions in the following areas cause recognizable syndromes:

- Orbital apex syndrome (Rollet syndrome)
- Superior orbital fissure syndrome (Rochon-Duvigneau syndrome)
- Sphenoidal fissure syndrome (no eponym, same as above)
- Petrosphenoidal space syndrome (Jacod syndrome)
- Cavernous sinus syndrome
  a. Lateral wall of cavernous sinus (Foix syndrome)
  b. Cavernous sinus cavity (Jefferson syndrome)
- Apex of petrous bone syndrome (Gradenigo syndrome)

The signs and symptoms result from an intracranial lesion arising from the floor of the middle cranial fossa. It could involve the nerves that pass through the foramen ovale, foramen rotundum, and superior orbital fissure. Tumors extend along any of these paths to produce ophthalmoplegia by involvement of the third, fourth, and sixth nerves and blindness or optic atrophy by spread to the optic nerve itself.

Anatomical guidelines The foramen ovale transmits the mandibular division of the fifth cranial nerve (V3); the foramen rotundum, the maxillary division of the trigeminal (V2); and the superior orbital fissure, the III, IV, VI as well as the first or ophthalmic division of the trigeminal nerve (V1).

The apex of the orbit encompasses the area of the superior orbital fissure plus the optic foramen. There is considerable overlap between the syndromes as the same nerves traverse different anatomical locations.

It should be noted that there is not always a clear difference between the orbital apex syndrome and the superior orbital fissure syndrome.

The superior orbital fissure syndrome was first described by Rochon-Duvigneau (27) in 1896. If the lesion is more anteriorly situated and also includes the optic foramen and hence the optic nerve, the condition is called the orbital apex syndrome of Rollet (also called Jacod syndrome, see below).

Clinical features

Orbital apex (Rollet) syndrome. The syndrome is characterized by pain in the region of V1 plus involvement of III, IV, and VI due to juxtaposition. Paralysis occurs either simultaneously or in succession. Resultant ptosis, proptosis, ophthalmoplegia, fixation and dilation of the pupil, blindness, and anesthesia of the upper eyelid and forehead occur. It differs from Jacod (petrosphenoidal) syndrome in which pain is largely over the V2 area. Blindness arises from optic nerve involvement (32,35). The syndrome can be difficult to differentiate from the superior orbital fissure syndrome that shares manifestations but in which there is no blindness.

Superior orbital fissure (Rochon-Duvigneau) syndrome. There is total ophthalmoplegia due to involvement of III, IV, and VI as well as sensory changes due to involvement of V1. Hence, ptosis, proptosis of eyeball, fixation and dilatation of pupil, and anesthesia of upper eyelid and forehead are present, as noted above. Rarely, V1 and V2 are both involved.

The syndrome may be secondary to fracture of the zygomatic complex with edema and bleeding or facial fractures of the Le Fort II and III types, infections of the retrobulbar space, meninges, cavernous sinus and CNS, a neoplasm arising in the nose and extending through the orbital floor after traversing the pterygopalatine fossa (Behr pterygopalatine fossa syndrome or Dejean orbital floor syndrome), or a retrobulbar hematoma in the cavernous sinus and in the orbital muscle cone space. Lesions causing the superior orbital fissure syndrome can easily extend to involve the cavernous sinus (14,21,28,34).

Petrosphenoidal space (Jacod) syndrome. The syndrome may be confused with the superior orbital fissure syndrome. Further confusion occurs because the orbital apex syndrome is often used synonymously.

The main clinical difference from the orbital apex syndrome is that pain is in the V2 distribution (8,18).

Cavernous sinus (Foix) syndrome. This disorder is due to tumors (rarely pituitary), intracranial aneurysms, or thrombosis involving the cavernous and/or lateral sinuses. Ophthalmoplegia results from involvement of III, IV, and VI. Although pain is experienced in both the V1 and V2 areas, it is most severe over V1 (3,8,11,19).

When thrombosis occurs, the patient is acutely ill with fever, headaches, and pain around the eye that is proptosed and swollen because of conjunctival edema. There is usually complete ophthalmoplegia with a fixed pupil.

Apex of the petrous bone (Gradenigo) syndrome. This consists of sixth nerve palsy, diplopia, strabismus, lacrimation, and pain behind the eye, that is, in the V1 region (10,13). The syndrome is uncommon since the antibiotic era (mastoid infection) (12,32), but has been reported following gunshot wound (2) or surgery (15). Horner syndrome may be present, but is rare.

Other syndromes involving eye movements

Duane syndrome. Named after Duane who fully described it in 1905, the syndrome is characterized by limitation of eye movement. On lateral gaze, the abducted eye becomes retracted and the eye opening narrows. In 15%–20%, the condition is bilateral.

Etiology is unknown although aberrant peripheral innervation has been postulated. The clinical features include profound loss of abduction, partial deficiency of adduction, ocular retraction on attempted adduction, oblique movement of the eye (both up and down) on adduction, narrowing of palpebral fissures on adduction, and defect of convergence.

In the study of 62 cases by O'Malley et al (24), 62% were female, and 65% involved the left eye. Esotropia occurred in 53% and amblyopia in 20%. Approximately 15% had anisometropia. Nearly all cases were isolated. In one case, transmission was from mother to daughter. The other involved concordance in monozygotic twins. There appears to be genetic heterogeneity, one mapping to 2q31, the other to 8q13 (1,1a).

The coexistence of Duane syndrome and *Marcus Gunn phenomenon* has been noted (17).

Fisher variant of Landry-Guillain-Barré syndrome. In 1956, Fisher (6) described three patients with acute external ophthalmoplegia, ataxia, and hyporeflexia. Ptosis and some degree of internal ophthalmoplegia (facial and bulbar weakness) can occur, but characteristically there is impairment of conjugate upward and lateral gaze, often leading to complete ophthalmoplegia. Usually it is benign with recovery complete. There is often a preceding upper respiratory tract infection but etiology is unknown. Hypersensitive response to a virus is probable (9).

Tolosa-Hunt syndrome. The main criteria for diagnosis (16,25,30) have been summarized by Dornan et al (4): steady nonthrobbing pain, often preceding ophthalmoplegia by several days, and paresis of any of the nerves passing through the cavernous sinus, that is, III, IV, VI, and V1 (sympathetic nerves and II occasionally involved). Symptoms may last for days or weeks. There is no obvious lesion and attacks may be repeated.

Remission is either total or subtotal. Etiology is unknown (29).

Syndromes of V

It must be emphasized that a single cranial nerve is rarely involved in a pathological process. Because of the intimate association of V with III, IV, and VI in the cavernous sinus and elsewhere, a host of eponymic syndromes exist. Diffuse processes, such as brain tumors at the base of the skull or tumors that invade the cranium from the nasopharynx, may involve the last four cranial nerves in combination with the fifth, but this is less common.

See the previous discussion for nerve V involvement in the orbital apex syndrome, superior orbital fissure syndrome, and syndromes of the cavernous sinus. Trigeminal neuralgia is discussed in "Some Disorders of Facial Pain" later in this chapter.

Other syndromes involving the Vth cranial nerve during its peripheral course

Raeder (paratrigeminal) syndrome. This syndrome is characterized by unilateral facial pain/headache with a trigeminal distribution. The pain is mostly in and around the eye. In addition, there is ptosis, miosis, and hyperemia because of an oculosympathetic defect (20).

Multiple parasellar cranial nerve involvement of III, IV, V, and VI can occur. Four of five patients originally described by Raeder had other cranial nerve involvement. Decreased sensation and muscular weakness in all three divisions of V have been described.

The syndrome is a combination of a Horner-like syndrome with ipsilateral motor and sensory V dysfunction. Neoplasms of the middle cranial fossa or in the space adjacent to V—hence paratrigeminal—are often responsible. Facial anhidrosis is absent. It is often seen in males in the fourth to sixth decades, but trauma has also been implicated.

There must be involvement of V. Evidence for this may be decreased sensation in the distribution of V, weakness, pain of the tic douloureux type and distribution, and pain over the ipsilateral part of the face. Facial pain in the distribution of V alone, although it may be present, is not sufficient (22).

Pterygopalatine fossa (Behr) syndrome. This syndrome, resembling that of Trotter (see Table 17–5), is because of a tumor or metastases in the pterygopalatine fossa, located behind the maxillary sinus and below the inferior surface of the sphenoid. It contains V2, the spheno-palatine ganglion, and the internal maxillary artery. The main symptoms are pain in the upper teeth, loss of sensation over the inferior orbital foramen, paralysis of the pterygoids, and blindness.

Trotter syndrome. First described by Trotter (31) in 1911, the syndrome consists of unilateral deafness, pain over V3, ipsilateral defective mobility of the soft palate, and subsequent trismus. A sensation of ear pressure, distention of the tympanic membrane, or repeated middle ear infections are common. The syndrome results from invasion of the lateral wall of the nasopharynx by tumor, usually an anaplastic carcinoma. Immediately below the sinus is the attachment of the levator veli palatini muscle, just laterally is the foramen ovale, and posteriorly is the opening to the eustachian tube. As the tumor extends, it compresses the tube (causing deafness) and invades the palatal musculature (decreasing pain in the temporal area, ear, lower jaw, teeth, and tongue, and resulting in anesthesia over the mental area). Trismus results from extension of the tumor into the pterygoids. The syndrome is seen most often in males during the third and fourth decades. There are usually no symptoms because of nasopharyngeal obstruction (23,31). The use of computer tomography has vastly aided diagnosis (7).

Godtfredsen (cavernous sinus-nasopharyngeal tumor) syndrome. Tumors arising in the nasopharynx, in addition to extending into the skull and producing ophthalmoplegia and trigeminal neuralgia, may also be associated with paralysis of the tongue. This is produced by compression of the hypoglossal nerve by enlarged, involved, retropharyngeal lymph nodes (11).

Syndromes of cranial nerves involving the midbrain and pons

Syndromes of the midbrain and pons are presented in outline in Table 17–5.

Table 17–5. Cranial nerve syndromes involving midbrain or pons

Syndrome	Location	Signs
Midbrain		
Weber	Base of midbrain anterior to red nucleus	Ipsilateral III Contralateral hemiparesis
Claude	Tegmentum, red nucleus, and brachium conjunctiva	Ipsilateral III (sometimes IV), sometimes reduction of conjugate gaze to opposite side. Contralateral ataxia dysmetria, dysdiadochokinesia
Benedict	Tegmentum; destruction of red nucleus where third nerve crosses it	Ipsilateral third plus contralateral movement disorder—Parkinsonian tremor, athetosis, hemibalismus
Nothnagel	Tectum	Paralysis of lateral gaze plus ataxia—unilateral or bilateral
Parinaud	Pretectum (pinealomas, craniopharyngiomas)	Paralysis of upward gaze and of convergence Pupils are responsive
Pons		
Millard-Gubler	Ventral pons VI, VII Corticofacial and corticospinal fibers before decussation	Facial paralysis, paralysis of adduction of eye Contralateral hemiparesis
Inferior syndrome of Foville	Caudate one-third of pons Supranuclear VI and VII medial lemniscus spinal root of inferior cerebellar peduncle	Lateral conjugate gaze toward side of lesion Crossed hemiparesis with diminished pain and temperature sensation Homolateral cerebellar signs
Superior syndrome of Raymond-Cestan or superior type of Foville	Rostral pons Includes medial lemniscus, spinothalamic tract Superior cerebellar peduncle	Paralysis of conjugate gaze to size of lesion Diminished pain, touch, temperature, vibration and position sense Cerebellar signs (ataxia), athetotic or ballistic movement, all on the opposite side
Brissaud and Sicard	Anterolateral and inferior pons, pyramidal tract before it crosses VII nucleus	Hemifacial spasms, crossed hemiparesis

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Marcus Gunn phenomenon [jaw-winking and winking-jaw syndromes (Marcus Gunn and inverse Marcus Gunn syndromes), Marin Amat phenomenon]

The short communication by Marcus Gunn (23) (often erroneously hyphenated), in 1883, describing the syndrome of unilateral congenital ptosis and rapid exaggerated elevation of the ptotic lid on moving the lower jaw to the contralateral side, stimulated immediate interest in this problem. By 1895, 33 cases had been reviewed by Sinclair (32) and since then at least another 200 cases have been published (2,3a,5,6,16,28,31,33). The syndrome is seen in approximately 5% of cases of congenital ptosis of the eyelid (28).

The name "jaw-wink" syndrome is not well chosen for the symptom is not a wink but an exaggerated opening of the eye. However, the term has been used so long and extensively that until the cause is clarified, its use will probably be continued. Although usually sporadic, there have been a few familial cases involving two generations (10,14,19,20,28). There is neither sex nor side predilection.

The cause is unknown, but it was originally assumed that the syndrome was based on aberrant innervation of the levator palpebrae superioris from the motor branch of V because of the close approximation of the nuclei of III and V. However, a supranuclear, or at least a combined supranuclear-nuclear, involvement has been suggested, and the view has gained support (28,33). The levator muscles on both sides are atrophic (22). A good review of theories of etiology has been compiled by Simpson (31).

The ptosis is congenital in over 90%. It may, however, arise spontaneously in older persons (14,31). Ordinarily the lid cannot be raised to any significant degree. Seven percent of patients have experienced the syndrome without having ptosis (28), and 3% have bilateral ptosis (5,8,30,35).

Superior rectus palsy has been found in 25% and double elevator palsy in another 25%. Between 35% and 60% exhibit amblyopia or strabismus (8,28). Correction of the strabismus was accompanied by opening the mouth in one patient (26). The pupillary and corneal reflexes are normal. The pupil in the ptotic eye may be smaller, but true Horner syndrome is not present. Marcus Gunn syndrome may be seen in association with Duane retraction syndrome (17) and with neurocristopathies (6,25).

Approximately 40% manifest the syndrome both on depressing the mandible and on moving it to the side opposite the ptotic eye (Fig. 17–15). Another 40% need only to have the jaw depressed. However, in some individuals the syndrome may be produced by movement of the lips, whistling, smiling, clenching the teeth, chewing, puffing out the cheeks, protrusion of the tongue, or sucking (8,28). It may even be precipitated by swallowing or, rarely, by moving the jaw to the ipsilateral side, or to both sides. The syndrome has also been triggered by closing the other eye. The syndrome may even temporarily disappear. Several muscles and cranial nerves come into play during these acts; the most important appears to be the external pterygoid. That the masseter and temporal muscles play no significant role was demonstrated by Dupuy-Dutemps (9). A comprehensive review of critical jaw movements was made by Simpson (31). Cleft lip has been found but is probably a chance association (2,28). CHARGE association has been noted in a case (35).

The so-called winking-jaw syndrome (inverse Marcus Gunn syndrome, corneomandibular reflex, pterygocorneal reflex) is manifested by a brisk movement of the mandible to the contralateral side when the cornea is touched. The jaw may also be thrust forward (13,34). The term inverse Marcus Gunn syndrome has also been used to refer to brisk ptosis of the upper eyelid on moving the mandible to the contralateral side (21) (Fig. 17–16). Both jaw-winking and winking-jaw syndromes are considered to be release phenomena because of a supranuclear lesion, caused either by malformation or by severe cerebral or brainstem lesions, that reunites the orbicularis oculi and external pterygoid muscles, which phylogenetically belong together (33,34).

The so-called Marin Amat (21) syndrome appears to be an intrafacial reaction on the part of regenerating facial nerve following facial palsy (1,12,18,27a,29,33,34). A partially ptosed eyelid droops further when the mandible moves from side to side.

Eye bobbing (elevation and depression of the globe) may also occur with mandibular movement. Synkinetic stimulation of the muscles of mastication and the superior rectus muscles has been suggested (27).

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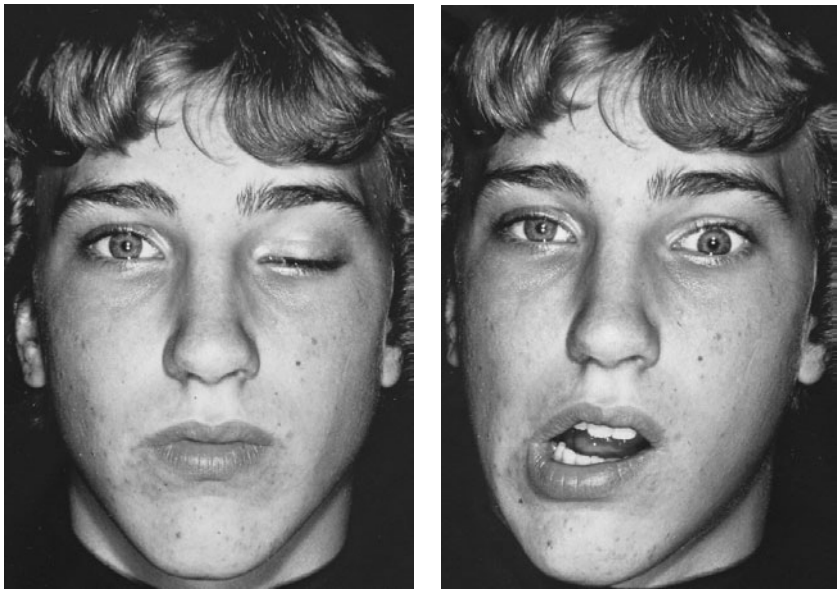
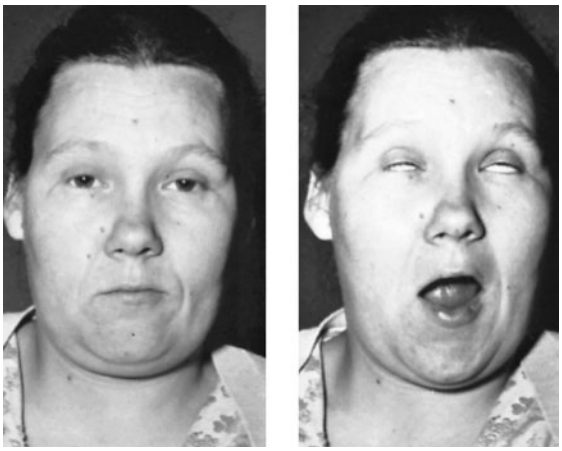


A B

Fig. 17–15. *Marcus Gunn phenomenon.* (A,B) Ptotic left eye exhibits exaggerated opening upon deviation of mandible. (From JD Bullock, J Pediatr Ophthalmol Strabismus 17:375, 1980.)



A B

Fig. 17–16. *Inverse Marcus Gunn phenomenon.* (Inverse jaw winking). (A) Note slight ptosis of single eyelid. (B) On opening jaw, there is drooping of eyelids with conjugate upward deviation of eyes. (From J Jancar, Ophthalmologica 151:548, 1966.)

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Some disorders of facial pain

Because of the plethora of possible combinations of involvement of cranial nerves, both within and outside the cranial cavity, a considerable number of eponymic syndromes have been created to describe these conditions. The interested reader is referred to some extremely comprehensive reviews (1–13). Attanasio (1), for example, lists 40 causes for facial pain. Those deemed to have greater importance are considered here.

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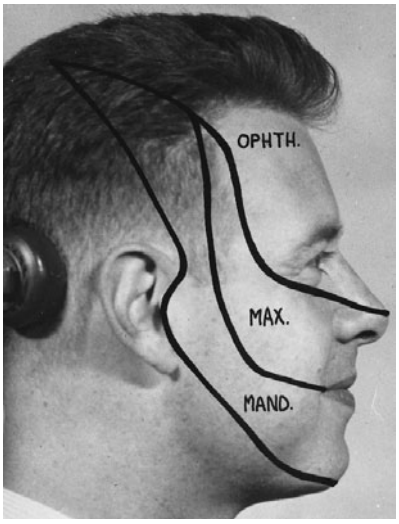
Trigeminal neuralgia (tic douloureux). Trigeminal neuralgia is characterized by extreme severe recurrent episodic attacks of unilateral pain distributed over a branch or, after many years, more than one branch of V (Fig. 17–17A). The reported incidence per 100,000 inhabitants in the United States is 2.7 for men and 5.0 for women (13). The pain may occur spontaneously or may be initiated by stimulation of a trigger zone that most often extends from the lateral border of the nose to the angle of the mouth (Fig. 17–17B). The pain may vary in intensity but, along with pain resulting from kidney stones, may be one of the most dreadful and dreaded pains experienced by humans. It occurs suddenly, without warning, a single spasm often lasting from 30 to 60 seconds. Because these brief paroxysms are repeated at short intervals, the pain may be



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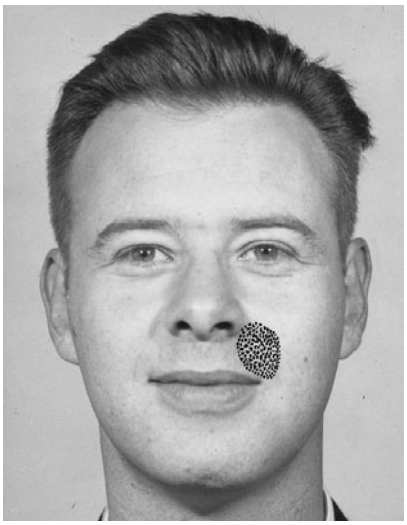

B

Fig. 17–17. (A) *Trigeminal nerve.* Areas supplied by the three sensory branches of the trigeminal nerve. (B) Trigeminal neuralgia. Most common "trigger zone" area.

stated to have lasted for a longer duration (1,4). The severe paroxysms not uncommonly are preceded by electric shock sensations lasting for only a few seconds. The severe pain disappears rapidly, but occasionally a patient may have a mild residual ache or burning that persists for several minutes. With time, a chronic burning facial pain may gradually develop (6).

Trigger zones are not necessarily present, but when they occur, they will often aid in diagnosis. The trigger may be tripped by mastication, talking, shaving, a draft of air on the face, or even the vibration from a loud noise. Within the mouth, a trigger zone may be located on the gingiva or at the base of a single tooth, giving the patient the erroneous notion that it is dental in origin causing, at times, unnecessary extraction of teeth. We have seen several patients who became edentulous. The patient may avoid brushing the teeth or applying cosmetics so as to avoid these areas. Talking may so often trigger the pain that the individual often presents with an immobilized face, talking through the teeth, with eyes expressing fear, and pointing to but not touching the affected area. In extreme cases, the patient may even be afraid to eat or drink (7,11).

The pain usually (60%) begins in the second or third branch of the trigeminal nerve, but rarely may progress to involve all three branches. Trigeminal neuralgia occurs more often on the right side. Approximately 5% of patients have bilateral involvement. In these cases the disorder usually starts with unilateral involvement, only rarely being followed by involvement of the other side by months or even years. It occurs twice as commonly in women as in men, and over 70% of the cases are seen in persons over 50 years of age. However, approximately 15% experience the onset prior to the age of 40. More than half of the patients have remission of 6 months or more, but the time between remissions gradually decreases (1,9,10). The so-called SUNCT syndrome (*s*hortlasting, *u*nilateral, *n*euraligiform headache attacks with *c*onjunctival infection and *t*earing) seems to represent trigeminal neuralgia with autonomic signs (2).

Diagnosis depends on the history and description of the pain. There is no sensory loss. No physical signs or laboratory tests are diagnostic. Ordinarily, there is no difficulty in making the correct diagnosis.

In most cases, there is compression or distortion of the nerve root by an aberrant arterial loop and/or venous channel (6,8). Perhaps in 5%–10% neoplasms or arterial aneurysms that impinge on the trigeminal nerve may result in trigeminal neuralgia (1,6,8,12). It has also been estimated that approximately 2%–4% of cases of trigeminal neuralgia have been associated with multiple sclerosis, but usually there are other signs of neurologic deficit present in addition to the pain and the patients are usually in their third or fourth decade (3,4). If suspected, serum IgG should be measured. Rarely, dental disorders such as split tooth, interradicular periodontal abscess, or pulpitis may simulate trigeminal neuralgia (7). Facial pains of nondental origin that may occasionally resemble trigeminal neuralgia include periodic migrainous neuralgia, antral carcinoma, temporomandibular joint syndrome (myofascial pain dysfunction), temporal (giant cell) arteritis, post-zoster neuralgia, benign brain tumors, and atypical facial pain with personality changes.

There are several published cases of familial aggregation (5).

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Glossopharyngeal neuralgia. Much rarer than trigeminal neuralgia (1:100 cases), glossopharyngeal neuralgia is characterized by unilateral paroxysmal stabbing pain in the posterior one-third of the tongue, pharynx, larynx, and soft palate lasting from a few seconds to a minute, followed by a burning sensation that may last from 2 to 5 minutes (3,6,7).

The pain usually extends to the ear. As in the case of trigeminal neuralgia, the pain is associated with a trigger zone that is usually located on the lateral wall of the pharynx, at the base of the tongue, or in the external ear area posterior to the mandibular ramus. Swallowing and talking usually trip the trigger, although it may also be precipitated by yawning, coughing, or consuming cold drinks. Trigger zones can often be

demonstrated in the tonsillar or pharyngeal area by touching these regions with a probe.

The syndrome seems to occur with equal frequency in both sexes, but involvement is slightly more common on the left side than on the right. Bilateral involvement is extremely rare, being seen in less than 1% of a series of 116 patients reported by Rushton et al (7).

The pain is usually of an intense, severe quality and occurs most often at night. It is followed by homolateral tearing and salivation caused by neuronal bombardment of the lacrimal and parotid glands. Between attacks, tinnitus, partial deafness, and facial tics may be experienced. Cocainization (10% cocaine or similar surface anesthetic agent) of the lateral pharyngeal wall and/or tonsil is ordinarily performed to ascertain whether one is dealing with true glossopharyngeal neuralgia, for this brings about immediate but temporary relief. Associated with the neuralgia may be bradycardia, hypotension, syncope, and cardiac arrest (1,3,4). These symptoms apparently result from activation of the glossopharyngeal-vagus complex that eventuates in cardiac slowing. This in turn will result in syncope or rarely cardiac arrest. Coughing is common during an attack of pain (2,5,8).

Approximately 55% occur after the fifth decade. When found in a younger age group (approximately 25% are younger than 40 years), it may be because of anomalous arteries at the cerebellopontine angle, inflammation of the arachnoid membrane, tonsillitis, perineural fibrosis, viral infection, or elongation of the styloid process (Eagle syndrome) (see below). Like trigeminal neuralgia, glossopharyngeal neuralgia may be associated with unpredictable remissions and recurrences.

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Post-zoster neuralgia (geniculate ganglion syndrome, Ramsay Hunt syndrome, cephalic zoster syndrome). Herpes zoster (shingles) is an acute self-limited disease because of the varicella-zoster virus. Although herpes zoster may occur even in the newborn (assuming an intrauterine chicken pox infection), most cases are seen in older patients. Men and women are affected with equal frequency (2,3,8).

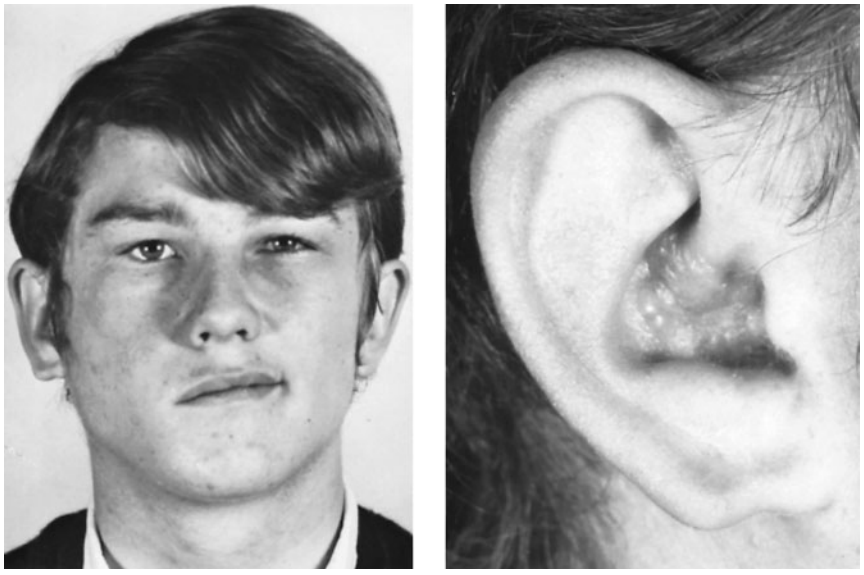
Injury to the nervous system is most severe in one or two dorsal root ganglia or in the corresponding sensory ganglia of the cranial nerves. There is inflammation of the white matter of the dorsal horn and, to a lesser extent, of the anterior horn. Similar involvement of the gray matter of the brainstem often accompanies involvement of the sensory ganglia of the cranial nerves.

Infection of the geniculate ganglion results in vesicular eruption of the external ear and oral mucosa, facial palsy of the lower motor neuron type, severe pain in the external auditory canal and pinna, and ipsilateral loss of taste and lacrimation. The syndrome comprises approximately 3%–9% of cases of facial palsy (Fig. 17–18). By measuring tear production, submandibular salivary flow, and evoked electromyography, one can estimate prognosis (6). There has been a consensus to limit use of the term Ramsay Hunt syndrome to those with involvement of the conchal zone and to exclude cases with involvement of other cranial or cervical nerves or ganglia.

Aleksic et al (1) have presented good evidence to support the contention of Ramsay Hunt that the syndrome arises from geniculate ganglionitis. The facial paralysis apparently results from interstitial neuritis with attendant edema within the bony canal. The combined loss of taste of the anterior two-thirds of the tongue and loss of lacrimation can be explained by a lesion at or proximal to the geniculate ganglion. Round cell infiltration of the facial nerve has been repeatedly demonstrated.

Pain in the ear is severe and paroxysmal and, as with zoster infection of other areas, it often precedes the cutaneous and mucosal lesions by a week. The ear becomes red and swollen followed by vesicular eruption of the auditory meatus and tympanic membrane. The concha, tragus, antitragus, anthelix and, rarely, the lobule may be involved. Rarely, there is no auricular eruption. Associated signs and symptoms may include diminished lacrimation, tinnitus, hearing loss, vertigo, nystagmus, hoarseness, and loss of superficial and deep sensation of the face. The regional lymph nodes are enlarged and tender. Pain persists for weeks after the eruption has disappeared. Among those 40 years or older, approximately one-third experience pain for months or even years.

Oral signs and symptoms include vesicles or eroded areas in the peritonsillar region, oral pharynx, and posterolateral third of the tongue, and pain in the same areas. Occasional loss of taste, diminished salivation,



A B

Fig. 17–18. *Cephalic zoster.* (A,B) Note peripheral right facial weakness and vesicular lesions of conchal area. (From SG Harner, Arch Otolaryngol 92:632, 1970.)

and palatal paralysis may be present. These changes may rarely precede the auricular signs (5).

Prior to the appearance of the cutaneous or mucosal lesions there is often a stinging sensation experienced in the area subsequently involved by the vesicles. The pustules form crusts that are shed after 2–3 weeks and generally the skin resumes its normal appearance. The trigeminal nerve is involved in 15%–20% of patients with herpes zoster, with the ophthalmic branch affected approximately 10 times as often as the maxillary and mandibular branches combined. The seventh, ninth, and tenth nerves may rarely (less than 1%) be involved (4,7).

Approximately 65% who manifest post-zoster neuralgia are over 70 years. It is rare in individuals less than 30 years of age. The neuralgia may last for many months or, in fact, even for years. Patients describe it as burning, aching, or boring. Not uncommonly it is associated with paresthesia in the involved area. The pain and paresthesia are often present throughout the day and may seriously interfere with sleep. In some cases, the patient may experience lancinating pain reminiscent of trigeminal neuralgia, but there is no trigger zone.

References [Post-zoster neuralgia (geniculate ganglion syndrome, Ramsay Hunt syndrome, cephalic zoster syndrome)]

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Still other facial pains

Cluster headaches (Horton's headache). Prevalence is at least eight times as common in men as in women and is noted in 1 in 1500 people. There is some familial aggregation (14). It usually appears between the ages of 30 and 45 years. It may be precipitated by alcohol, which is a vasodilator. The pain is unilateral, occurs with great regularity, and involves the region of the orbit and temple with occasional spread to the neck, upper jaws, or occiput. Its onset is rapid and may reach excruciating intensity and subside after a period varying from a quarter of an hour to 2 hours. The pain becomes so dreaded that in spite of being free of pain, the patient becomes emotionally exhausted. The attacks may occur as often as 5–10 times during a day, and are so severe that they may awaken the patient from sleep in the early morning hours (alarm clock headache). The patient then arises because attacks are more painful when the patient is recumbent. The pain is boring, burning, and is associated with hyperemia of the eye, profuse lacrimation, and stuffiness or obstruction of the nostril on the ipsilateral side. Often there is edema of the eyelid. Usually the attacks subside spontaneously after several weeks, although remissions are common. Narrowing of the pupil and palpebral fissure has been noted in approximately 15% of patients (1,2,4,5,9).

Atypical facial pain. Atypical facial pain is usually described by exclusion (7). It is not trigeminal neuralgia, glossopharyngeal neuralgia, post-zoster neuralgia, or pain secondary to disorders of the teeth, pharynx, ears, or eyes. It is usually poorly localized, intense, constant, and often described as deep. Frequently, the pain does not follow normal anatomic distribution of the trigeminal nerve, commonly crossing the midline or involving portions of the face not limited to the sensory distribution of a single nerve (15). The pain often is described as lasting for weeks, months, or years and being constant in quality. Atypical facial pain is more common than trigeminal neuralgia. Rushton et al (13), in a study of 100 patients, classified atypical facial pain under three headings: (*a*) psychogenic, (*b*) organic, and (*c*) indeterminate. Patients with psychogenic facial pain constituted over half of their 100 patients. Although the patient complained primarily of facial pain, there were associated depressive reactions, schizophrenia, or conversion hysteria. Most were in the fourth and fifth decades of life and there was a marked preponderance of female patients. Approximately half attributed the onset of the facial pain to a definite incident such as a dental procedure or being struck in the face. The diagnosis is justified when the pain does not follow normal anatomic distribution. There are no signs of organic disease and often there is a history of emotional illness (11,14,15). It typically affects middle aged females.

Organic facial pain. In one-third of their series of 100 patients, Rushton et al (13) further classified organic facial pain into five subgroups: (1) vasodilating pain, (2) dental disease, (3) neuritis, (4) neoplasms, and (5) miscellaneous organic conditions. Vasodilating facial pain resembles that of Horton's headache. The onset, character, and duration of pain are similar. However, the location is atypical, the pain being in the lower portion of the face in contrast to the head and eye pain of typical histaminic headache. But otherwise the duration of the pain and the numerous recurrent episodes within a 24-hour period closely simulate histaminic cephalgia. Furthermore, ergotamine tartrate stops the pain of a typical episode.

Dental disease. Atypical facial pain may be caused by previously unrecognized dental disease. The pain was poorly localized in the face and in no patient was it limited to the involved tooth until late in the course of the disorder. Clinical and radiographic studies were normal. Only late in the disorder was the final diagnosis of pulpitis made. Extraction of the responsible tooth stopped the pain. Several other authors have attributed a series of atypical facial neuralgia to incompletely healed tooth sockets (10,12).

Neuritis. Eight of the 100 patients described the facial pain as burning, itching, sticking, or jabbing. A slight but definite sensory loss limited to the division of the trigeminal nerve was exhibited in each instance.

Indeterminate facial pain. Fifteen of the 100 patients described by Rushton et al (13) were classified as having atypical facial pain of indeterminate cause. The duration of the pain was short compared with that in those with psychogenic facial pain. In at least half the patients, the pain started after the age of 50 years. Remissions were common and most of the patients derived substantial, although temporary, relief with the use of ordinary analgesics. Chewing, touching, or rubbing the face seemed to cause the pain to become worse, but other characteristics of trigeminal neuralgia were not present.

Angina pectoris. We have seen several patients who described pain in the mandible and neck upon exertion. This preceded pain in the chest by several weeks (7).

References [Cluster headache (Horton's headache) and other facial pains]

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Trigeminal neuropathy. Trigeminal neuropathy is a protracted disorder of sensation confined to the distribution of the fifth cranial nerve either unilaterally or bilaterally. The term trigeminal neuritis is avoided here because that implies an inflammatory reaction for which it is extremely difficult to present histologic proof. It is to be contrasted with trigeminal neuralgia that is characterized by brief attacks of very sharp pain without sensory impairment. In trigeminal neuropathy, the pain is described as an ache or as burning, boring, pulling, or drawing (1,7). Some patients complain of paresthesia, others of pain involving the area supplied by any of the three divisions of the trigeminal nerve or combinations thereof. The discomfort may persist for hours, days, or weeks. In a study of 61 patients with trigeminal neuropathy, Goldstein et al (4) considered six possible etiologies: dental surgical procedures, mandibular denture pressure, nondental surgical procedures, mechanical trauma, stilbamide intoxication, and a miscellaneous group of causes. Approximately one-third of the patients noted onset of symptoms secondary to a dental surgical procedure, in most cases following tooth removal. Presumably this is because of injury to the sensory fibers of the trigeminal nerve resulting from needle puncture during anesthesia. Goldstein et al (4) suggested that it is advisable to caution patients with deeply impacted teeth that a sensory disturbance such as trigeminal neuropathy may follow removal of impacted third molars. Almost 5% experience dysesthesia after mandibular third molar extraction (5). They suggested that the patient should be seen frequently during the course of the neuropathy, especially if the patient becomes alarmed during nerve regeneration when a sensation of "pins and needles" or tingling may be manifest. Trigeminal neuritis may also occur following alveolar osteitis (dry socket). Pressure from a mandibular denture on the mental nerve at its exit from the mental foramen may produce trigeminal neuropathy. This usually results from extensive alveolar resorption because of periodontal destruction, causing the nerve at the mental foramen to lie on top of the alveolar ridge. Pressure from movement of a mandibular denture may produce pain or paresthesia over the distribution of the mental nerve. It is highly recommended that the reader peruse in detail the paper of Goldstein et al (4) for a variety of other causes for trigeminal neuropathy including such rare findings as intracranial aneurysms. The series of patients reported by Spillane and Wells (7) are extremely valuable. The combination of paresthesia and facial pain should cause the clinician to consider trigeminal neuropathy, tumors of the Gasserian ganglion or its sensory root, pontine tumors, and vascular abnormalities in the region of the ganglion. One should also consider multiple sclerosis. This has already been discussed in association with trigeminal neuralgia, but occasionally the only complaint is paresthesia of the face.

References (Trigeminal neuropathy)

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Nasopharyngeal and cranial lesions causing facial pain. Excellent reviews of the neurologic manifestations of malignant nasopharyngeal tumors are those of Thomas and Walz (2) and Devine et al (1). Prior to the onset of neurologic signs or symptoms, patients often present with pains in the head, face, or ear, swelling of cervical lymph nodes, and nasal or pharyngeal symptoms. These may antedate such obvious neurologic complications as diplopia, visual loss, or facial paresthesia by several years. Frequently several cranial nerves are involved that give rise to a host of eponymic syndromes. If only a single nerve is involved, Thomas and Walz (2) found the sixth nerve to be involved in over two-thirds of their patients, the fifth nerve in approximately half, and the ninth nerve in over a third. The most common binary combination is cranial nerves V and VI (Gradenigo syndrome). Somewhat less common are conditions discussed earlier such as the syndrome of the parapharyngeal space involving cranial nerves IX, X, and XII; the superior orbital fissure syndrome (III, IV, V, and VI); the petrosphenoidal syndrome of Jacod (II, III, IV, V, and VI); the Collet-Sicard syndrome (IX–XII); and unilateral involvement of all cranial nerves, the so-called Garcin syndrome. Most patients have either squamous cell carcinoma or lymphoepithelioma. The 5-year survival rate is approximately 25%. Encroachment of the tumor on the nasopharynx may be manifest as trismus. One of the most important symptoms is increased pain during the night. If the pain awakens the patient, it is almost certain that a nasopharyngeal tumor is present (2).

References (Nasopharyngeal tumors and cranial lesions causing facial pain)

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Dental pain. Hyperemia of the pulp and associated early inflammation are extremely difficult to localize. With progression, however, the clinical signs become more obvious. Extension of the inflammatory process to the periodontal ligament makes the diagnosis easier. An early sign of pulpitis is increased response to cold stimulation. With increased degeneration of the pulp, the response to cold appears to decrease and eventually disappears. This is followed by increased pain with application of heat that may be extremely severe. Patients will frequently put cold water in their mouths to assuage the pain. Subsequently, pulpal degeneration eliminates this symptom. The patient commonly will no longer complain about thermal stimuli producing a toothache. In the absence of clinical or radiologic evidence of dental caries, there is always the possibility of a hairline fracture of a tooth. This is usually not evident on the radiograph or on casual visual examination. At times, the use of a disclosing solution may reveal the crack. There may be painful response to percussion. Ordinarily, percussion is of little diagnostic aid in the early course of pulpitis, but as the inflammatory process extends through the apex of the tooth, painful response to percussion is nearly always noted. Referred dental pain often taxes the clinician's skills. Such pain rarely crosses the midline except in such cases in which the affected tooth is in the midline. Pain from either the maxillary or mandibular teeth may be referred to the ear region, whereas referred pain from infected teeth is nearly always limited to the quadrant of the jaw in which the tooth is located.

Symptomatic elongated styloid process (Eagle syndrome). The styloid process may exceed its mean length of 25 mm or the stylohyoid ligament may be mineralized in 4%–28% of the general population. Involvement is nearly always bilateral. Rarely does an elongated styloid process produce pain, whereas some of those of normal length may be symptomatic. Although it appears that a true clinical entity exists, there is no satisfactory pathophysiologic explanation. Eagle (4–6) focused attention on the elongated styloid process as a source of pain. There are many comprehensive reviews of the literature (1–3,7–10,12,13,15).

The syndrome presents clinically with pain in the throat that is frequently referred to the ear. Usually there is a sensation of a foreign body in the tonsillar area producing dysphagia. It is believed to be because of physical irritation of nerves or vessels passing near the elongated styloid

tip (7); in the absence of an elongated process, it has been ascribed to insertion tendinosis at the junction of the lesser horn and stylohyoid ligament.

The diagnosis is established by palpation of the styloid process through the tonsillar fossa, which in the case of a symptomatic styloid process produces pain. Symptoms similar to those of the classic elongated styloid process syndrome may also be observed in fractures of the styloid process (3,14).

References [Symptomatic elongated styloid process (Eagle syndrome)]

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Glossodynia (glossopyrosis, burning tongue, oral-lingual paresthesia). Alteration in sensation of the oral mucous membrane in the absence of observable alterations is of considerable problem to the clinician because it is so frequent and because the etiology is found so rarely. Although the lateral anterior border of the tongue is most frequently the site of the paresthetic alteration, other portions of the oral cavity may be involved, so technically the terms stomatopyrosis, stomatodynia, or burning mouth may be used.

As the tissues involved almost invariably look normal, there is only the statement of the patient to describe the sensation experienced. This may be reported as burning, itching, or pain of the mucous membranes. Our experience is consonant with that of other clinicians with regard to its marked predilection for middle-aged or older women. Although there have been an inordinate number of local and systemic disorders suggested (various deficiency states such as pernicious anemia and sundry vitamin deficiencies), it seems apparent that these are rarely etiologic. Fear of oral cancer or other psychological factors appears to play a major role. The patient commonly complains that spicy foods are causative, but they seem rather to make the condition more apparent to the patient, and are not etiologic. Several have experienced glossodynia following antibiotic therapy, the prolonged use of antihistaminics, and/or diuretics, but the precise relationship is not evident (1–8).

References [Glossodynia (glossopyrosis, burning tongue, oral-lingual paresthesia)]

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Oromandibular dystonia with blepharospasm (Meige syndrome, Brueghel syndrome)

Blepharospasm and oromandibular dystonia syndrome appears to be a disorder of basal ganglia. It presents in adult life, is usually nonprogressive, and is not genetic, although it has been reported once in three sisters (3). It has been referred to both as Meige syndrome and Brueghel syndrome, given that it has been alleged that Peter Brueghel the Elder illustrated the syndrome in the sixteenth century in one of his paintings. It most commonly occurs in the middle aged or elderly. There is a 2:1 female predilection (2). Approximately 150 cases have been reported (1–12).

It is characterized by spontaneous, repetitive, nonrhythmic symmetric dystonic spasms, first involving the orbicularis oculi muscles (blepharospasm) that begin unilaterally but soon become bilateral and progress to the muscles of the lower face, jaw, and tongue, making speech and swallowing difficult (Figs. 17–19A,B). The blepharospasm is often preceded by or associated with photophobia or tearing. The dyskinesia may fluctuate considerably from day to day, being aggravated by emotional stress and fatigue and disappearing with sleep. With time, the lower facial musculature becomes involved, being manifested as yawning, jaw opening, and abnormal tongue movements. It resembles the orofacial dyskinesia that is phenothiazine induced. Rarely do the muscles other than those of the head and neck become dystonic. It has occurred in association with parkinsonism (3,6).

In the adult form without blepharospasm, mutations have been mapped to chromosome 14q22 in the *GCH1* gene (9a).

References [Oromandibular dystonia with blepharospasm (Meige syndrome, Brueghel syndrome)]

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A B

Fig. 17–19. *Oral mandibular dystonia with blepharospasm.* (A) Blepharospasm and spasm of jaw closure and mouth-pursing. (B) Spasm of jaw opening and mouth retraction. (From CD Marsden, J Neurol Neurosurg Psychiatry 39:1204, 1976.)

Syndromes involving the VIIth nerve

We deal here with only the Melkersson-Rosenthal syndrome, asymmetric crying facies (cardiofacial syndrome), and autosomal dominant geniospasm (chin quivering).

Melkersson-Rosenthal syndrome. The syndrome consists of unilateral or bilateral facial paralysis, chronic swelling of the face (especially the lips) and lingua plicata (scrotal tongue). Familial occurrence has been described, but most cases have been sporadic (6,18). Smeets et al (9) described a translocation and suggested that the gene is located at 9p11. We are skeptical regarding its significance. A decreased CD4/CD8 ratio has also been documented in one patient (3). The syndrome is remarkably variable in its expression (5). Mair et al (7), studying 23 patients, found the triad in only 9, two signs in 13 patients, and a single component in the remaining patient. The reader is referred to a review of over 250 cases (17).

The swelling, noted in 75%, begins suddenly, in most cases prior to facial paralysis but sometimes after or simultaneously with it (2,4,8,15,16). It may begin during childhood but average age of onset is approximately 35 years (1). The upper lip is most affected (Figs. 17–20) and may be involved (Fig. 17–21). The swollen lip (40%) may assume large proportions—at times being three to four times thicker than normal. The edema recurs in most patients, resulting in permanent enlargement of the lips. The eyelids, nose, cheek, and chin may be affected in 20%. Lip swelling as a single phenomenon is known as Miescher cheilitis granulomatosa. It may well be related to Crohn's disease (12).

The facial palsy begins suddenly in childhood or adolescence. It is present in approximately 25%. It is peripheral and clinically indistinguishable from Bell's palsy. It may be partial, complete, or occasionally bilateral. Relapses often occur, but most patients ultimately recover. The paralysis may precede attacks of swelling by years. The paralyzed side does not always correspond to that of the swelling. Rarely, defects in taste over the anterior two-thirds of the tongue are noted (10,11,13).

Simultaneously with the swelling of the skin, the oral mucosa is often affected in a similar way. The swollen buccal mucosa is cushion-like, divided by furrows of varying depth. The buccal, palatal, and sublingual mucosa may be involved (Fig. 17–22A,B). Approximately 40% manifest lingua plicata, a condition found in 10% of the general population (Fig. 17–23). The gingivae are involved in 15% (14,17).

Histopathologic changes include lymphedematous alterations and/or noncaseating sarcoid-like granulomatous picture similar to those of Crohn's disease and sarcoidosis (1,4a) (Figs. 17–24).

The *Hughes syndrome*, sarcoidosis, Crohn's disease, allergic gingivostomatitis, and hereditary angioneurotic edema must be excluded.

References (Melkersson-Rosenthal syndrome)

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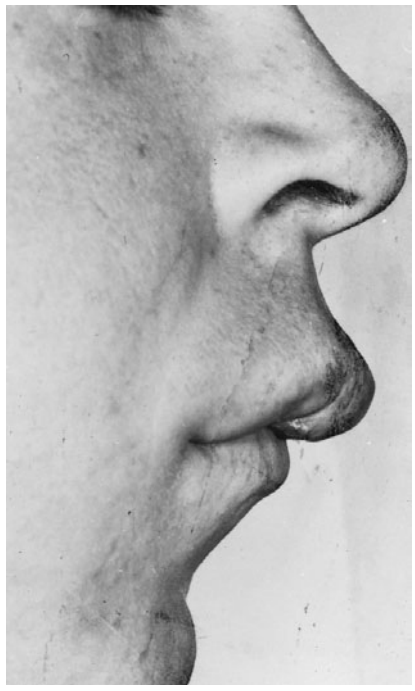
Fig. 17–20. *Melkersson-Rosenthal syndrome.* Swelling of upper lip of 20-year-old man with the syndrome.



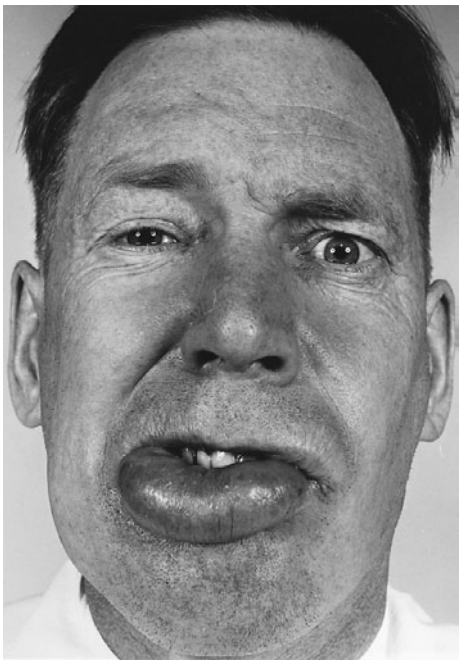


Fig. 17–21. *Melkersson-Rosenthal syndrome*. Markedly swollen lower lip; left-sided facial palsy.

Fig. 17–23. *Melkersson-Rosenthal syndrome.* Plicated tongue of the patient shown in Figure 17–20.

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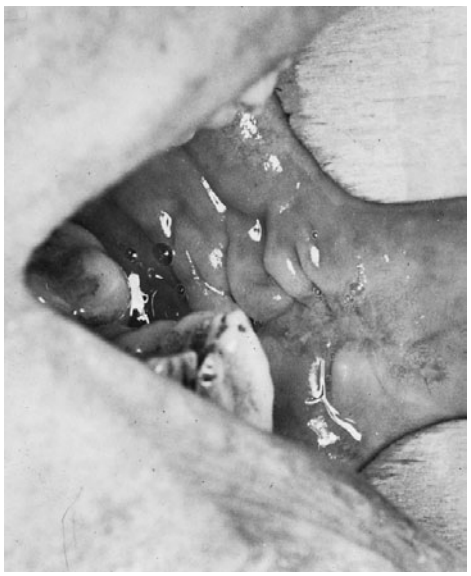
Asymmetric crying facies (cardiofacial syndrome). In 1967, Cayler (3) was the first to point out the association of asymmetric crying facies with other congenital anomalies, especially those of the cardiovascular, genitourinary, and respiratory systems. Employing the term "cardiofacial syndrome," Cayler (4) and others (1,16) suggested that

Fig. 17–22. *Melkersson-Rosenthal syndrome.* (A) Plicated swelling of the buccal mucosa in a patient with Melkersson-Rosenthal. (B) Plicated palatal mucosa in another patient with the syndrome. (A courtesy of H Schuermann, Bonn, Germany. B courtesy of A Lodin, Stockholm, Sweden.)



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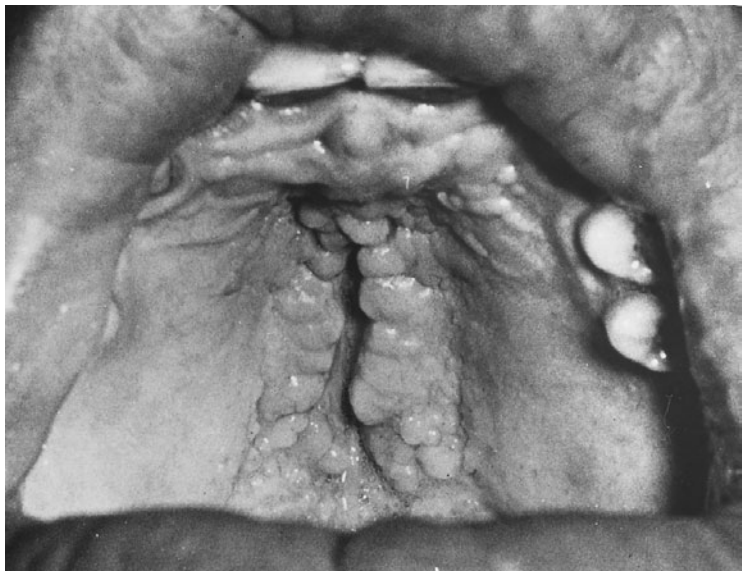

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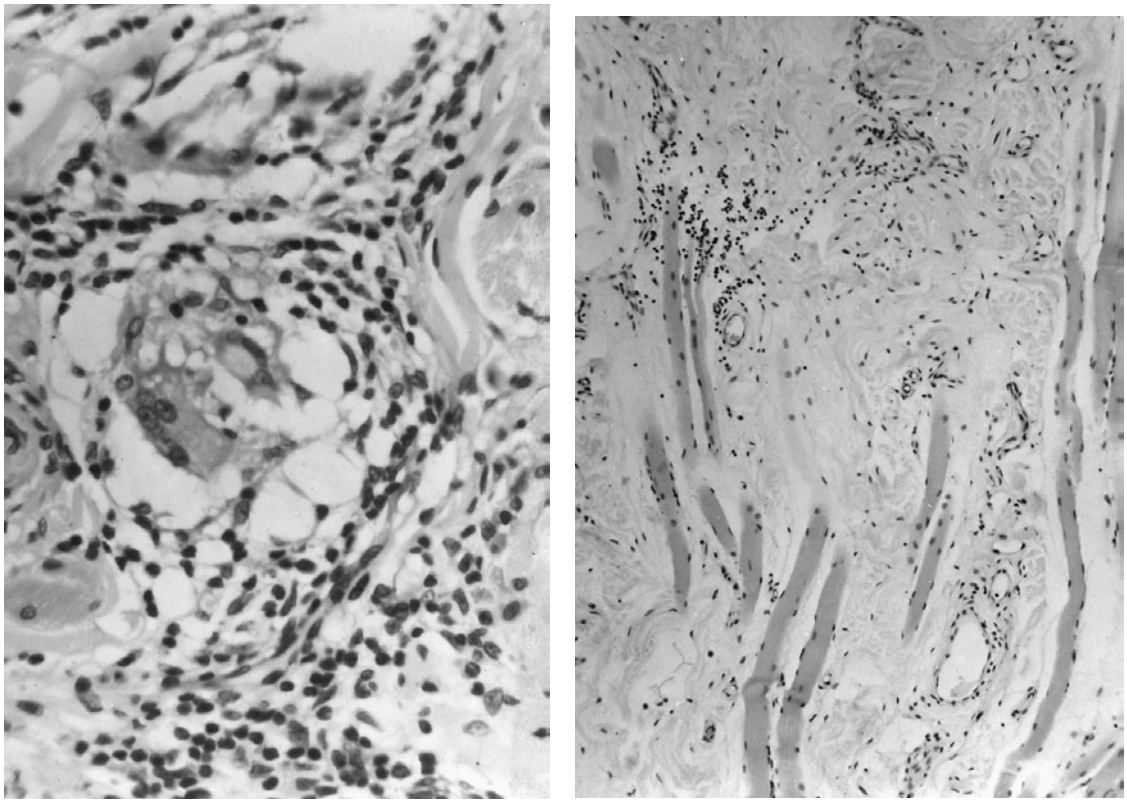

A B

Fig. 17–24. *Melkersson-Rosenthal syndrome.* (A) Giant cell in a sarcoid-like granuloma in lip. (B) Replacement of muscle fibers with edematous fibrous tissue in lip of patient seen in Figure 17–20.

between 5% and 10% of infants with asymmetric crying facies had congenital heart disease.

The frequency of the disorder in various series has ranged from 1 in 120 to 1 in 160 newborns (1,16,18,22). Some authors have found a left-sided predilection, whereas others have found none. Several authors reported autosomal dominant inheritance with variable expressivity (4,9,11,13,14,16). Monozygotic twins with concordance for Cayler syndrome have been reported (20). Both had tetralogy of Fallot and T-cell anomalies. However, discordance was found in monozygotic twins by Goodship et al (8). The spectrum of anomalies remarkably overlaps that seen in the *oculoauriculovertebral spectrum* and may in some instances be the minimal expression of it (6,22). There is also overlap with *velocardiofacial syndrome* and, in fact, the gene has been mapped to 22q11 (2,7,8).

Most authors attribute the defect to unilateral agenesis or hypoplasia of the anguli oris depressor muscle (15). However, Monreal (14) suggested that the side of the lip that pulls lowest is the abnormal one. Because the muscles involved act only to depress the lower lip margin, the defect does not interfere with sucking or smiling and does not foster drooling. The lips are symmetric at rest, the asymmetric facies becoming apparent only during crying. In most cases, lower facial weakness persists, but occasionally it may diminish to some degree (Fig. 17–25A,B). Lin et al (12) reported that 70% had associated findings. Pape and Pickering (17) noted that associated defects tended to occur on the same side as the partial lower facial palsy, but exceptions are many. The cardiovascular anomalies found in 45% most often include VSD, PDA, and tetralogy of Fallot. Also to be found may be right aortic arch, double aortic arch, pulmonic stenosis, coarctation of aorta, ASD, atrioventricularis, communis, tricuspid atresia, single ventricle, hypoplastic right ventricle, hypoplastic pulmonary arteries, and bicuspid aortic valve (11,18,19,23).

Skeletal anomalies, seen in 20%, may include hemivertebra, fused vertebrae, sternal and rib anomalies, and hypoplastic or absent radius and/or thumb (17).

Genitourinary anomalies, noted in 25%, may include absent or hypoplastic kidney, ectopic kidney, polycystic kidneys, bifid scrotum, hypogonadism, cryptorchidism, and hypospadias (17). Neuroblastoma has also been reported on one occasion (10).

Gastrointestinal tract anomalies are relatively rare (5%). They include tracheoesophageal atresia or fistula, laryngomalacia, bronchial stenosis, absent bronchus, absent lung lobe, and a variety of other anomalies such as anal stenosis, imperforate anus, and absent thymus have also been described. Failure to thrive is seen in 15% (12).

In one study, approximately 10% had either cleft lip/palate or isolated cleft palate (17). There are few reports of microcephaly and mental retardation (4,21). These and other central nervous system anomalies have been reported in 10% (12).

One must exclude Crisponi syndrome (5). This autosomal recessive syndrome, seen in Sardinia, is characterized by marked muscular contraction of facial muscles on touch or while crying, trismus, and salivation. Neck muscle hypertonia is evident. The face appears large with chubby cheeks, broad nose, anteverted nares and long philtrum, marked feeding problems, irregular hyperthermia, and camptodactyly. Early death occurs during an episode of marked fever.

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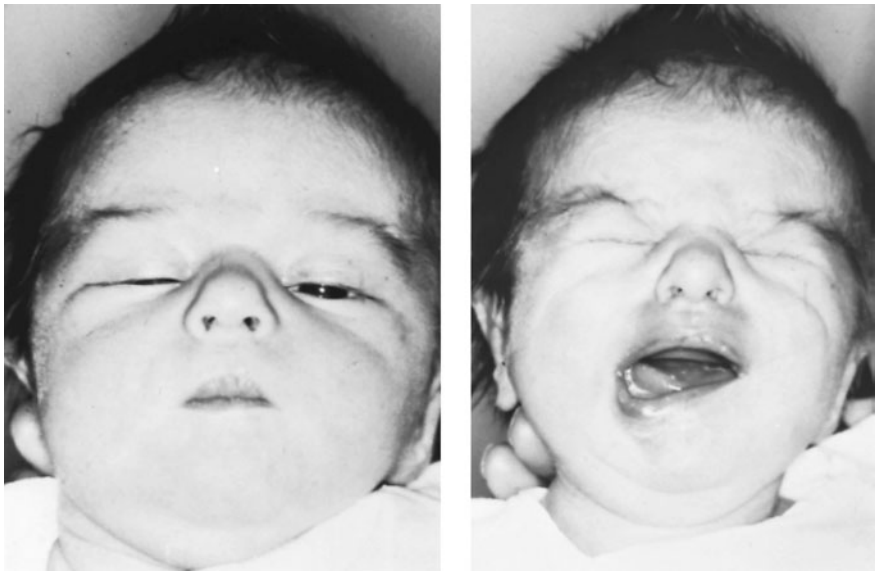

A B

Fig. 17–25. *Asymmetric crying facies.* (A) Face at rest. (B) Asymmetry during crying. (From G Cayler, Sacramento, California.)

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Autosomal dominant geniospasm (chin quivering). First reported by Massaro (10) in 1894, hereditary geniospasm or chin quivering is characterized by paroxysmal, rhythmic up-and-down movement of the chin and lower lip. This arises from involuntary contractures of the mentalis muscle. Numerous additional families have been described (1–9,11–13).

These movements may vary in duration from seconds to hours. They may be triggered by anxiety. The geniospasms usually become evident in early infancy and tend to abate with age. The tongue may be inadvertently bitten (7,8).

Inheritance is autosomal dominant with approximately 80% penetrance (1,2,5,7,12). There is genetic heterogeneity. One of the genes has been mapped to 9q13–q21 (7).

Essential tremor can involve the tongue or jaw (7).

References [Autosomal dominant geniospasm (chin quivering)]

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Gustatory lacrimation (paroxysmal lacrimation, crocodile tears syndrome, Bogorad syndrome, and gustolacrimal reflex)

The syndrome of lacrimation that accompanies eating was first described by Oppenheim (see 5) in 1913, and in far more detail, by Bogorad (3), in 1928, who called it the "syndrome of crocodile tears,"

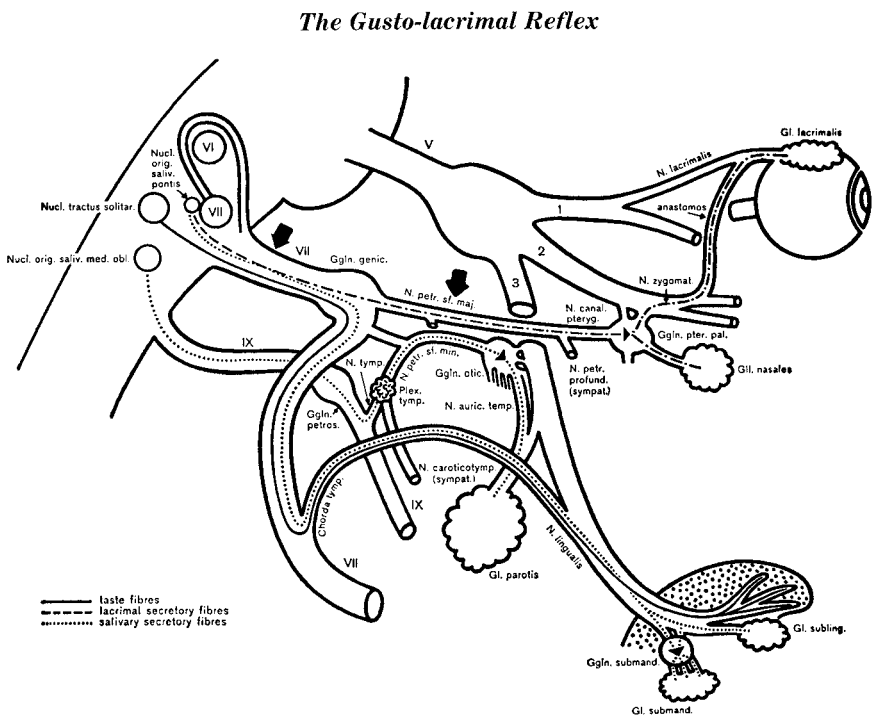

Fig. 17–26. *Gustatory lacrimation.* Diagram shows two possible mechanisms for production of the syndrome. Most often, lesion is proximal to geniculate ganglion and in regeneration, fibers destined for the submandibular and sublingual salivary glands may become interchanged with those for the lacrimal gland. The lesion may also be distal to the geniculate ganglion and involve interchange of fibers of the greater and lesser superficial petrosal nerves. [From A Axelsson and JE Laage-Hellman, Acta Otolaryngol (Stockholm) 54: 239, 1962.]

referring to the tale that the crocodile weeps hypocritical tears while devouring its victims (5). Since the original report, over 125 cases have been recorded. Ford (6,7) wrote the first report in English and linked the syndrome with gustatory sweating and flushing (auriculotemporal or Frey syndrome), both conditions caused by misdirected regrowth of nerve fibers. Ford used the term *paroxysmal lacrimation* to describe the disorder. To parallel the use of the term gustatory sweating and flushing, the present authors suggest the use of gustatory lacrimation. Axelsson and Laage-Hellman (2) have employed gustolacrimal reflex.

In so-called acquired cases, the syndrome has followed traumatic, neoplastic, or inflammatory conditions of the facial or greater superficial petrosal nerves (1,8,9,12,14,21). By the time motor function is becoming restored, the patient usually notices that when eating, tears flow from the eye on the affected side. The syndrome is not associated with the common form of Bell's palsy, in which the lesion is distal to the geniculate ganglion, but occurs only when the lesion is proximal to the ganglion (6). Five percent to 10% of cases of facial palsy are associated with crocodile tear syndrome (1,16,23,25). Rarely the syndrome is bilateral and/or congenital (10,11,13,22). The syndrome can be monitored by a thread test.

Congenital cases have usually been associated with abducens palsy or Duane syndrome (2,15,19,20). Ramsay and Taylor (18) postulated that the association of two conditions would be a lesion causing nuclear degeneration or dysgenesis in the vicinity of the abducens nucleus. The paradoxical aspects result from substitute innervation of the lateral rectus by fibers from the oculomotor nerve and lacrimal gland by fibers subserving salivation.

The facial nerve has several components: a motor component supplying the muscles of facial expression; a sensory component, which carries gustatory impulses from the anterior two-thirds of the tongue and proprioceptive impulses from the face; and an autonomic-parasympathetic component. These latter fibers arise in the superior salivary nucleus and provide secretory and vasodilatory function to the submandibular and sublingual glands via the nerve of Wrisberg, the chorda tympani, and the lingual nerve, as well as to the lacrimal gland via the nerve of Wrisberg, the greater superficial petrosal nerve, the vidian nerve, the sphenopalatine ganglion, and the zygomaticotemporal nerve. Proximal to the geniculate ganglion, all these components are in contiguity.

If a lesion occurs proximal to the geniculate ganglion, then during regeneration, fibers destined for the submandibular and sublingual glands may become partially interchanged with those destined for the lacrimal gland. Thus, when the gustatory stimulus is evoked, lacrimation is produced (Fig. 17–26).

In the exceptional cases cited by Boyer and Gardner (4), the syndrome appeared after surgery on the greater superficial petrosal nerve for relief of headache. During the course of surgery, the lesser superficial petrosal nerve was injured, as it runs only 2 mm lateral to the greater superficial petrosal nerve in the middle cranial fossa. In regeneration, the fibers of the two nerves became interchanged, producing the syndrome. This was proved by resection of the glossopharyngeal nerve, which abolished the disorder. The syndrome has also been seen in association with neurosyphilis, acoustic neuroma, vascular disease, and facial palsy in association with herpes zoster of the ear.

Facial contracture or diffuse facial muscle response is often associated with tearing. If, for example, the teeth are shown, the forehead may wrinkle and the eyelid close. Conversely, wrinkling the forehead or closing the eye may cause the corner of the mouth to be retracted and the nasolabial fold to deepen. This indicates that impulses formerly directed toward isolated muscle groups are diffusely distributed over the face, thus bolstering the concept of misdirected fiber regeneration. This has been called *the Marin Amat phenomenon.*

This syndrome should not be confused with lacrimation seen in association with facial paralysis, where the tearing is because of ectropion, which permits tears to flow out of the conjunctival sac. The latter is not associated with hypersecretion of the lacrimal gland and is unaffected by eating. The condition has been found in association with the *branchio-oto-renal syndrome* (17).

Crocodile tear syndrome has been found in association with Dandy-Walker syndrome in *Wildervanck syndrome* (8a).

References [Gustatory lacrimation (paroxysmal lacrimation, crocodile tears syndrome, Bogorad syndrome, and gustolacrimal reflex)]

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Gustatory sweating and flushing-auriculotemporal and chorda tympani syndromes (Frey syndrome)

The earliest references to the syndrome of gustatory sweating and flushing appear to be those of Duphenix (8), in 1757, and Dupuy (9), in 1816. In 1897, Weber (43) recognized that the syndrome was related to the auriculotemporal nerve. However, the syndrome was brought to the attention of the medical public in 1923 by Frey (11). The syndrome is often referred to under her name. Several hundred cases have been published subsequently. Laage-Hellman (21–24) showed that the syndrome, far from being rare, is a virtually constant complication of conservative parotidectomy. Other investigators have found a 60% complication rate (18). Hogeman (17) presented an excellent historical survey.

It should be pointed out that the term auriculotemporal syndrome is misleading, as the skin innervated by the greater auricular nerve, the lesser occipital nerve, the long buccal nerve, or any cutaneous branch of the cervical plexus may be involved.

The syndrome is clinically manifested by sweating, flushing, a sense of warmth, and, sometimes, mild pain in the preauricular and temporal areas during eating of foods that produce a strong salivary stimulus. Rarely it may present as trigeminal neuralgia (4). The syndrome not only accompanies conservative parotidectomy (5,21,25) but may follow suppurative parotitis (9,11,16,32), herpes (7), direct trauma to the parotid region or mandibular condylar head (14,27,31,36,39) or diabetes (29,37). However, the preauricular approach to the joint is not associated with the syndrome (40). Some patients exhibit only sweating or flushing (17,21). The syndrome occasionally occurs in infants secondary to forceps trauma (2,3,6,33). A bilateral example has been described (19).

The etiology in most cases is damage to the auriculotemporal nerve. This nerve, in addition to supplying sensory fibers to the preauricular and temporal areas, carries parasympathetic fibers to the parotid gland and sympathetic vasomotor and sudomotor fibers to the skin of the same area. Injury to the auriculotemporal nerve denervates the sweat glands and vessels of the skin over its distribution, in addition to producing sensory disturbance (15).

Both the parasympathetic and sympathetic nerves of the face are cholinergic, hence compatible, and in the process of regeneration, parasympathetic fibers become misdirected and grow along sympathetic pathways (12,21–24). Thus, a gustatory stimulus produces sweating and flushing.

That the syndrome is caused by misdirection of parasympathetic fibers is shown by the ability of procaine, injected over the auriculotemporal nerve, to abolish the syndrome. Severing of the auriculotemporal, glossopharyngeal (12), or Jacobson (16) nerve, local atropine injection, blockage of the otic ganglion (13,17), and local application of 3% scopolamine hydrobromide cream (22), aluminum trichloride hexahydrate (35), or 1% glycopyrrolate cream (28) have all been shown to inhibit or abolish the reaction. Conversely, acetylcholine injection increases the phenomenon (13).

The time of the first appearance of the fully developed syndrome varies considerably. Most observers have noted its occurrence within 2 months to 2 years (average, 9 months) postoperatively (13,21–24). There are cases in which the syndrome has appeared in a few days after surgery. Misdirected regrowth of fibers cannot explain the few cases in which the syndrome has appeared a few days postoperatively (38); the alternate possibility of transaxonal excitation exists.

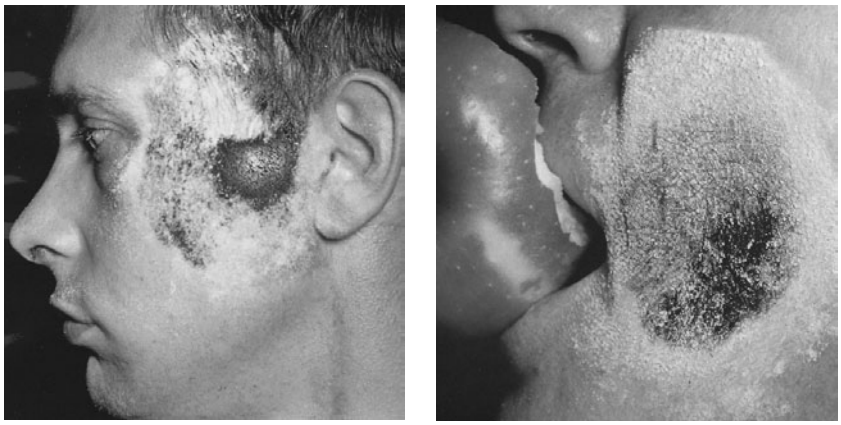
As a rule, once the syndrome appears, the area of skin involved increases (23) and remains increased for life (17). However, approximately 5% of patients (21) experience regression and disappearance of the symptoms. The area affected varies both in degree and in extent, in some persons being seen at the corner of the mouth or extending down to the angle of the mandible, an area supplied by the greater auricular nerve (21) (Fig. 17–27A). RJ Gorlin saw a patient whose sole area of gustatory sweating was a half-dollar-sized area near the corner of his mouth where he had driven a scissor blade many years prior to development of the syndrome. Presumably parasympathetic fibers came from those supplying the minor salivary glands of the cheek (Fig. 17–27B). A similar example was reported by Storrs (39). RJ Gorlin has seen two children with gustatory sweating involving the maxillary division of the trigeminal. In neither case was there history of prior trauma.

Related to the auriculotemporal syndrome is the *chorda tympani syndrome* (1,10,14a,41,42,44) in which the sweating and flushing are limited to the skin of the chin and submental region. This syndrome may accompany surgery or injury to the submandibular gland (21). It has been shown to be abolished by blockage of the lingual nerve proximal to the chorda tympani.

Gustatory otorrhea has also been reported (34).

The auriculotemporal syndrome should not be confused with excessive sweating sometimes seen in persons who have just eaten spicy or sour foods (26). In this case, the sweating appears limited to the forehead, tip of nose, and upper lip. Neither should it be confused with signs or symptoms of hysteria or postsympathectomy sweating.

To demonstrate sweating, the simplest method is application of the starch-iodine test (15 ml of 1% iodine, 5 ml castor oil, 80 ml of 95% alcohol) (21). A more quantitative estimate can be made by using plastic tape (13,20).



A B

Fig. 17–27. *Gustatory sweating and flushing-auriculotemporal syndrome.* (A) Following meals there is profuse sweating immediately in front of ear. This is demonstrated by starch-iodine test. (B) Patient drove scissors into cheek as a child. Severe sweating and flushing are noted at mealtime.

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Gustatory rhinorrhea

Rhinorrhea following parotid surgery, maxillectomy, or septoplasty has been reported by several authors (1–5). Rhinorrhea, that is secretion of thin mucus from the nose during ingestion or other gustatory stimulation, has occasionally accompanied the *auriculotemporal (Frey) syndrome*. Vollrath (5) reported unilateral tearing and ipsilateral rhinorrhea accompanied by sweating 2 years following midface fracture. The etiology appears to be regeneration of damaged nerve fibers of the lesser superficial petrosal nerve. These fibers contain parasympathetic

components that lead to the parotid gland. The regeneration occurs through abnormal connections via the greater superficial petrosal nerve to the vidian nerve, the sphenopalatine ganglion, and the long sphenopalatine nerve to reach the nasal mucous glands. Fibers directed to the palatal mucous glands when misdirected would innervate nasal glands and mucosa. During maxillectomy or septoplasty, trauma to the sphenopalatal nerve is common.

References (Gustatory rhinorrhea)

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Angelman syndrome

The syndrome was first described by Angelman (1), a British pediatrician, in 1965. Early authors used the name "happy puppet syndrome," a term we consider pejorative. Over 300 examples have been clinically described. The frequency has been estimated as 1 per 10,000 to 1 per 20,000 live births (14,40,45). Several excellent reviews are available (11,12,14,15).

Familial cases are noted in approximately 7% (13,54). Affected females are capable of reproduction (41a). The syndrome has been reported in sibs (3,13,25,29,32,52,60,62). These cases represent a mutation in the *UBE3A* gene or a small deletion in the center that controls imprinting on 15q (see below) (42,43). In these cases, there is neither deletion nor uniparental disomy (see below) (8,33). There is no sex predilection. Deletions of chromosome 15q11–q13 have been found in 65% (8,26,49,63). The same deletion is seen in Prader-Willi syndrome. In Angelman syndrome, the deleted chromosome is maternal in origin (16,22,23,33,37) while in Prader-Willi syndrome. the deletion is paternal (24,44). This results from genomic imprinting in which genes are expressed differently depending on whether they were inherited from the mother or the father. Angelman syndrome and *Prader-Willi syndrome* are located very close together and are oppositely imprinted. Uniparental paternal disomy, rarely (3%–5%) causes Angelman syndrome (9,37,38). Those with either deletion or uniparental disomy have a recurrence risk of less than 1% (58). Bottani et al (6), Gillessen-Kaesbach et al (30), and Fridman et al (27a) suggested that patients resulting from uniparental disomy are more mildly affected. Others have not substantiated this finding (54), except for pigment dilution, which is more marked in deleted cases. Maternal germline mosaicism has been suggested (38a). DNA methylation plays a role in the imprinting process (18,48). Approximately 25% of Angelman syndrome patients exhibit neither a deletion nor uniparental disomy. A dominant mutation or inversion in the imprinting center (5,17,29) accounts for 2-3%, and about 5% are due to a gene mutation (*UB3A/E6-AP*). No cause for the remaining 20% has been found (9,36,46,47,60). The gene codes for a ubiquitin-protein ligase involved in degradation of protein (36,60). There is up to a 50% recurrence risk in this group of cases if the mutation is present in the mother (47,58). The risks for recurrence is especially well addressed by Stalker and Williams (58).

Smeets et al (56) described a family in which a translocation between chromosomes 6 and 15 resulted in deletion of the paternally derived chromosome 15 in a patient with Prader-Willi syndrome and inheritance of two different copies of chromosome 15 from the father of a cousin with Angelman syndrome. Chan et al (13), Freeman et al (27), Webb et al (61), and Greger et al (31) discuss other chromosomal 15 abnormalities that can produce Angelman syndrome. At most these cases constitute a few percent. Recurrence risk is case-specific (58). An odd phenotype characterized by obesity and muscular hypotonia has been noted to be related to an imprinting defect (30a).

Facies. Although patients resemble one another markedly in later childhood, early diagnosis is often difficult for the facies is not evident in infancy (23,28). Head circumference, normal at birth, becomes microbrachycephalic with age due to occipital flattening. The scalp hair tends to be fair (70%) due to deletion of a pigment (P) gene (35). Prognathism (80%), midfacial retrusion (90%), frequent protrusion of the tongue (70%) with drooling and chewing (90%), thin upper lip 80%), macrostomia (75%), and pointed chin (95%) are characteristic (Fig. 17–28). The teeth are widely spaced (75%), probably due to tongue pressure. Cleft palate (44) and cleft lip (53) have been documented rarely.

Skeletal changes. Small stature has been noted in approximately 70%. Moderate progressive scoliosis and joint contractures may develop with time in approximately 35%. Only a few older patients have been described (51).

Eyes. The eyes appear deeply set. There is decreased pigmentation of the choroid and iris stroma in 70% and optic pallor or atrophy in over 40% (19). About 30% have Brushfield spots. Blue irises are noted in approximately 90% (14,45). Strabismus is documented in 40%. Keratoconus may develop in older patients (55).

Central nervous system. Patients have severe mental retardation with intelligence quotients below 40. There is no speech or, at most, a few words, but comprehension, especially of signs, is not as severely affected (34). Patients exhibit unprovoked and prolonged bursts of laughter. Motor development is always retarded with sitting at 12–20 months and walking at 3–6 years. Toilet training may not be achieved until 4 years (11). In approximately 50%, a cheerful smiling affect is noted after the first year of life. Generalized hypotonia is evident at birth in over 60% but changes in the extremities with time. Hypotonia in the trunk (90%) and hypertonia of the extremities (85%) produce a stiff jerky stiff-legged, broad-based gait. The arms are held flexed. All exhibit ataxia. Jerky movements become apparent during the first few months of life. Approximately 10% are never able to walk unaided. Deep tendon reflexes are brisk in 85%. One is impressed by their constant hyperactivity, hand flapping, ataxic uncoordinated movements, and tremulousness. These behaviors decrease with age. Probably 80% exhibit epilepsy beginning between 18 and 24 months of age. The seizures range from hypsarrhythmia, to myoclonic, to generalized grand mal types. The seizures may be difficult to control, but generally decrease in severity and number by 10 years of age when they may cease entirely (57). Electroencephalogram (EEG) changes have characteristic large amplitude slow spike wave pattern (2–3 cycles/sec) (7). Abnormal sleep patterns are present in 85%. Sleep appears to occur in short bursts. In most cases, this improves in late childhood but in infancy is truly vexing to parents. Melatonin is helpful in many cases (Wagstaff, unpublished, 1998). Those with UBE 3A mutations tend to be overweight later in life (47). Affected females are capable of reproduction (41a).

Slow feeding due to poor suck has been noted in infancy and frequent regurgitation or reflux is noted in 75% (57). Many parents report fascination with water and music.

Radiographically, there is flattening in the occipital region and tilting of the cranial base so that the sella turcica is obliquely positioned. Computed tomography scans show diffuse brain atrophy in 30% (23) and MRI demonstrates abnormally long Sylvian fissures with no branching point (41).

Laboratory aids. High resolution chromosome analysis in association with FISH studies have been used to establish deletion (4,59). Uniparental disomy is diagnosed by means of chromosome specific microsatellite markers (50,60). Methylation analysis, with a methylation-sensitive SNRPN probe will detect all cases of deletion, uniparental disomy, or imprinting mutation (39). All these studies have been validated for use on chorionic villus sampling or amniotic cells for prenatal detection of imprinting defects (9,10,20,21,59,64).

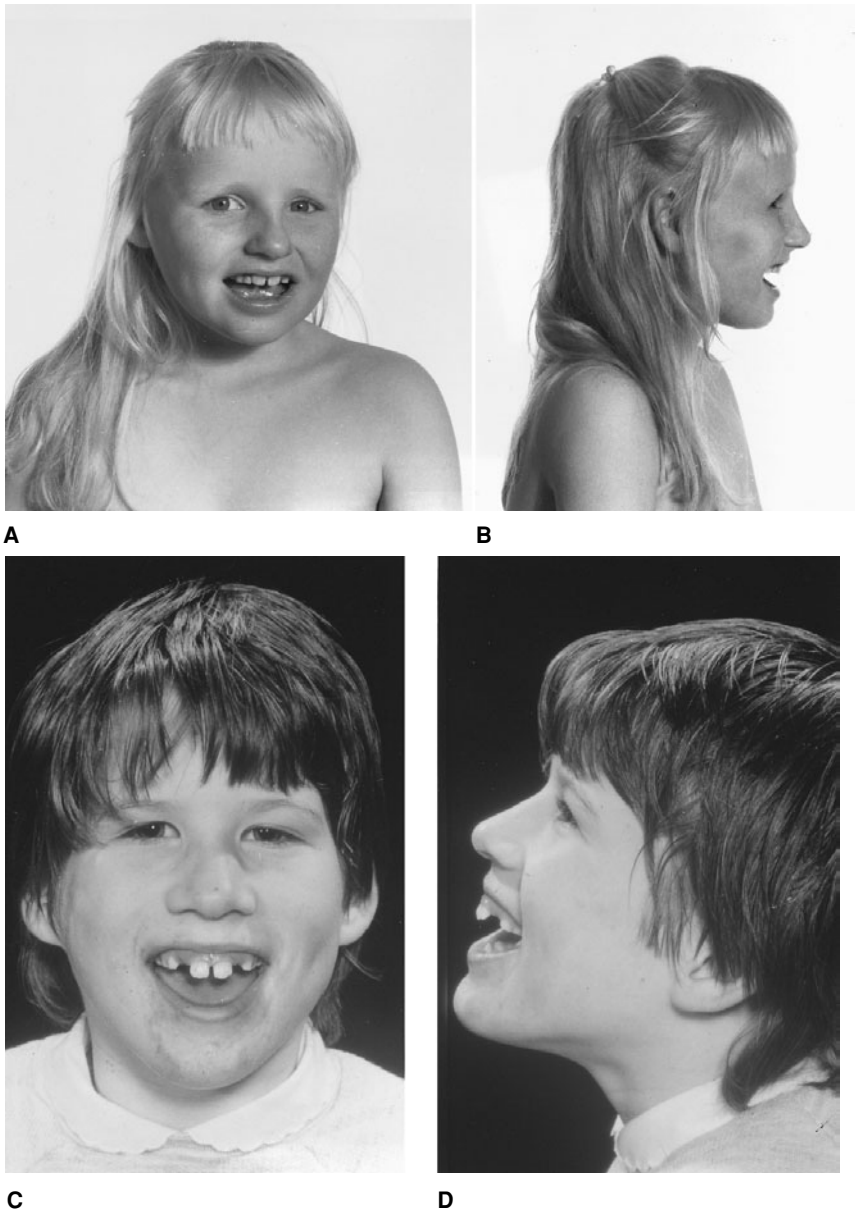

Fig. 17–28. *Angelman syndrome.* (A–D) Note protruding tongue, mandibular prognathism. Patients exhibit pointless activity, ataxic uncoordinated puppetlike movements, and unprovoked prolonged paroxysms of laughter. (A,B courtesy of J Tolmie, Glasgow, Scotland. C,D from M Baraitser et al, Clin Genet 31:323, 1987.)

Diagnosis. Rett syndrome must be excluded as must *ATR-X syndrome* and methylenetetrahydrofolate deficiency (2).

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Syndromes of lower cranial nerves and medulla

In both nuclear and infranuclear lesions, simultaneous involvement of IX, X, and XI is common. The association of these three cranial nerves in various combinations with XII, the cervical sympathetic chain, and rarely the spinothalamic tracts has led to a plethora of eponymic syndromes, only a few of which are discussed here (Fig. 17–29). They may be roughly divided into central medullary lesions (approximately 10%) and peripheral lesions (approximately 90%). The central lesions may be vascular in origin (Avellis syndrome, Cestan-Chenais syndrome, Wallenberg syndrome, and Dejerine syndrome), or they may be due to other causes, such as syringobulbia, multiple sclerosis, poliomyelitis, neoplasms, or trauma (1,3,15,19,27).

Wallenberg syndrome was originally considered different from the other medullary syndromes, that is, those of Babinski-Nageotte and Cestan-Chenais, by the absence of motor signs in trunk and limbs. However, a unilateral infarction can extend contralaterally to catch the already crossed corticospinal fibers, and there may be little justification for designating these as separate disorders. In spite of the long list of eponyms, only two syndromes are of practical importance: (1) medial medullary syndrome—rare, and (2) lateral medullary syndrome—common. The other syndromes do not help with localization nor do they aid in identifying the vessels involved. Because they still appear in the literature, some of these will be mentioned. The lateral syndrome is that of Wallenberg, the medial is Dejerine syndrome, and where both medial and lateral are involved, Cestan-Chenais syndrome is the appropriate designation. Syndromes involving the medulla are listed in Table 17–6.

Avellis syndrome. This syndrome is usually because of occlusion of the vertebral artery. It is characterized by combined involvement of the nucleus ambiguus and spinothalamic tracts with ipsilateral paralysis and anesthesia of the soft palate, pharynx, and larynx, contralateral loss of pain and temperature sensation of the trunk and extremities, frequent

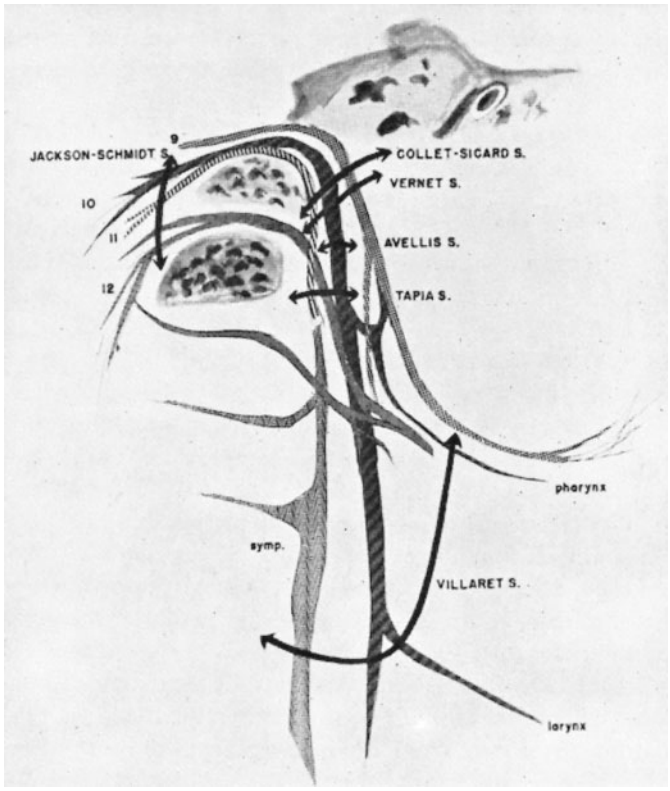

Fig. 17–29. *Syndromes of lower cranial nerves and medulla.* Diagram showing involvement of last four cranial nerves in several syndromes. (From SG Harner, Arch Otolaryngol 92:632, 1970.)

contralateral loss of proprioception and tactile senses, and, rarely, ipsilateral Horner syndrome (4,5,7,10,12).

Schmidt syndrome. This is now thought not to be a simple syndrome. The original report (one paragraph) did not localize the pathology with any clarity (29).

Jackson-Mackenzie syndrome. The original patient had multiple infarctions—so that the localizing value of the syndrome is limited.

Table 17–6. Syndromes involving the nuclei in the medulla

Syndrome	Other name	Comment
Avellis		Corticospinal tract, and X nucleus
Schmidt	Vago-accessory syndrome	Location uncertain; more than one lesion probable
Jackson–Mackenzie	Vago-accessory-hypoglossal syndrome	Corticospinal tract, and X, XII nuclei
Wallenberg	Lateral medullary syndrome	Spinal V, IX, X, XI lateral spinothalamic, spinocerebellar, pupillodilatory fibers
Cestan–Chenais	Lateral medulla syndrome plus medial medulla syndrome	
Babinski–Nageotte		Location uncertain; more than one lesion present
Dejerine	Anterior bulbar syndrome or medial medullary syndrome	Pyramids, medial lemniscus, hypoglossal fibers

Wallenberg syndrome. The main clinical features are ipsilateral paralysis and anesthesia of the soft palate, pharynx, and larynx, ipsilateral loss of the corneal reflex and anesthesia of the face for pain and temperature, ipsilateral Horner syndrome, ipsilateral ataxia, contralateral loss of temperature and pain sensation of the trunk and extremities, and, rarely, involvement of VI–VIII (18,38).

Dejerine syndrome. Hemorrhage or thrombosis of the anterior spinal artery (which supplies the pyramids, medial lemniscus, and emerging hypoglossal fibers) produces ipsilateral paralysis of the tongue, contralateral pyramidal paralysis of the arm and leg, and, occasionally, contralateral loss of proprioceptive and tactile sensation.

Cestan-Chenais syndrome. This syndrome indicates involvement of the lateral and medial medulla. It is caused by thrombosis of the vertebral artery below the point of origin of the posterior inferior cerebellar artery. It differs from the Wallenberg syndrome by the presence of pyramidal tract signs (hemiplegia and contralateral diminution of touch and proprioceptive senses). Pain and temperature sensations are normal (6).

Vernet (jugular foramen) syndrome. The syndrome is characterized by ipsilateral paralysis of IX, X, and XI with resultant paralysis of the soft palate, larynx, pharynx, sternocleidomastoid muscle, and part of the trapezius muscle, anesthesia of the posterior soft palate, and loss of sensation and taste over the posterior third of the tongue (34,35). Approximately one-half of the cases have been attributed to brain tumors. However, more recently, among 17 cases of Vernet syndrome, only two patients had neoplasms (32). In most there was no obvious cause. Full or partial recovery occurred within a month.

Villaret (retroparotid space) syndrome. The syndrome combines ipsilateral paralysis of the last four cranial nerves and Horner syndrome (enophthalmos, ptosis, miosis) (24,26). Occasionally, VII is also involved. The syndrome is because of a lesion in the retroparotid space, which is bounded posteriorly by the cervical vertebrae, medially by the pharynx, anteriorly by the parotid gland, laterally by the sternocleidomastoid muscle, and superiorly by the skull near the jugular foramen.

Collet-Sicard syndrome. The disorder is manifest by unilateral involvement of the last four cranial nerves. It was described in the injured of World War I by Collet and later by Sicard. The syndrome may also occur as a result of tumors, inflammatory lesions, aneurysm of the internal or external carotid (31), or fibromuscular dysplasia of the carotid (16). The lesion is typically extracranial and involves the jugular foramen and the anterior condylar or hypoglossal foramen through which XII passes. Currie (8) expressed doubt whether this syndrome should be preserved. The original patient might have had a lateral medullary syndrome with contralateral weakness and sensory loss because of an earlier infarction higher in the brain stem or in the medial medulla.

Tapia (vagohypoglossal) syndrome. The main features include unilateral paralysis of the muscles of the tongue, and unilateral paralysis of the vocal cord and soft palate (34). The pharynx, sternocleidomastoid, and trapezius muscles are usually spared. There is dysphonia but no dysphagia. The lesion is localized to the crossing of the X–XI nerves below the nodose ganglia (30). A finding of trauma is more common than finding tumors (2).

Garcin (half-base) syndrome. The syndrome is usually because of a malignant tumor invading the base of the skull, but meningiomas, basal meningitis, and trauma have all been implicated. Typical progression may be to complete ophthalmoplegia (13,21,23,24,26,28,37). It may be somewhat more common in Chinese due to high incidence of nasopharyngeal carcinoma. Tumors of the nasopharynx can cause all or nearly all cranial nerves on one side to become involved without signs of motor or sensory disturbances of the extremities and without evidence of

increased intracranial pressure (papilledema or spinal fluid changes). Radiographic alterations are often apparent in the skull base.

Progressive bulbar palsy. In adults, we shall consider briefly Duchenne syndrome, whereas in children, Fasio-Londe syndrome will be described.

Duchenne syndrome (progressive bulbar palsy, glossopharyngolabial paralysis). The condition is principally seen in individuals in their sixth and seventh decades. The syndrome can occur in amyotrophic lateral sclerosis in which it is characterized by a slowly ascending process that involves the motor nuclei of the medulla and often the pons and midbrain (9,22). XII is usually involved first. Early signs are bilateral fasciculations and atrophy of the tongue. X is then affected with resultant dysphagia for both liquids and solids, dysarthria, and thickened nasal speech. Atrophy and fasciculations of the palatal and pharyngeal musculature may be seen. Involvement of the nuclei of V and VII causes paralysis and wasting of the muscles of facial expression and mastication. The nucleus of the accessory nerve is less often affected (14,33).

Fasio-Londe syndrome. Childhood onset of progressive bulbar palsy may be part of infantile and childhood spinal muscular atrophies. Age of onset varies between 2 and 10 years. Unilateral facial weakness, dysphagia, and chewing difficulties are early signs. There is often spread to involve most lower cranial nerves. It is doubtful whether this condition is a pure progressive bulbar palsy distinct from the more frequent group of spinal muscular atrophies.

Horner syndrome. Horner syndrome is characterized by enophthalmos, miosis, partial ptosis, ipsilateral vascular dilatation, and anhidrosis of the face, neck, and arms. The syndrome may also be seen in association with involvement of V and X in Wallenberg syndrome. Alternating Horner syndrome has been described following cervical spinal cord injury (25). The cause is not known but movement of fluid within an intramedullary cystic cavity (posttraumatic) has been postulated (11). This stimulates the sympathetic nerve, causing the signs to alternate. Dural adhesions following a cervical spine injury were postulated by Ottomo and Heimburger (25).

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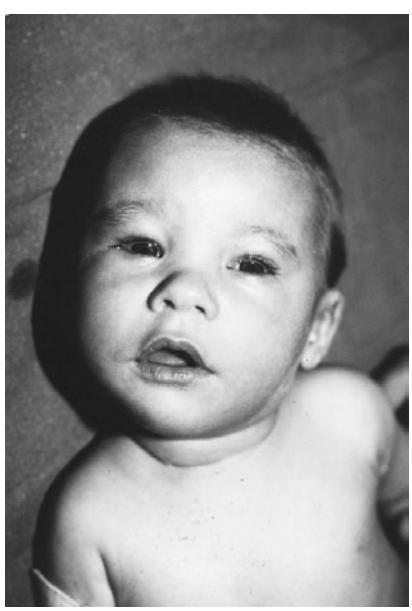
X-linked mental and somatic retardation, genital hypoplasia, and sensorineural hearing loss (Juberg-Marsidi syndrome)

Juberg and Marsidi (2), in 1980, reported a male child and two maternal uncles with mental and somatic retardation, unusual facies, microgenitalism, and sensorineural hearing loss. Mattei et al (3) described an additional large kindred with seven males. Tsukahara et al (7) reported another case.

Inheritance is clearly X-linked. The gene has been mapped to Xq12–q21 (1,5), being allelic to *X-linked alpha-thalassemia/mental retardation syndrome* (6,8). Methylation plays a role (1).

Clinical findings. Birth weight was low and growth did not exceed the 3rd centile. Head circumference was reduced. The two uncles reported by Juberg and Marsidi (2) died at 9 years and 20 months, respectively. One child described by Mattei et al (3) died at 10 months.



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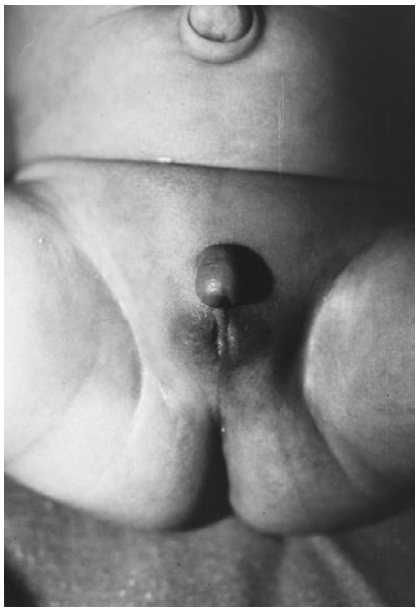

B

Fig. 17–30. *X-linked mental and somatic retardation, genital hypoplasia, and sensorineural hearing loss* (*Juberg-Marsidi syndrome*). (A) Face of patient showing high forehead, upslanting palpebral fissures, flat nasal bridge. (B) Genital hypoplasia in the same patient. (From JF Mattei et al, Clin Genet 23:70, 1983.)

Craniofacial findings. All had high foreheads, upslanting palpebral fissures, prominent epicanthal folds, and flat nasal bridge (Fig. 17–30A). The pinnae were hyperfolded with a large helix.

Ocular system. Small palpebral fissures were found in most of the affected. Light retinal pigmentation was noted in some of the affected (2).

Central nervous system. Severe global delay was evident in all affected. Hypotonia was evident in infancy. Most patients learned to walk. Some had seizures.

Musculoskeletal system. Camptodactyly of the second or third finger, clinodactyly of the index finger, asymmetrically sized halluces, and retarded bone age were found.

Genitourinary system. All affected had rudimentary scrotum, undescended testes, and micropenises (2,3) (Fig. 17–30B). Some had vesicoureteric reflex and small kidneys.

Auditory findings. Bilateral sensorineural hearing loss dating from infancy ranged from moderate to severe, but was not otherwise characterized because of severe mental retardation. In one child, hearing deficit involved higher tones below 60 dB.

Laboratory findings. Delayed bone ages was a constant finding.

Diagnosis. Renier et al (4) reported three male sibs and two maternal uncles with microcephaly, mental retardation, epilepsy, spastic paraplegia, and sensorineural hearing loss with X-linked inheritance. In Gustavson syndrome, an affected kindred similar to that of Juberg and Marsidi was described (1a) but the genitalia were normal.

References [X-linked mental and somatic retardation, genital hypoplasia, and sensorineural hearing loss (Juberg-Marsidi syndrome)]

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Bobble-head doll syndrome

The term "bobble-head doll syndrome" was coined by Benton et al (1) in 1966 to refer to abnormal head movements or progressive tremors due to various lesions (ventricular cyst, arachnoid cyst, aqueductal stenosis, tumors of corpus callosum) that intermittently block the third ventricle and are associated with hydrocephalus. These mostly anterior-posterior but occasionally side-to-side movements disappear or decrease markedly following surgical drainage of the block. The movements are slower in rate (1–3/sec) than those in benign familial tremors and can be decreased or stopped by will. They disappear in sleep and in recumbent position. The movements are occasionally accompanied by trunk or hand tremor.

The tremor may be seen in infancy but nearly always occurs before the sixth year of life (1–6).

We object to the use of the term but await an alternative term.

References (Bobble-head doll syndrome)

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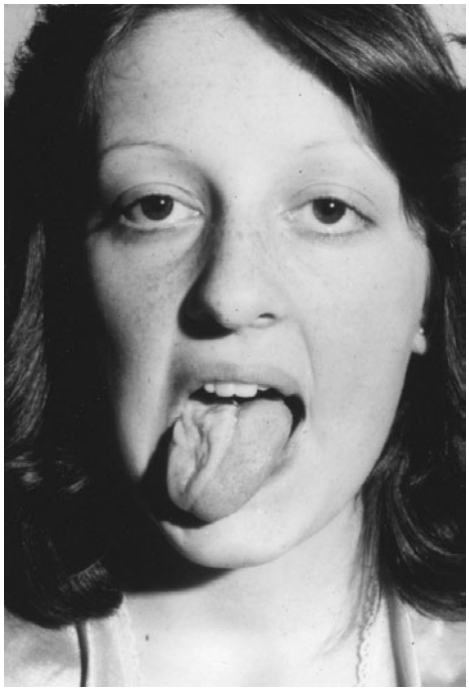

Fig. 17–31. *Unilateral hypoglossal palsy.* Patient had temporary paralysis of XII on right side following flu shot.

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Unilateral hypoglossal palsy

There have been a number of examples of unilateral hypoglossal (XII) palsy following flu shots or infectious mononucleosis (1–7). It usually appears about 3 weeks after onset of the disease or a few days after the injection and often clears spontaneously. There have been a few reports secondary to aneurysm or tumor. Some examples are idiopathic (Fig. 17–31).

The normal half of the tongue pushes the non-innervated half toward the weak side.

References (Unilateral hypoglossal palsy)

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Neck-tongue syndrome

Neck-tongue syndrome is a rare disorder characterized by paroxysmal neck pain in combination with ipsilateral paresthesia of the tongue (1–6). About 30 cases have been described (1).

Rotation of the neck triggers the sensory signs ipsilaterally. Malformations, degenerative processes, and masses result in compression of the C_2 root. The lingual manifestations result from sensory fibers originating in the lingual nerve which joins the dorsal roots of C_2 by way of the hypoglossal nerves.

References (Neck-tongue syndrome)

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Chapter 18
Syndromes with Contractures

Fetal akinesia deformation sequence (Pena-Shokeir I syndrome, FADS)

Pena and Shokeir (29) and Punnett et al (32), in 1974, described children with intrauterine growth retardation, multiple congenital joint contractures, facial abnormalities, short gut, and pulmonary hypoplasia (Fig. 18–1). About 80 cases have subsequently been reported. The frequency has been estimated at 1/10,000 births. Shokeir (36) proposed that the syndrome be referred to as Pena-Shokeir syndrome, type I and that the cerebro-oculo-facial syndrome (COFS) be called Pena-Shokeir syndrome, type II. Moessinger (26) and Toriello et al (37) proposed abandonment of the term and replacement with *fetal akinesia sequence*. The disorder has been classified as a form of arthrogryposis. It is heterogeneous, the phenotype reflecting decreased fetal movement from many different causes (10,20,37): neurogenic atrophy (4,25), congenital myopathy (23), maternal myasthenia gravis (3,16,34), fetal edema (11), and oligohydramnios. The most critical survey is that of Hall (12). Porter (31) published a comprehensive review of the lethal arthrogryposes.

The phenotypic features have been found in sibs (9,29,37) and parental consanguinity (9,33,36) has been reported. Inheritance for at least some examples appears to be autosomal recessive (9,30,35), although more than half of the reported cases are sporadic. High levels of antibodies against human muscle acetylcholine receptors have been demonstrated (15,33,38).

In most cases, the infant is either stillborn or dies within the neonatal period. Only a few have survived (18,23). Polyhydramnios, short gut syndrome, small placenta, or short umbilical cord have been noted in 50% (4,18). Hydrops fetalis is a common finding. Most have intrauterine growth retardation that may have resulted from reduced muscle and bone mass secondary to prolonged immobilization and disuse.

Facies. Hypertelorism, high nasal bridge, depressed nasal tip, low-set malformed pinnae, microstomia, and microretrognathia are present in nearly all cases. Epicanthal folds are present in approximately 20%. The neck is short in 60% (Fig. 18–2). Macrocephaly has been noted in a few examples (9,19,28).

Musculoskeletal system. There are moderate contractures at the hips, elbows, wrists, knees, and ankles because of reduced intrauterine movement. The chest is small with an increased antero-posterior diameter. The lungs are severly hypoplastic. Comptodactyly and clubfeet or rockerbottom feet are essentially constant features. Mild webbing of the neck or elbows has been seen in a few cases (5,25,38) (Fig.18–2A).

Radiographic changes include micrognathia, long and narrow tubular bones, multiple joint dislocations, and malposition of fingers, especially angular subluxations at the interphalangeal joints (17) (Fig. 18–3). A few infants have exhibited variable polydactyly (17,32,37). Chen et al (6) emphasized that the gracile bones may predispose to multiple perinatal fractures.

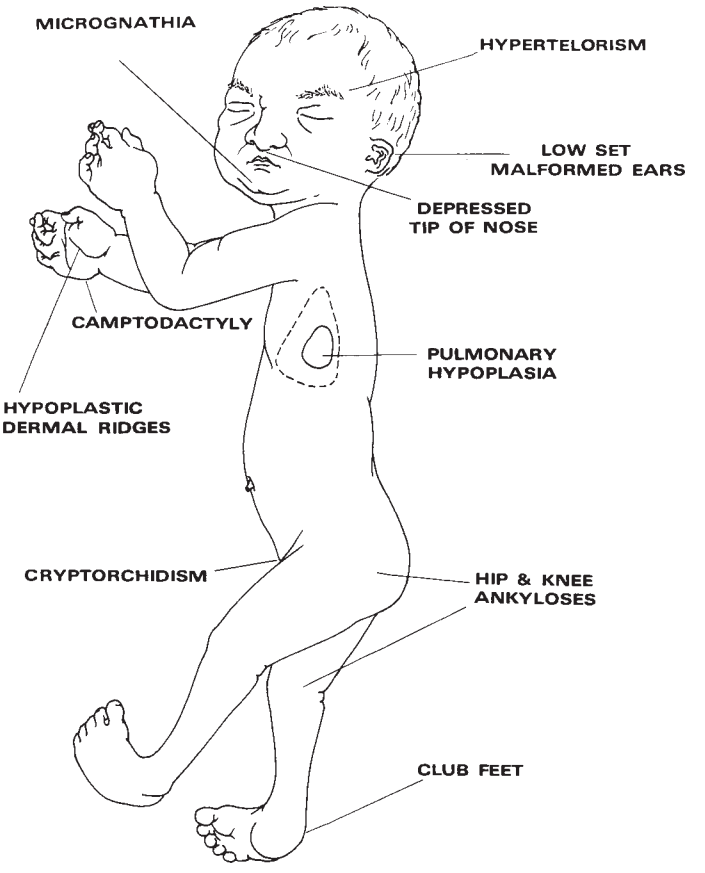
Genitourinary abnormalities. Probably all affected males have cryptorchidism and 20% have hypospadias. Clitoral enlargement and/or labial abnormalities are present in 15%. Various urinary tract anomalies occur in 30% (21).

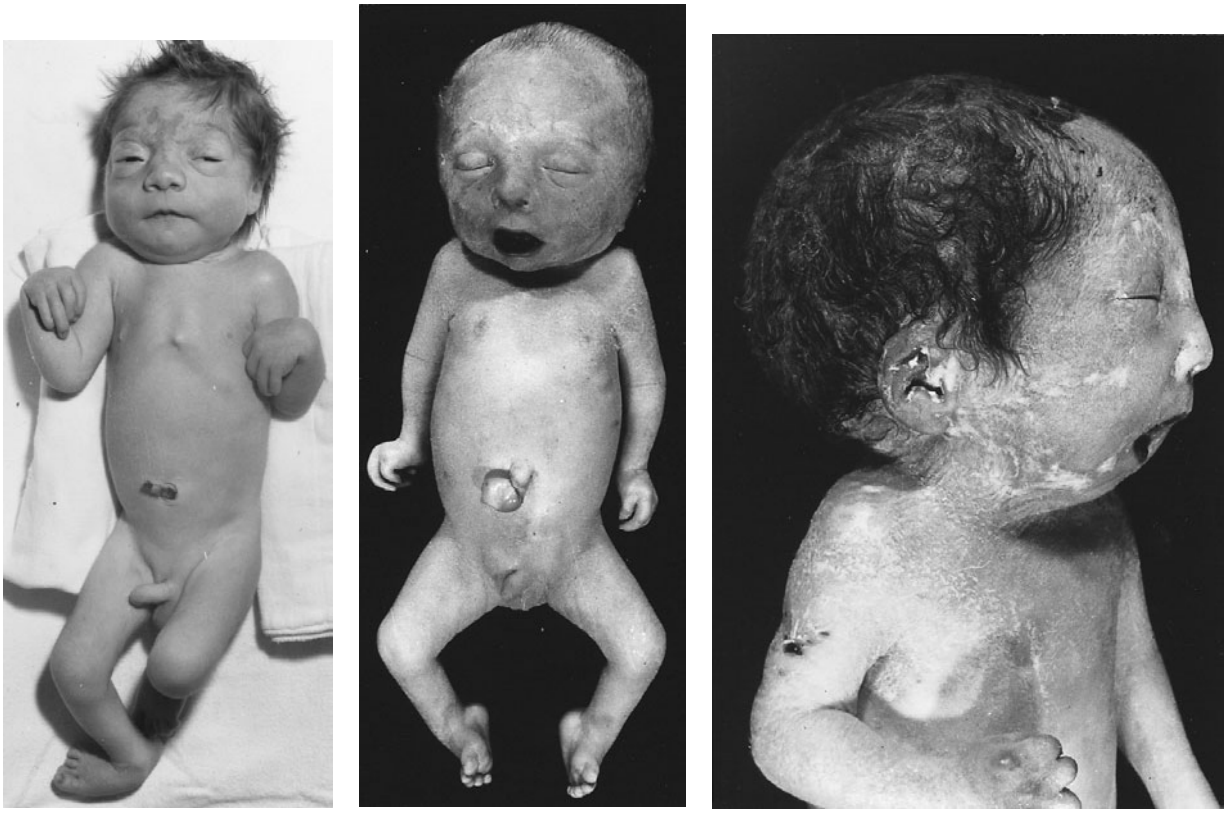
Cardiac anomalies. Various congenital heart anomalies have been described in 25% (21).

Oral manifestations. Small mandible and cleft palate are frequent (37).

Pathology. Apart from measurable lung hypoplasia, present in nearly all cases, internal organs have been essentially normal, although laryngeal stenosis has been reported (1,6,17). Muscle biopsy may show focal atrophy and replacement with fibrous connective tissue or fat or may be normal. Neuropathologic findings consist of a marked paucity of anterior horn cells in the spinal cord and widespread neuronal loss in the central nervous system (2,10,19,25), or may be normal. Pathogenesis appears to be related to a number of different mechanisms in different families, resulting in muscle weakness and intrauterine fetal immobility. This is implied by the congenital joint contractures and webbing, and facial features (25). If any one of the phenotypic features is seen in a patient, the others should be looked for. Thymus and systemic hypoplasia has been noted (14a).

Fig. 18–1. *Fetal akinesia deformation sequence*. Main dysmorphic features. (Adapted from SDJ Pena and MHK Shokeir, J Pediatr 85:373, 1974.)



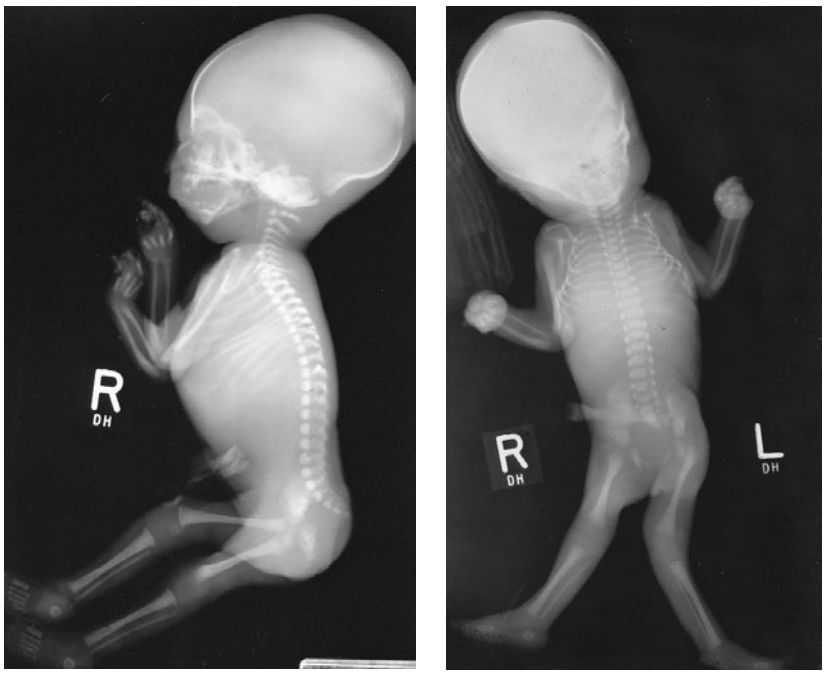


A B C

Fig. 18–2. *Fetal akinesia deformation sequence*. (A) Note suborbital creases, hypertelorism, nevus flammeus of forehead, micrognathia, arthrogryposis (camptodactyly, club feet), and pectus carinatum. (B,C) Similar phenotypes. (A from HH Punnett et al, J Pediatr 85:375, 1974. B from P Moerman et al, J Pediatr 103:238, 1983.)

Differential diagnosis. Arthrogryposis, a group of conditions of diverse etiology and characterized by congenital joint contractions and web formation, must be excluded (17). The anomalies of the extremities somewhat resemble those in *trisomy* 18 (27). Lung hypoplasia is much more prominent in Pena-Shokeir I syndrome. The syndrome of multiple ankyloses and facial anomalies must also be excluded (39).

Various recessive inherited *lethal multiple pterygium syndromes* have been reported. In addition to the ankyloses, camptodactyly, lung



A B

Fig. 18–3. *Fetal akinesia deformation sequence*. (A,B) Anteroposterior and lateral views of stillborn infant showing gracile bones, fixed deformity of many joints, hip dislocation, and micrognathia. (From CS Houston and MHK Shokeir, J Can Assoc Radiol 32:215, 1981.)

hypoplasia, and facial abnormalities, multiple joint webs and/or cardiac hypoplasia were found (24). These conditions share many features of fetal akinesia deformation sequence (2,11,14) because both have decreased movement. There is some facial resemblance to *Potter sequence*.

Erdl et al (8) reported sibs with Pena-Shokeir phenotype who also exhibited endocrine hyperplasia, trilobate lung, and major CNS malformations.

Hall et al (13) reported an autosomal dominantly inherited disorder characterized by small mouth and jaw, limited jaw movement in infancy, mild short stature, mild microcephaly, large ears without an anthelix, and severe flexion contractures of the hands and feet that led to subluxation of fingers and club feet. A dominantly inherited syndrome of similar anomalies of the hands and rockerbottom feet because of vertical talus (digitotalar syndrome) but with no facial anomalies was described by Sallis and Beighton (34).

Laboratory aids. Sonography has been employed for prenatal diagnosis based on associated hydrops (22,28).

References [Fetal akinesia deformation sequence (Pena-Shokeir I syndrome, FADS)]

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Cerebro-oculo-facial-skeletal syndrome (Pena-Shokeir II syndrome, COFS)

In 1974, Pena and Shokeir (15) reported a disorder consisting of microcephaly, cataracts, and other eye anomalies, characteristic facies, flexion contractures, and generalized osteoporosis. They revisited the syndrome in 1978 (16). It probably was described earlier in sibs by Lowry et al (13) although we cannot completely exclude the possibility that the sibs had Cockayne syndrome (5). The disorder is a form of fetal akinesia.

Affected sibs and parental consanguinity indicate autosomal recessive inheritance (15,21). There may be two types, one having more severe cardiac and renal problems (4). About 40 cases have been reported to date. A balanced translocation that involved 1q23 and 16q13 was reported by Temtamy et al (24). The original Manitoba kindred was shown to have a mutation in the Cockayne syndrome group B gene (14a).

About half of the infants are small for dates. There is failure to thrive. All exhibit progressive postnatal growth deficiency and progressive demyelinization of the central nervous system. Average life span is about 4 years.

Facies. Head circumference is small in 95%. At least 90% have microphthalmia and blepharophimosis. About 75% exhibit cataracts (7,10,12,22). In those that survive, the face is flat, and hypertelorism, small mouth, thin downward-slanting upper lip, micrognathia, cleft palate, and low-set pinnae are noted (20).

There is a prominent nasal root in 100%. The pinnae are large in 70%, and the upper lip overhangs the lower one. The chin is small in nearly all. The neck is not short (Fig. 18–4).

Musculoskeletal. Kyphosis and/or scoliosis are noted in 70%, and camptodactyly with overlapping fingers is a constant feature. Flexion contractures, especially of the elbows and knees, are noted in 80%. About 70% manifest rockerbottom feet because of vertical talus. Dislocated hips, acetabular dysplasia, coxa valga, and osteoporosis are also

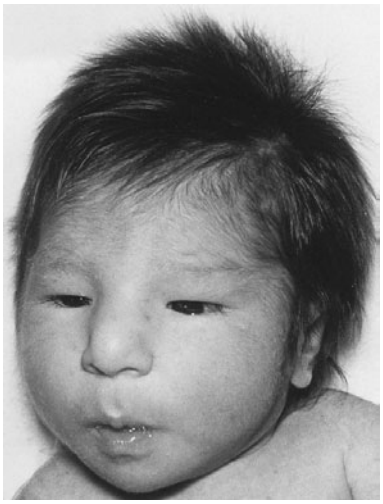

Fig. 18–4. *Cerebral-oculo-facial-skeletal syndrome*. Facies showing microcephaly, blepharophimosis, prominent nasal root, small mouth, micrognathia. (Courtesy of SDJ Pena, Winnipeg, Manitoba, Canada.)

frequent features. The second metatarsal may be proximally placed due to hypoplasia of the second cuneiform bones (Fig. 18–5).

Central nervous system. About 95% exhibit microcephaly and mental retardation. Perhaps 40% of those autopsied have had hypoplasia or agenesis of the corpus callosum, cerebellar hypoplasia, and intracranial groove foldings (12,21). Gershoni-Baruch et al (6) suggested addition of congenital muscular dystrophy. Intracranial calcification has been cited by a number of authors (1,3,12,19,24).

Other findings. The nipples are widely set in about 50%. Single palmar creases have been seen in about 30% and longitudinal foot groove folding in 70%. Renal anomalies have also been reported (18).

Differential diagnosis. There appears to be a form of COFS characterized by early death. The infants exhibit the facial and musculoskeletal anomalies of classic COFS syndrome. Low birthweight is common. Visceral anomalies include agenesis of the corpus callosum, cerebellar hypoplasia, renal hypoplasia or agenesis, horseshoe kidney, absence of hemidiaphragm, malrotation of colon, hypoplasia of spleen, and multiple foci of calcification of heart and kidneys (14,17). Whether this represents a different disorder or an allelic form is not known.

We are not entirely convinced that the COFS syndrome differs from the Bowen-Conradi syndrome found in Hutterites (2,8). The latter disorder is stated not to be associated with microphthalmia, blepharophimosis, cataracts, or large pinnae whereas COFS syndrome patients do not have dolichocephaly or cryptorchidism. There is otherwise a remarkable overlap in phenotypes.

Several authors have suggested that the COFS syndrome represents a severe allelic form of *Cockayne syndrome*. The usual pattern in Cockayne syndrome is normal growth until 2 years of age, then gradual delay in overall development, small head, and unsteady gait. Joint problems and kyphosis are mild. Arthrogryposis and *trisomy 18* must be excluded. Winter et al (25) noted an overlap with the *Neu-Laxova syndrome*. A COFS-like syndrome was reported in an infant with osteopetrosis and myopathic changes (11).

One must exclude *Pena-Shokeir syndrome, type I*, characterized by pulmonary hypoplasia. A condition called CAMFAK, characterized by microcephaly, cataract, and kyphosis and similar to Cockayne syndrome (23), must be excluded.

Laboratory aids. Hwang et al (9) found extensive necrosis of iliac crest cartilage cells. However, necrotic chondrocytes can also be seen in various chondrodysplasias: *achondroplasia, diastrophic dysplasia*, and *Dyggve-Melchior-Clausen syndrome*.

References [Cerebro-oculo-facial-skeletal syndrome (Pena-Shokeir II syndrome, COFS)]

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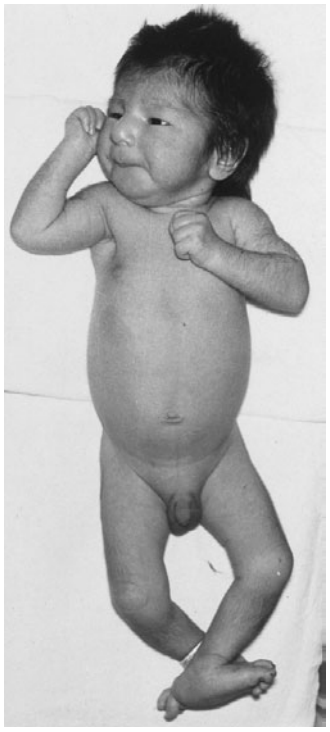

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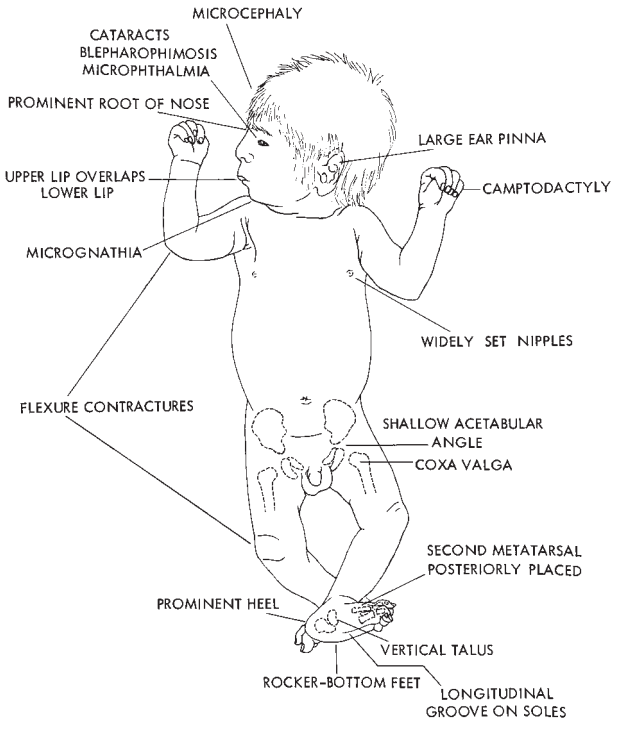

B

Fig. 18–5. *Cerebral-oculo-facial-skeletal syndrome*. (A) Note camptodactyly, widely set nipples, rocker-bottom feet. (B) Diagram depicting most important characteristics of COFS syndrome. [From SDJ Pena et al, Birth Defects 14(6B):205, 1978.]

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Neu-Laxova syndrome

Neu et al (20), in 1971, and Laxova et al (12), in 1972, independently reported sibs with a lethal syndrome of marked intrauterine growth retardation, ichthyosis, marked microcephaly, characteristic facies, and flexion deformities. At least 50 examples have been published. Cases resembling the COFS syndrome have been described (13,30). Consanguinity (2,4,5,9,11,12,14,17,19, 20,23,25,27,28,32) has been noted in 40%, and affected sibs (2,4,12–14,19,20,23,28,29,32) have been reported. Inheritance is clearly autosomal recessive. Curry et al (3) suggested that there is heterogeneity, one form having no edema and no increased fat layer (5) whereas the other form has a prominent fat layer (18) (vide infra). The syndrome may have a higher frequency in Pakistanis (17).

A history of multiple spontaneous miscarriages is frequent. Polyhydramnios is seen in 40%. The placenta is remarkably small for gestational age (4,5,10,23,27,32,33), and there is a short umbilical cord in 35% (1,5,7,10,13,20,23,27,29,32). In some cases, the umbilical cord has only two vessels. All have severe intrauterine growth retardation. At full term the infant usually weighs between 850 and 1500 g. Crown-heel length ranges from 25 to 35 cm. Nearly all are stillborn or die within hours after birth. The longest survivor lived approximately 8 weeks (14).

Many of the findings such as polyhydramnios, intrauterine growth retardation, generalized edema, deformed swollen limbs, osteopenia, and short survival can be explained by protein loss through skin fissures. Some structural deformities may be secondary to intrauterine mobility, similar to those seen in *restrictive dermopathy*.

Facies. Facial appearance is striking. There is microcephaly (OFC at birth 23–26 cm) in 85% and a markedly sloping forehead in 75%. There appears to be premature closure of sutures and fontanels, probably secondary to small brain size (9,12,13,18,20,22). The nose is flat and simple with a broad nasal bridge in 70%. The nares are usually small or, rarely, almost absent. The cheeks are full. The upper and lower eyelids exhibit extreme ectropion and are very hypoplastic, giving the impression that they are completely missing. Apparent hypertelorism is noted in 50%, and exorbitism is noted in 40% (20,23,34). The pinnae are low-set in 60% and very often large and deformed. The lips are everted. Bilateral cleft lip-palate has been seen (18,30). Micrognathia has been present in about 50%. The head appears to sit directly upon the shoulders in 75% (Fig. 18–6).

Musculoskeletal alterations. Most patients have short contracted limbs. The hands and feet are swollen and the digits hypoplastic, with or without nails in 60% (24). Frequently the fingers overlap. About 50% have rocker bottom feet. Syndactyly of fingers and toes is extremely common. A detailed anatomic study of the upper limbs was carried out by Shved et al (29).

The bones have a stick-like appearance due to undertubulation. There is underossification of the bones of the hands and feet. The ilia are dysplastic and there is poor ossification of pubic bones with lack of ossification of sacrum and coccyx. Possibly the condition termed by Spranger et al (31) cerebroarthrodigital syndrome is not specific for a single disorder since their patient 3 appears to have Neu-Laxova syndrome.

Central nervous system. Severe microcephaly (85%) with variable anomalies such as brain atrophy, agenesis of the corpus callosum (40%), dilated ventricles (25%), lissencephaly (40%), and holoprosencephaly, agenesis of vermis (40%), hypoplasia of corpora quadrigemina, and hypoplasia of the cerebellum (40%) have been found (13,17,20,21). There are reduced numbers of nuclei in the pons, cerebellum, and brainstem. The cerebellar cortex has a two-layer lamination. The anterior and lateral columns of the spinal cord are absent (13) (Fig. 18–7).

Urogenital. Both unilateral renal agenesis and hypoplasia of external genitalia have been reported in approximately 35% (12,13,22,23,27).

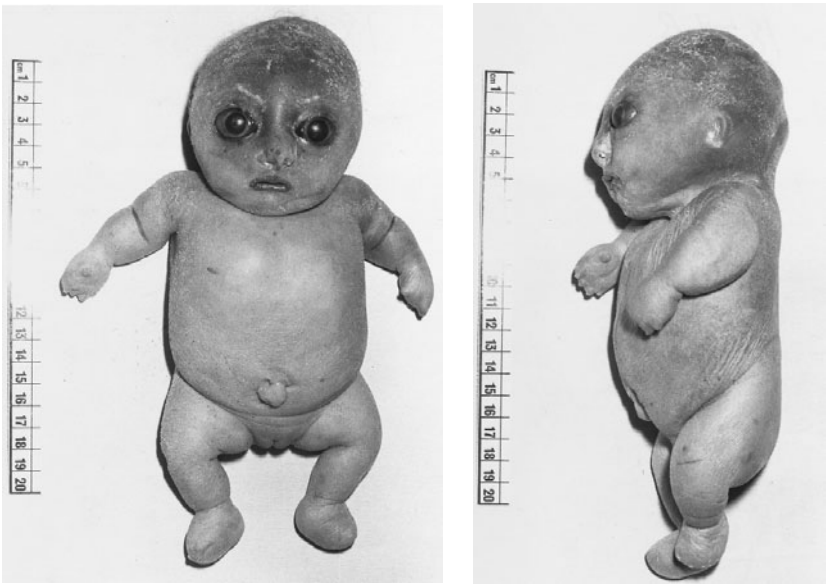
Skin. Scaly, yellowish ichthyotic skin has been described in approximately 50% (19). There may be massive accumulation of adipose tissue beneath the epidermis, surrounding atrophic muscle bundles (9,14,18).

Cardiac anomalies. Various anomalies have included ASD, VSD, PDA, and transposition of great vessels.

Oral manifestations. Cleft lip-palate has been reported in approximately 25% of the cases (9,18,22–24,32,33).

Differential diagnosis. There is some similarity (intrauterine growth retardation, lissencephaly, agenesis of corpus callosum, cataracts, joint contractures, overlapping fingers) to patients with *cerebro-oculo-facial (COFS) syndrome* that die at an early age (33). Silengo et al (30) suggested that they are the same disorder. Collodion baby and severe congenital ichthyosis must be excluded (6,27).

The skeletal alterations as noted above are seen in several clinically different disorders (26). Scott et al (26) and Elliott et al (4a) reported patients with long clavicles, 11 thick ribs, very short arms, hypoplasia of the metacarpals and phalanges, tall narrow ilia and diaphyseal widening.



A B

Fig. 18–6. *Neu-Laxova syndrome*. (A,B) Characteristic facies with globular head, widely opened palpebral fissures, protuberant globes, squashed nasal tip, rudimentary pinnae, small mouth, and short neck. Limbs are short; hands and feet are swollen with absent or hypoplastic digits without nails. (From CI Scott et al, Am J Med Genet 9:165, 1981.)

Perhaps the common denominator is a primary neural tube-neural crest dysplasia.

Restrictive dermopathy and harlequin fetus should be excluded.

Laboratory aids. The disorder has been diagnosed prenatally by ultrasonography at 6–8 weeks for accurate dating, at 12–16 weeks for reduced fetal limb movement, at 16–24 weeks for facial and skeletal abnormalities, the detection of intrauterine growth retardation, and polyhydramnios and at 34–36 weeks for lack of fetal swallowing, fetal edema, and ocular hypertelorism with exorbitism (2,8,15,16,18,22,25,28,32).

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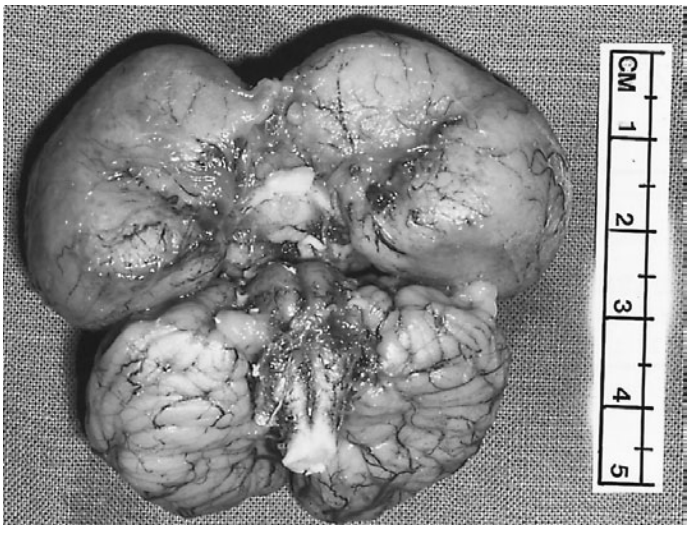
Fig. 18–7. *Neu-Laxova syndrome*. Forebrain grossly maldeveloped with bilaterally symmetrical unconvoluted and unilobed cerebral masses. (From CI Scott et al, Am J Med Genet 9:165, 1981.)



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Multiple pterygium syndrome

Multiple pterygium syndrome was buried in the early literature, most often under the nonspecific diagnosis of arthrogryposis (21,35) or *Noonan syndrome* (10,31). The syndrome consists of growth retardation, multiple pterygia involving the neck, fingers, and antecubital, popliteal, and intercrural areas, and cleft palate. Credit should go to Matolcsy (22) for clearly defining the entity. Approximately 70 cases have been reported to date. The patient reported by Celiköz (4) clearly has this disorder. Thompson et al (38) have elegantly reviewed the evolution of the phenotype.

The syndrome has autosomal recessive inheritance. Affected sibs (3,5, 9,17,18,22,24,25,34–36,38) as well as parental consanguinity (10,12,38) have been reported. It is apparently more common among Arabs (24, 38,40). Recurrent chest infections, probably the results of congenital kyphoscoliosis, may result in early death (5,21,38). Approximately 75% are small for their gestational ages.

Facies. The palpebral fissures are mildly downslanting in 50%. There is mild ptosis of the lids in 30% and epicanthal folds in 15% (Fig. 18–8). Approximately 50% of the patients have puffiness around the eyes. The mandible is small in 60%. In some patients there is a central neck web (vide infra).

Musculoskeletal alterations. Growth is usually retarded below the third percentile, the patient's adult height rarely exceeding 135 cm.

The popliteal pterygia, noted in 45%, may markedly inhibit walking and, even if only mild, may produce bizarre stance and gait. Pterygia occur in the cervical area in 95%. They may resemble those seen in Turner and Noonan syndromes. They completely surround the neck rarely (Fig. 18–9). In approximately 15%, a pterygium extends from the chin to the sternum (11,26,43). In 50%, there is mild soft-tissue syndactyly between the fingers.

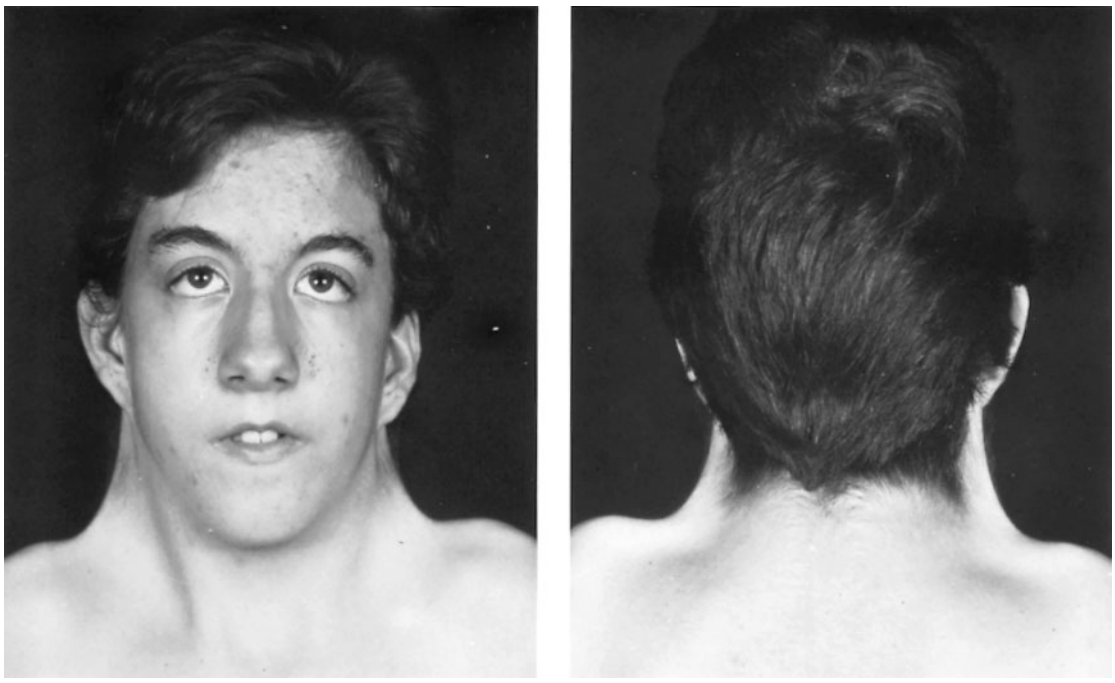
Flexion deformity of the digits, the thumbs being flexed and apposed, occurs in 60% (1,19,25,33) (Fig. 18–10). Talipes calcaneovalgus, either unilateral or bilateral, and rocker-bottom feet have been noted in 35% (1,30). Kyphoscoliosis, often congenital, and other vertebral anomalies (failure of posterior fusion of vertebrae, fusion of cervical vertebrae) are found in 60%. The axillae (55%) and antecubital fossae (35%) are the sites of webs. Intercrural webs are found in 40% of both males and females. In the presence of an intercrural web, the penis and scrotum are retropositioned. They may be associated with cryptorchidism and/or inguinal hernia (22,25). In females, the labia majora may be absent (1). Body asymmetry has been noted (40).

Abnormal fiber distribution has been described (41).

Radiographic changes include vertebral segmentation anomalies such as fusion of cervical vertebrae and rib anomalies (25%), tall narrow vertebral bodies (30%), vertical talus with talipes calcaneovalgus or equinovarus (65%), and camptodactyly of fingers and toes (65%) (38). The patellae may be absent.

Miscellaneous findings. Congenital heart defects have been found in 25% of those in whom a cardiac examination was recorded (9,12,30,38).

Fig. 18–8. *Multiple pterygium syndrome*. (A,B) Note antimongoloid obliquity of palpebral fissures, pterygium colli, low-set posterior hairline. [From C Scott, Birth Defects 5(2):231, 1969.]



A B

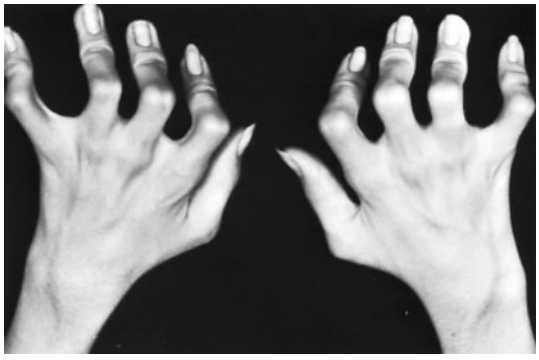
Fig. 18–9. *Multiple pterygium syndrome*. Pterygia of neck, axillas, and popliteal areas. [From C Scott, Birth Defects 5(2):231, 1969.]

Oral manifestations. Cleft palate has been found in approximately 35% (2,4–6,17,20,28), and a hearing deficit has been noted in several patients (29,38). Hennekam (14) reported three affected sibs whose tongues had flattened spoonlike tips (lingua cochlearis).

Differential diagnosis. The syndrome should be distinguished clearly from autosomal dominantly inherited *popliteal pterygium syndrome*. Although both share popliteal pterygium, the cervical, axillary, and elbow webbing as well as the finger contractures and vertebral anomalies and difference in inheritance pattern should furnish a clear distinction. There is also overlap with the *femoral hypoplasia-unusual facies syndrome*. Elbow webbing is discussed under *popliteal pterygium syndrome*. A possible new autosomal recessive form of multiple pterygia was noted by Aslan et al (2a).

Pterygia about the neck may be seen in *Turner syndrome, LEOPARD syndrome, Noonan syndrome*, and in some cases of *craniocarpotarsal dysplasia*. Pashayan et al (27) described multiple pterygium syndrome in a patient with mosaic *Klinefelter syndrome*. The patient also exhibited cataract and glaucoma. Some patients with *fetal akinesia sequence* have pterygium formation.

Fig. 18–10. *Multiple pterygium syndrome*. Marked flexion deformity of digits. [From C Scott, Birth Defects 5(2):231, 1969.]



A dominantly inherited syndrome of multiple pterygia, ptosis, and skeletal abnormalities has been reported by Frias et al (7). Short stature was not present. The skeletal anomalies included malsegmentation of vertebrae, pelvic dysplasia, and some carpal and tarsal bone fusion.

Kawira and Bender (15) described a dominantly inherited disorder of short stature, cervical vertebral anomalies, scoliosis, nuchal and axillary pterygia, and distal arthrogryposis.

Haspelagh et al (13) and other authors (32,39) have reported a syndrome of mental retardation, postnatal growth retardation, multiple pterygia with distal muscular wasting, hypogonadism, and characteristic facies (trigonocephaly, frontal bossing, epicanthal folds, low-set angulated pinnae, microretrognathia). Haspelagh syndrome has been shown to be due to an unbalanced reciprocal 6q/9p translocation (5a). Cleft palate was noted in two of four children. Another family with autosomal dominant inheritance did exhibit short stature (23).

Nuchal hygromas may be noted prenatally on ultrasound (8,42).

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More lethal multiple pterygium phenotypes

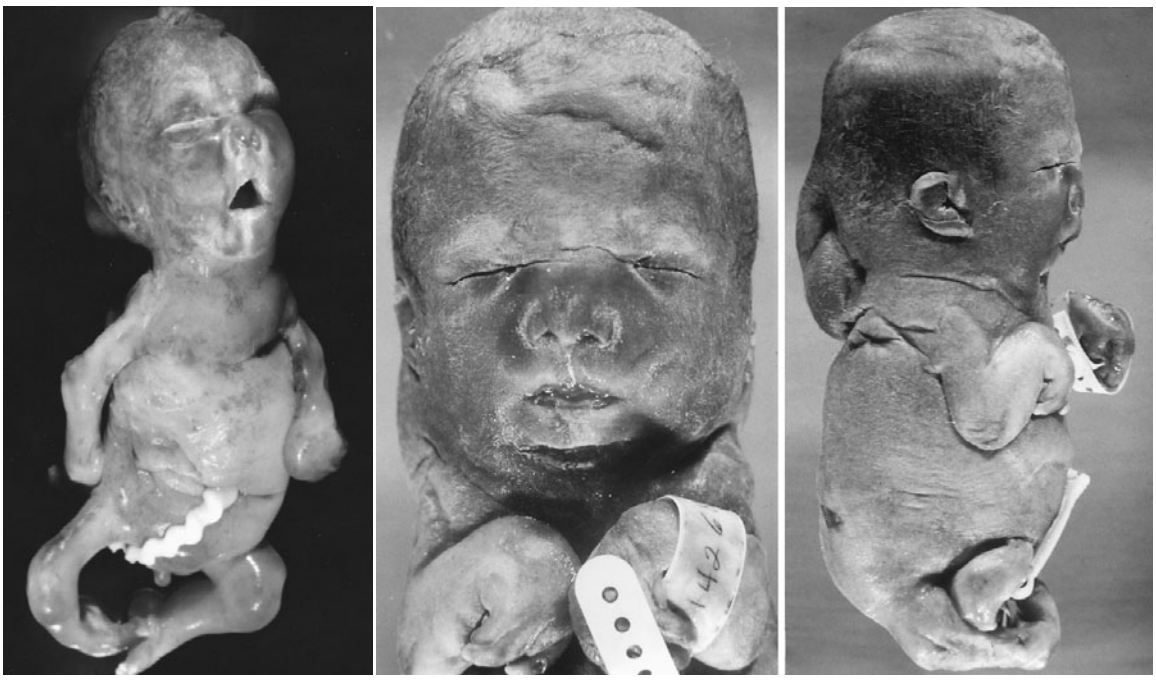
Several additional lethal multiple pterygium phenotypes have been reported. Nearly all have autosomal recessive inheritance (1), but only one has been mapped as of 2000 (vide infra) (28). An X-linked recessive type has been documented (20) and mapped to Xq26 (14a). The pterygia may result from embryonic onset fetal akinesia from several causes (5). All are characterized by death or miscarriage during the second trimester and by the presence of multiple congenital contractures with skin webs across joints, apparent hypertelorism, cystic hygromatous masses in the neck with residual edema and loose skin, thin crowded ribs, and hypoplastic lungs and hearts (11,21). The pregnancies frequently are complicated by polyhydramnios. Cleft plate may be present. The conditions may not always be diagnosable prenatally (14). A survey of 36 published cases is that of de Die-Smulders et al (6). A consistent pathologic work-up was advocated by Froster et al (7).

Theories of pathogenesis include an abnormally fragile collagen (6) and aplasia of developing muscle fibers (22).

Distinction among the types is based on age of onset of intrauterine growth retardation, the extent of neck swellings, and whether and where bony fusions and modeling errors of the bones occur. The syndrome seems to represent a combination of jugular lymphatic obstruction sequence and fetal akinesia. Martin et al (19), however, have denied that such division can be made. Hall (10) presented a very lucid discussion of the problem. Hall (10) divided cases into three groups based on time of onset, timing and extent of neck swellings, and presence or absence of bone fusions. De Die-Smulders et al (6) separated cases into three groups: early, late, and the Finnish type. The first two categories were divided according to the presence of hydrops and/or hygroma colli and length of survival. The Finnish type (vide infra) had specific neuropathological changes in the spinal cord and brain stem.

The first of these disorders (Fig. 18–11A) was characterized by intrauterine growth retardation that is recognized at birth (8,9,15). Hypertelorism (95%), downslanting palpebral fissures (75%), short flat nose (95%), tented upper lip, hypoplastic alae, long philtrum, cleft palate (60%), micrognathia (100%), low-set malformed pinnae (95%), mild neck edema, small chest, and lung hypoplasia (90%) are evident. The

Fig. 18–11. *Lethal multiple pterygium syndrome*. (A) Eighteen-week fetus showing hydrops, nuchal edema, flat upturned nose, long philtrum, gaping mouth, receding chin and multiple pterygia. (B,C) Note cystic hygromas, small mouth, flat nose, talipes, and hand contractures. (A from G Isaacson et al, Am J Med Genet 17:835, 1984. B,C from H Chen et al, Am J Med Genet 17:809, 1984.)



A B C

abdominal musculature is decreased and there may be genital anomalies and atresia of the gut. The pterygia are tightly flexed. There is no bony fusion of the extremities.

The second form, illustrated by cases 2 and 6 of Chen et al (3), Clementi et al (4), and Lockwood et al (17) has short broad limbs and hypertelorism. There is marked cystic hygroma formation that extends from the neck to the mid-back (Fig. 18–11B,C). Generalized scalp edema is also evident. Intrauterine growth retardation is recognized at 20–30 weeks of gestation. Often there is hydramnios and swollen placenta. Fusion of bones (humerus–ulna, radius–ulna, spinous processes of vertebrae, epiphyseal cartilages of long bones) and clubfoot are prominent.

The third form [3 (cases 4,5),27] is characterized by hypertelorism, upward slanting palpebral fissures, open eyes, openmouth, hypoplastic nose, absent mandibular angle, micrognathia, and redundant skin at the nape. Some have cleft lip and/or cleft palate. The legs are thin with decreased muscle mass. There are fused long bone cartilages and failure of normal modeling of the femur and tibia. Intrauterine growth retardation is recognized at 19–25 weeks.

The fourth or Finnish form (12,13,28), has so far been limited to fetuses from Finland. Its incidence in that country is approximately 1 in 19,000 births. The gene has been mapped to 9q34 (18). There are intrauterine growth retardation, fetal hydrops, multiple contractures, and abnormal facies, especially micrognathia (Fig. 18–12A). Pulmonary hypoplasia and muscular atrophy, thin tubular bones that are fractured in 30%, paucity of anterior horn cells, and degeneration of descending tracts were evident at autopsy (Fig. 18–12B).

A possible fifth entity was reported by Robinson et al (24). Malignant hyperthermia was a major complications. An X-linked recessive form was characterized by defectively modeled long bones and broad ribs, clavicles, scapulae, and cystic hygroma (26). Still another type was reported by Spearritt et al (25) that does not conform to any of the aforementioned categories. This type has been subsequently labelled type III lissencephaly (23).

Most examples have been diagnosed during the second trimester by ultrasound because of cystic hygroma and hydrops (2,16,17). *Pena-Shokeir fetal akinesia sequence* shares many clinical features but does not exhibit cystic hygroma or hydrops. The placental changes resemble those of triploidy (22). Infants with the latter often survive the third trimester or are born alive.

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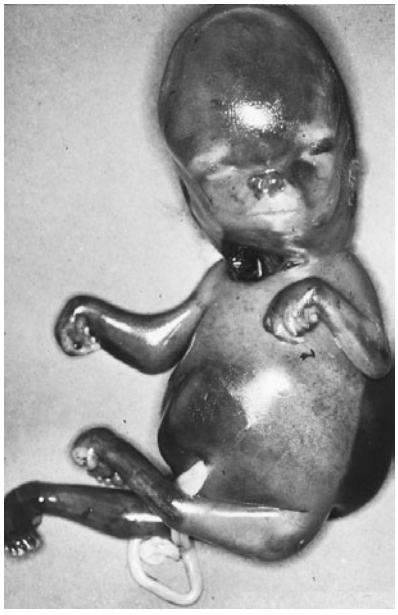

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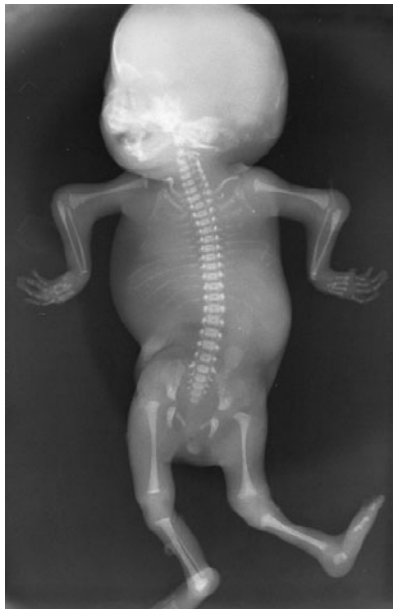

B

Fig. 18–12. *Lethal multiple pterygium syndrome*. (A) Fetal hydrops, multiple pterygia, and talipes. (B) Extremely thin fishbone-like ribs, narrow clavicles, overtubulation of long bones. (From R Herva et al, Am J Med Genet 20:431, 1985.)

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Popliteal pterygium syndrome (facio-genito-popliteal syndrome)

The first recorded case would appear to be that of Trélat (50) in 1869. Fewer than 110 cases have been described to date. There have been many extensive reviews of the syndrome (8,11,15,17,33,38). Prevalence is approximately 1 per 300,000 births. Rintala and Lahti (41) suggested the term "facio-genito-popliteal syndrome."

Most have been isolated examples. The condition has been transmitted from an affected parent to one or more children (11,13,21,24,30,37,38). Although there have been affected sibs with normal parents (Escobar syndrome) (8,48), nevertheless, massive evidence suggests autosomal dominant inheritance with variable expressivity and incomplete penetrance (10,11,15,21,38,43). One study says the popliteal pterygium syndrome maps to the van der Woude region at 1q32 (29), another (44) that it does not. Excellent critical analyses are those of Hunter (23) and Froster-Iskenius (14).

Facies. The most obvious facial alterations are cleft lip and/or cleft palate and filiform adhesions between the eyelids (20%) (3,11,19,24, 28,33,35,36,49,51). Pits of the lower lip are common (vide infra). Rarely, there is choanal atresia (52a).

Cutaneous and musculoskeletal anomalies. Certainly the most striking and most common (70%) component, the popliteal web, extends from the heel to the ischial tuberosity, limiting extension and abduction as well as rotation of the leg (Fig. 18–13A,B). In all but a few cases (22,26,38,41,51), these webs have been bilateral. Along the free edge of the pterygium runs a hard, inelastic, subcutaneous cord or fibrous band or calcaneoischiadicus muscle (2). The sciatic nerve lies free within the web, deep to the fibrous band approximately halfway between the free edge and the apex, being covered by a fibromuscular septum. Special caution must be taken in repairing the skin fold. The popliteal vessels are normally situated in the popliteal space. In many cases, muscle groups are absent or muscle insertions are abnormal. There may be a minimal pterygium of a single limb (Fig. 18–13C).

Approximately 20% exhibit hypoplasia or agenesis of digits (9,16,20,21). Twenty percent have varus or valgus deformities of the foot (7,16,21,50), and over 50% manifest variable syndactyly of the second to fifth toes and in 15% in the fingers, most often 3–4 (5,6,7–9,11,12,16,20,23,37–39,42,46). Ectrodactyly may rarely occur (3). Spina bifida occulta has been documented in 20% and scoliosis or lordosis in 10% (16,26). Bipartite or absent patella has been documented rarely (38).

The skin over the hallux may have a somewhat pyramidal form, one vertex extending over the nail in approximately 40% (6,31,47). If present in a child with cleft lip and/or palate, *even in the absence of a distinct popliteal pterygium*, we believe that this anomaly is sufficiently distinct to make the diagnosis. The toenails, most often the second, are hypoplastic and triangular in approximately 30% (13,15,20,24,37,42,49) (Fig. 18–13D).

Genitourinary system. Anomalies in the male have included cryptorchidism in 40% (1,11,13,42), absent, cleft, or ectopic scrotum in 35% (5,7,16,37,41,42,53), small penis in 40%, and inguinal hernia in 10% (15,42) (Fig. 18–14A). In the female, absence or displacement of the labia majora in 60% (1,16,21,38,42) and enlarged clitoris in 20% (16,21,25,44) have been noted (Fig. 18–14B). Hypoplastic uterus has also been described (16).

An intercrural pterygium extending between the thigh, ventral to the anus, is found in approximately 20% (9,12,15) (Fig. 18–14C).

Oral manifestations. Cleft lip and/or cleft palate have been reported in approximately 85%. Pits or sinuses of the lower lip (11,15–21,24–28,33,35,38,39,50) have been noted in approximately 60% (Fig. 18–15A). Congenital bands or threads of mucous membrane extending between the jaws (syngnathia) have been reported in approximately 30% (2,4,5,7,10,20,21,28,33,37,38,41,49,52,54) (Fig. 18–15B). A band between gingiva and the lower lip has been described (32).

Differential diagnosis. The popliteal pterygia make this syndrome distinctive. It is possible that the patients described by Neuman and Shulman (32) with cleft palate, lip pits, oral mucosal adhesions, and ankyloblepharon represent incomplete expression of the syndrome. Lip pits and ankyloblepharon may each occur as an isolated phenomenon or in combination with cleft lip and/or cleft palate. Various extreme types of bifid scrotum may occur as isolated anomalies. *Hay-Wells syndrome* (*AEC*) includes both ankyloblepharon and cleft lip or cleft palate. Pterygia of the axilla, neck and antecubital, and popliteal areas constitute *multiple pterygium syndrome*. Pterygia-like alterations of the lower extremities occur as part of the caudal regression complex. Antecubital pterygia are seen as an autosomal dominant trait (34,45). They may also occur in association with the nail-patella syndrome.

Bartsocas-Papas syndrome is a lethal autosomal recessively inherited popliteal pterygium syndrome. Findings include low birthweight, mental retardation, mild growth retardation, microcephaly, filiform adhesions of eyelids, corneal ulceration, hypoplastic nasal tip, microstomia, cleft lip-palate, soft-tissue syngnathia, micrognathia, supernumerary nipples, aplastic labia majora, bicornate uterus, and lanugo hair. Anomalies of the extremities comprise popliteal pterygia, pes equinovarus, hypoplastic or absent phalanges, syndactyly of fingers and toes, and synostosis of hand bones. There are no vertebral anomalies.

Laboratory aids. Prenatal diagnosis has been accomplished ultrasonographically (37a).

References [Popliteal pterygium syndrome (facio-genito-popliteal syndrome)]

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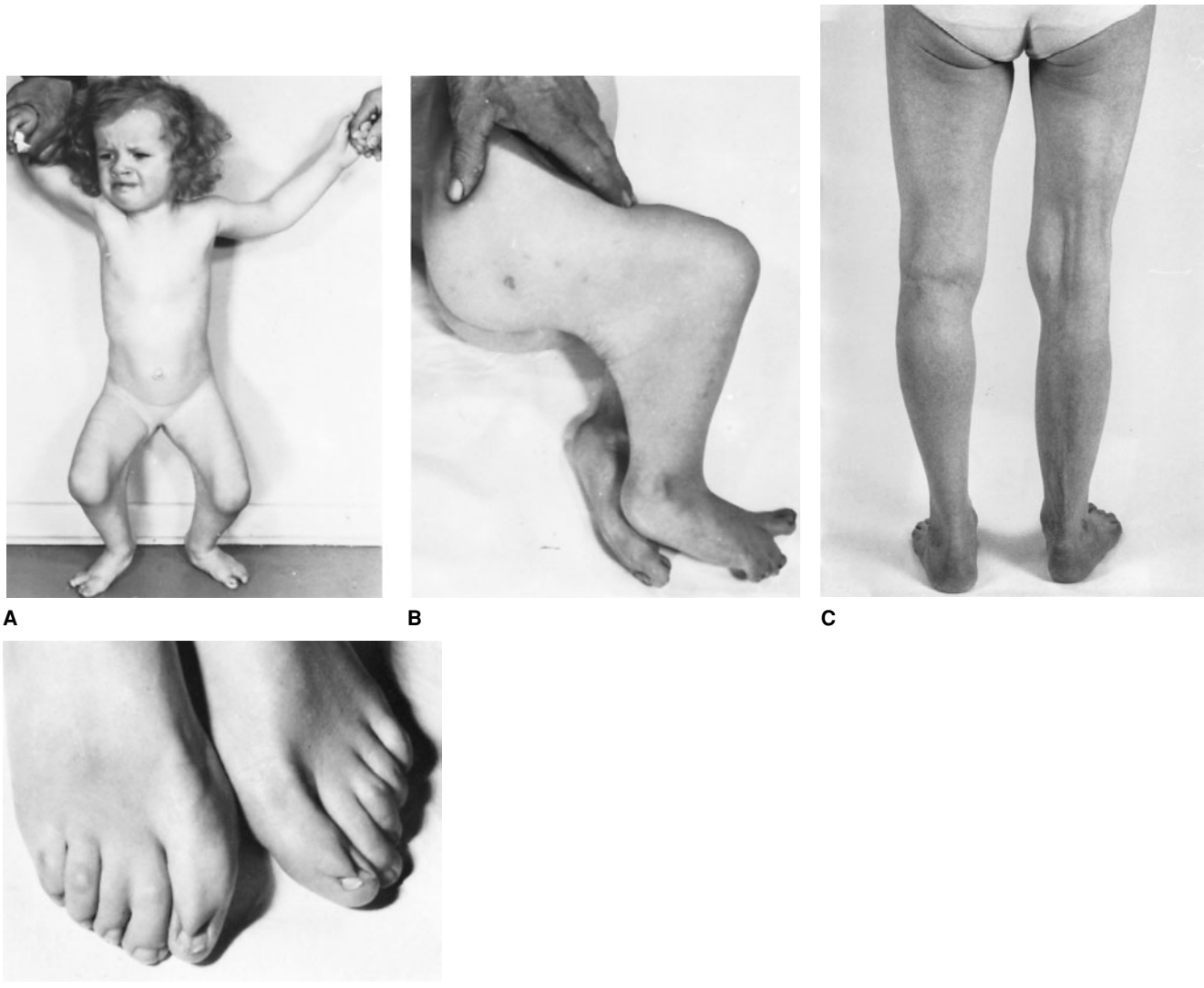
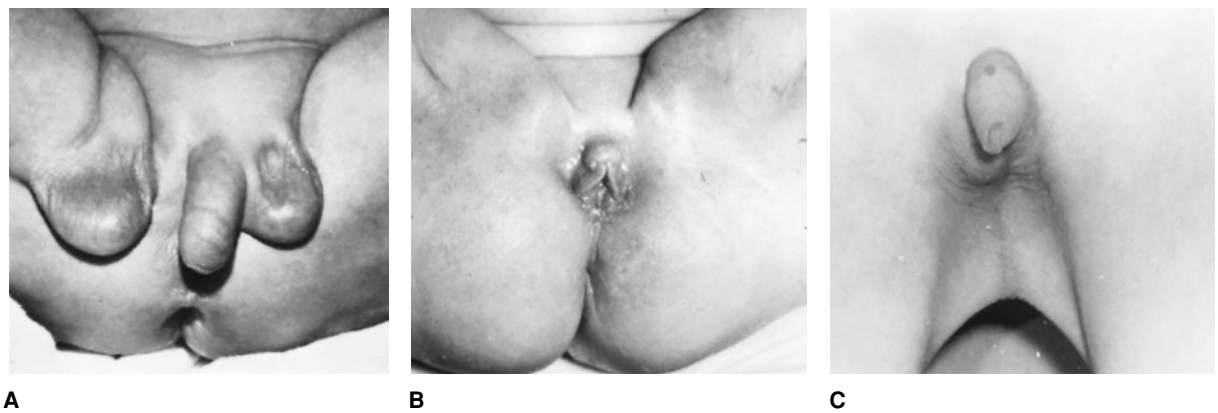
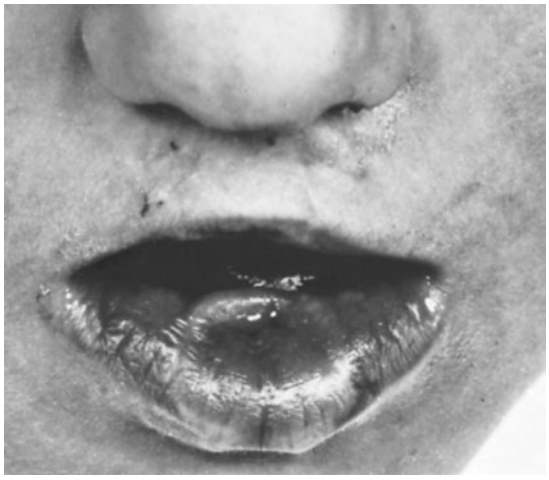


Fig. 18–13. *Popliteal pterygium syndrome*. (A) Child with repaired bilateral cleft lip-palate, bilateral popliteal pterygia, and hypoplasia of external genitalia. (B) Side view showing popliteal pterygium. Sciatic nerve is located in web under free margin. (C) Minimal popliteal pterygium on right. (D) Pyramidal skin folds extending to free edge of hallucal nails. (A,B from G Dahman, Z Orthopad 95:112, 1962. C from PHM Spauwen et al, J Craniomaxillofac Surg 22:276, 1994. D from D Klein, J Genet Hum 11: 65, 1962.)

Fig. 18–14. *Popliteal pterygium syndrome*. (A) Testicle displaced to upper right thigh. (B) Agenesis of labia major and enlarged clitoris. (C) Intercrural pterygium. (A from A Rintala and A Lahti, Scand Reconstr Surg 4:67, 1970.)





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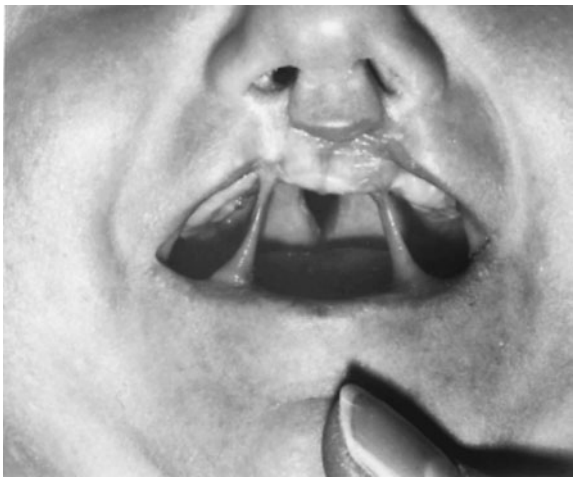

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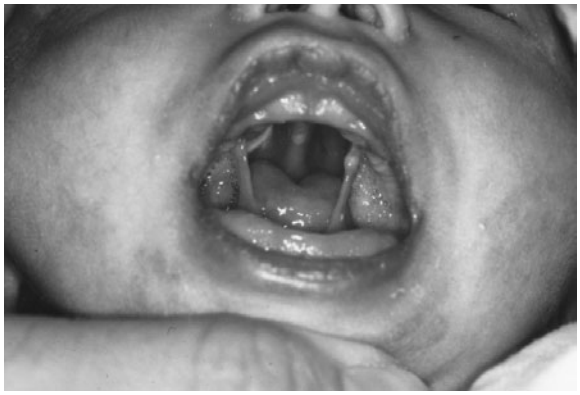

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Fig. 18–15. *Popliteal pterygium syndrome*. (A) Repaired bilateral cleft lip, lower lip pits. (B,C) Bilateral synechiae connecting upper and lower jaws. (A,B from A Rintala and A Lahti, Scand J Plast Reconstr Surg 4:67, 1970.)

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Bartsocas-Papas syndrome

Bartsocas and Papas, in 1972, reported four sibs with what they interpreted as a lethal syndrome of popliteal pterygium, bizarre facial clefts and other facial anomalies, and abnormalities of the extremities. Subsequently, approximately 15 additional examples have been reported (1–6,9–13). We cannot classify the patient reported by Marquardt (8). The patients reported by Hennekam et al (7) were atypical. A case may have been reported as early as 1600 (15).

Inheritance is clearly autosomal recessive with both parental consanguinity (1,1a,3,11,13) and multiple affected sibs (1,1a,3,5,6,9,13) having been documented. Nearly all have been of circum-Mediterranean origin (10).

Birthweight tends to be low. In one example, there was polyhydramnios (7). At least 9 of 13 documented children died within the first few days of life, although there have been a few examples that have lived for years (2,4,13). In one child who was reported at the age of 8 years, intelligence was normal (13).

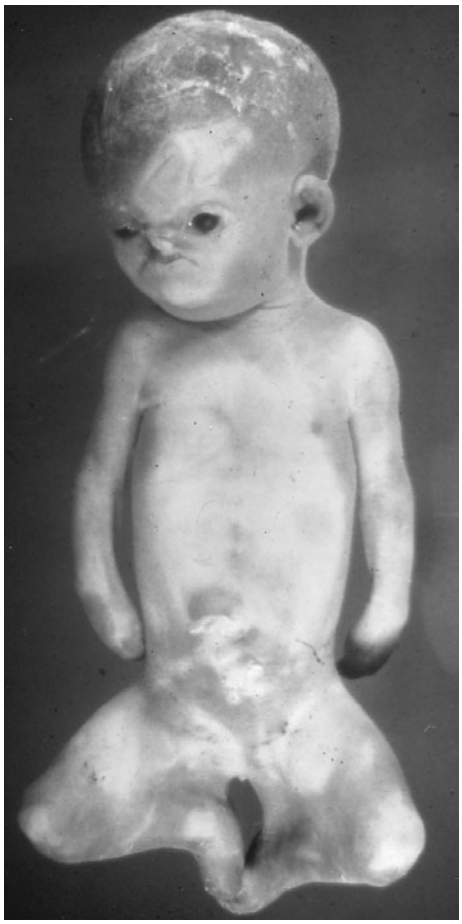
Craniofacies. The anterior fontanel may be wide (7). The scalp hair, eyebrows, and eyelashes are nearly always absent. Ankyloblepharon filiforme has been a constant finding. Corneal leukomas have been noted in approximately half the patients (1,1a,5,6,9,12). Most patients have upslanting palpebral fissures. Coloboma of the upper eyelids has been noted in at least one case (4). Most remarkable are the bizarre facial clefts that do not follow lines of fusion but extend into a cleft palate. The nasal tip is usually hypoplastic. Microphthalmia has been found in one patient (4). In an older patient, conical crown form was noted in the erupted incisor teeth (4). The maxilla is often hypoplastic. Variable soft tissue adhesions between the upper and lower jaws or between the upper and lower lip have been seen in the majority of patients (10a) (Fig. 18–16).

Extremities. Complete soft-tissue syndactyly of the fingers and toes with aplasia of the thumbs and absent nails is characteristic. Marked popliteal pterygia are a constant feature, much more severe than those seen in the autosomal dominant *popliteal pterygium syndrome* (Fig. 18–17). Talipes equinovarus is a virtually constant feature. Radiographically, there is agenesis of the first rays with symphalangism of digits 2–3 in the hands and 3–4 in feet, and agenesis of the fifth toes. There are reduced numbers of metacarpals and metatarsals, and in a few cases there have been rudimentary radius, ulna, and tibia.

Genitourinary findings. In females, there is aplasia of the labia majora and bicornuate uterus. Males exhibit hypoplastic penis, which is very often fused inferiorly with the scrotum.

Miscellaneous findings. Anomalies have included hypoplastic nipples, supernumerary nipples, anal atresia, absence of diaphragm, esophageal atresia, tracheo-esophageal fistula, and absent kidney (3,7).

Diagnosis. The findings are so characteristic that differentiation from other lethal popliteal pterygia syndromes is evident (5,6,11).



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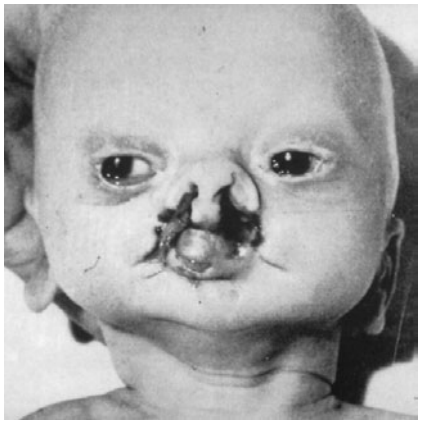

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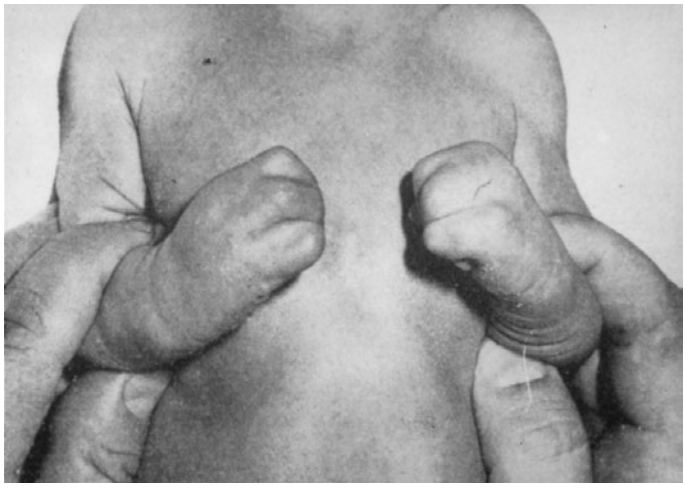
Fig. 18–16. *Bartsocas-Papas syndrome*. (A) Absence of digits, extensive popliteal pterygia. (B) Face showing ectropion, anteverted nostrils, multiple clefts that do not follow lines of embryologic fusion. (A from M Martinez-Frias et al, Am J Med Genet 39:34, 1991. B courtesy of C Bartsocas, Athens, Greece.)



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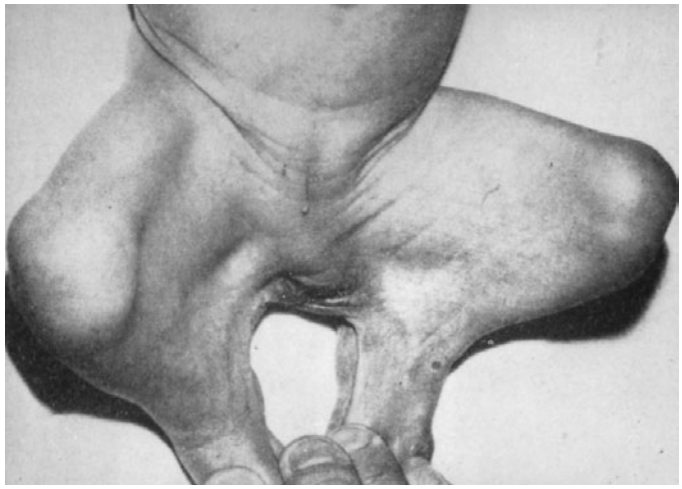

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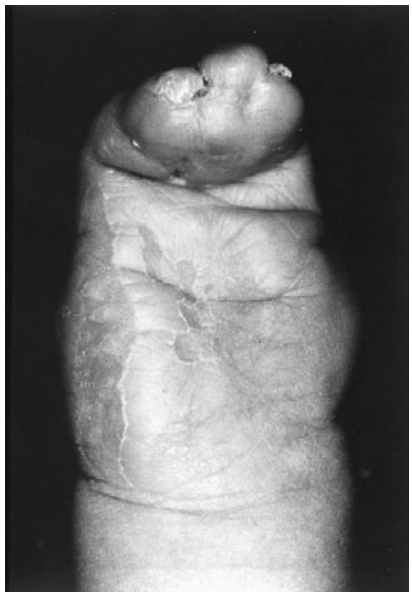

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Fig. 18–17. *Bartsocas-Papas syndrome*. (A) Note digital fusions. (B) Extensive popliteal pterygia. (C) Fused digital hand mass, absence of thumbs. (Courtesy of C Bartsocas, Athens, Greece.)

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Chondrodystrophic myotonia (Schwartz-Jampel syndrome, osteochondromuscular dystrophy)

In 1962, Schwartz and Jampel (37) described a syndrome characterized by growth retardation, osteochondrodysplasia, continuous muscle contracture at rest, and unusual facies. The same children were reported by Aberfeld et al (1,2). An earlier case is that of Catel (8). Approximately 90 examples have been subsequently reported.

The syndrome has autosomal recessive inheritance. Affected sibs (3,4,6,10,13,17,19,22,25,32,43) and parental consanguinity (3–6,19, 31,36,42) have been noted. The neonatal form is especially common in the United Arab Emirates (3,4). An affected father and son were reported (30), but this may have resulted from uniparental disomy (39). Electromyographic abnormalities have been found in parents of affected children (32,43). Identical twins have been reported (34). The gene *HSPG2* maps to 1p26–p34 (14-29). Mutations are found in perlecan, the major proteoglycan in basement membranes (30). However there appears to be genetic heterogeneity (7,18), type 1B not mapping to this area (vide infra).

Most examples present in late infancy (type 1A) (11,12). However, a considerable number become evident in the neonatal period (types 1B and 2) (1,7,11,16,20,22,35,38). The latter have feeding, choking, or respiratory difficulty within the first few weeks of life (3,4,7,16,22).

Facies. The facies, usually normal at birth, is usually clinically recognizable at 1–3 years of age (Fig. 18–18). It has been documented during the neonatal period (12). There is then progressive tonic contraction of facial muscles into a pinched or frozen smile with puckered or pursed lips and narrow palpebral fissures because of medial displacement of the outer canthi. Ptosis of eyelids, micrognathia, and short neck are evident.

Eyes. In addition to ptosis, blepharospasm, and blepharophimosis, myopia is noted in approximately 50%. In a few cases, congenital cataracts have been observed.

Musculoskeletal alterations. Height is reduced below the 10th centile (40). Limitation of motion at the hips is evident usually within the first 6 months of life but rarely is there prenatal onset (12). Gait becomes waddling and progressively difficult because of stiff hips and knees and crouched stance. The child fatigues easily (Fig. 18–18A). There is hyporeflexia. Obstructive sleep apnea has been noted (9).

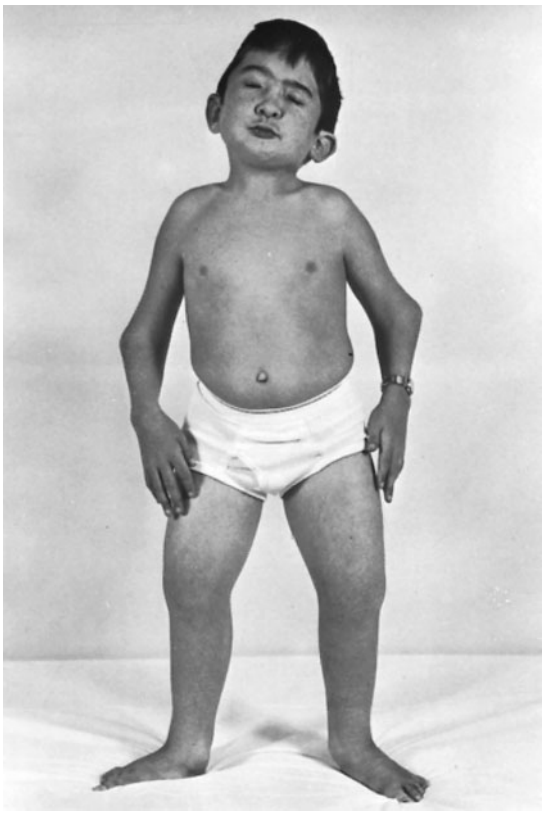
Skeletal changes (Table18–1) include pectus carinatum, kyphoscoliosis, lumbar lordosis, platyspondyly, iliac base shortening with acetabular hypoplasia, severe coxa vara, pes planus, and osteopenia, depending on the form of the syndrome (Fig. 18–19). The long bones may be bowed with metaphyseal widening with epiphyseal irregularity in type 2 (18,24,26,44). Occasionally cervical kyphosis may be marked.

Giedion et al (18), surveying 86 examples, concluded that there were three forms. Type 1A is the classic form. It is recognized in childhood and exhibits only mild bone dysplasia. Type 1B is evident at birth, radiographically resembles Kniest dysplasia, and has poor prognosis because of severe respiratory and feeding problems. Type 2 is also evident at birth but the femora resemble those in Pyle disease. As noted above, there is evidence that type 2 does not map to 1p36.1–p34. There is good evidence that type 2 is the same as Stüve-Wiedemann syndrome (10,41).

Choking on cold liquids and mild muscular hypertrophy have been described during early childhood in the early onset forms (2,25). Difficulty in intubation has been discussed (12,22,44). Weakness is not a prominent feature. Myotonia is a constant feature but Moodley and Moosa (28) noted a child who did not have myotonia. Repetitive contracture decreases the myotonia. There is continuous muscle fiber activity at rest. It has been suggested that the abnormal discharges originate in the muscle component of the neuromuscular junction rather than the nerve, perhaps in the sarcolemmal membrane (16,40). There is no true myotonia since the continuous repetitive discharges are abolished with curare (16). Malignant hyperthermia during anesthesia may result in death (38,44).

Other findings. High-pitched voice and moderate generalized hirsutism have been reported (1,3,25,32,33,43). Mental retardation has been observed in 25%. The myotonia may result in drooling and indistinct speech.

Oral manifestations. The lips are pursed, that is, the perioral muscles are contracted. The palate is highly arched.



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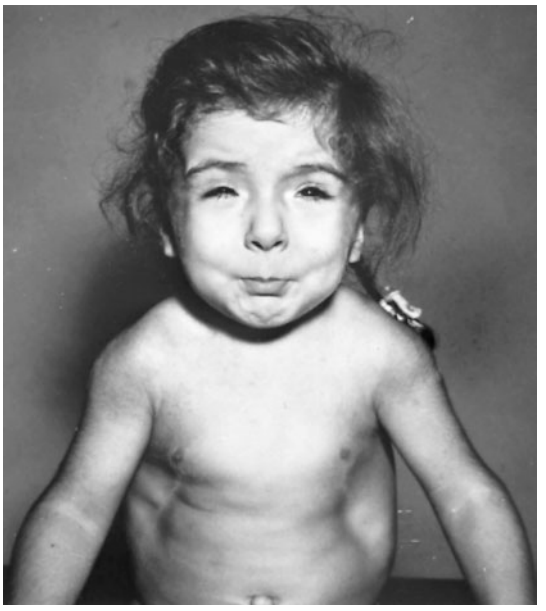

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Fig. 18–18. *Chondrodystrophic myotonia*. (A) Note puckered mouth, mildly narrowed palpebral fissures, flexion at hips, knees, and elbows. (B) Three-year-old female. Note blepharophimosis, rigid facial expression, pigeon-breast deformity with lateral chest constriction. (A from WM Fowler Jr et al, J Neurol Sci 22:127, 1974. B from O Schwartz and RS Jampel, Arch Ophthalmol 68:52, 1962.)

Differential diagnosis. The facies resembles to some degree that of *craniocarpotarsal dysplasia*. There is some overlap in phenotype with *Marden-Walker syndrome*. Continuous muscle contraction at rest can also be seen in Isaacs-Mertens syndrome, stiff-man syndrome, and other

Table 18–1. Schwartz-Jampel syndrome

	Type 1A	Type 1B	Type 2
Time of manifestation			
Myotonia	Early childhood	Infancy or childhood	Birth
Bone dysplasia	Childhood	Birth	Birth
Radiologic changes			
Long bones	Mild, epimetaphyseal dysplasia, enlarged epiphyses at knees	Short limbed dysplasia with "dumbbell" femora (Kniest-like), epiphyses enlarged at knees.	Short limbed dysplasia with bowed legs becomes Pyle-like in childhood, epiphyses flat at knees
Spine	Mild platyspondyly	Moderate platyspondyly, coronal clefts	—
Pelvis	Narrow sacrosciatic notch	Some flaring of iliac wings, supraacetabular notch	—
Typical examples	Kozlowski and Wise (24) Schwartz and Jampel (37) Aberfeld et al (1,2) Giedion et al (18, case 1)	Horan and Beighton (20) Giedion et al (18, cases 2,3) Hunziker et al (21)	Al-Gazali et al (3,4) Giedion et al (18, cases 4,5)

Modified from A Giedion et al, Eur J Pediatr 156:221, 1997.

disorders. Congenital myotonia may be seen in *myotonic dystrophy*, dominant and recessive myotonia congenita, paramyotonia congenita, and other disorders (2). An autosomal dominant disorder with expressionless facies, microstomia, blepharophimosis, short stature, and distal arthrogryposis has been reported. Hearing loss was noted as well as cleft palate (19).

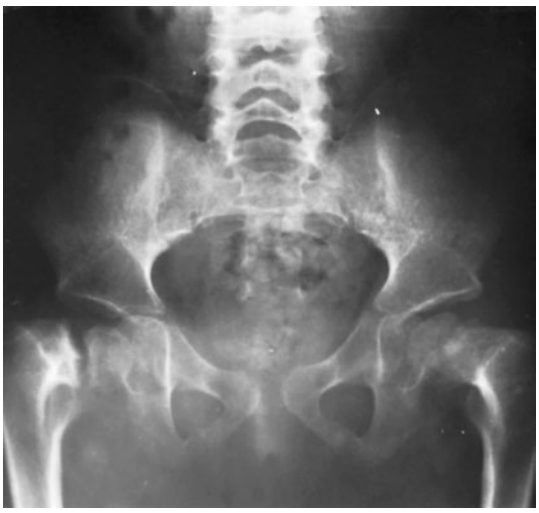
Spranger et al (40a) believe that *Burton disease, kyphomelic dysplasia*, and *micromelic chondrodysplasia* may be subsumed under Schwartz-Jampel syndrome.

Laboratory aids. Ultrastructural studies of muscle have shown inconsistent findings.

Standards for normal palpebral fissure size according to age have been established (15). Mollica et al (27) found reduced numbers of B and T cells. Ben Becher et al (5) and Kirschner et al (23) noted reduced IgA levels.

Prenatal diagnosis has been accomplished (21).

Fig. 18–19. *Chondrodystrophic myotonia*. Severe coxa vara. (From PR Huttenlocher et al, Pediatrics 44:945, 1969.)



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Marden-Walker syndrome

Marden and Walker (17), in 1966, first reported a syndrome of failure to thrive, mental retardation, microcephaly, immobility of facial muscles, absent Moro and decreased deep-tendon reflexes, blepharophimosis, strabismus, micrognathia, anteverted nostrils, pectus carinatum or excavatum, muscle weakness and reduced muscle mass, multiple congenital joint contractures, arachnodactyly, kyphoscoliosis, and transverse palmar creases. Subsequently, similarly affected children were reported (1,4,5,7,8,15,20,22,24,25). Approximately 30 examples have been described.

Inheritance is autosomal recessive as affected sibs and parental consanguinity are documented (3,11–13,16,21).

Facies. The face appears mobile with sagging cheeks. Blepharophimosis is a constant feature. Ptosis and exotropia-esotropia are present in approximately 70%. The nostrils are anteverted. The ears are low-set and malformed in 85% (Fig. 18–20).

Central nervous system. Microcephaly is noted in approximately 60% (13,17,22,25). Mental retardation is severe. Decreased deep tendon reflexes and hypotonia are common. Dandy-Walker cyst and/or hypoplasia of cerebellar vermis and hemispheres have been described in 35% (5,6,18). There is reduction in anterior horn cells (21).

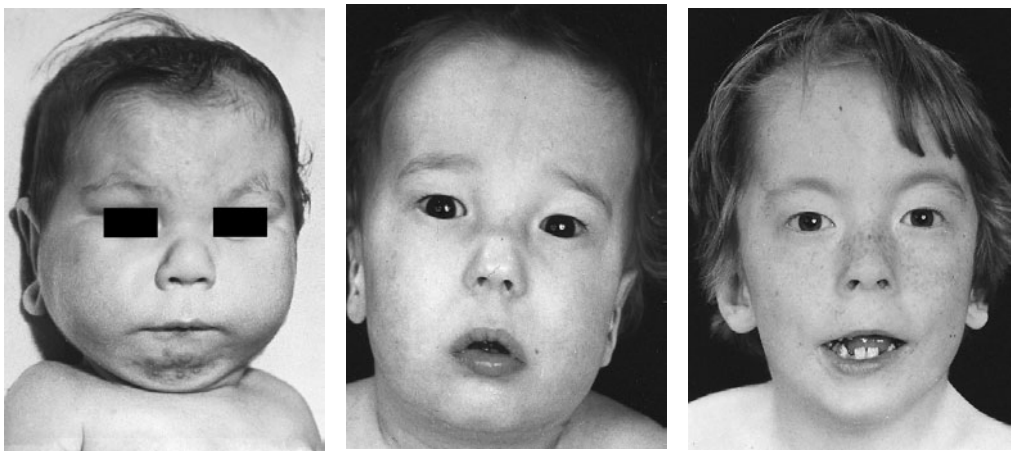
Musculoskeletal. Arachnodactyly (75%) (1,13,17,19,22), flexion contractures of the digits (65%) (13,17), talipes equinovarus (50%) (5,13,17,19), reduced muscle mass (100%) (5,13,17,19,22,25), contractures of the elbow, hip, and knee joints (95%), pectus excavatum and/or carinatum (60%) (13,19,25), and kyphoscoliosis (75%) (1,5,13,19,25) have been documented. The joint contractures tend to resolve during the first year of life. A single palmar crease has been found in 75%.

Heart anomalies. Various inconsistent congenital cardiac anomalies have been found (1,11,17,25).

Renal anomalies. Renal microcysts have been noted (2,17).

Oral manifestations. Cleft palate has been found in approximately 35% (1,3,14,17,19).

Differential diagnosis. There is some similarity to *Schwartz-Jampel syndrome*, but, in the Marden-Walker syndrome, failure to thrive, mental retardation, myopathy, and contractures are congenital rather than presenting at 1.5–2 years, and myotonia and generalized bone diseases are absent. An autosomal dominant disorder with expressionless face, microstomia, blepharophimosis, short stature, and distal arthrogryposis has been reported by Gripp et al (9). A *Marden-Walker-like syndrome* without psychomotor retardation with unusual facies and arachnodactyly, but



A B C

Fig. 18–20. *Marden-Walker syndrome*. (A) Blepharophimosis, short upturned nose, small mouth, micrognathia. (B,C) Facies of sibs. In addition to mental retardation, both had tall forehead, blepharophimosis, hypertelorism, and immobile facies. (A from JC Ramer et al, Am J Med Genet 45:285, 1993. B,C from F Howard and P Rowlandson, J Med Genet 18:50, 1981.)

without microcephaly, mental retardation, and hypotonia has been described (10,23). We view this syndrome as unrelated.

Laboratory aids. Fitch et al (5) found reduction in the size of scattered muscle fibers of both histochemical types. No percussion myotonia or myotonic discharges on the electromyogram were elicitable.

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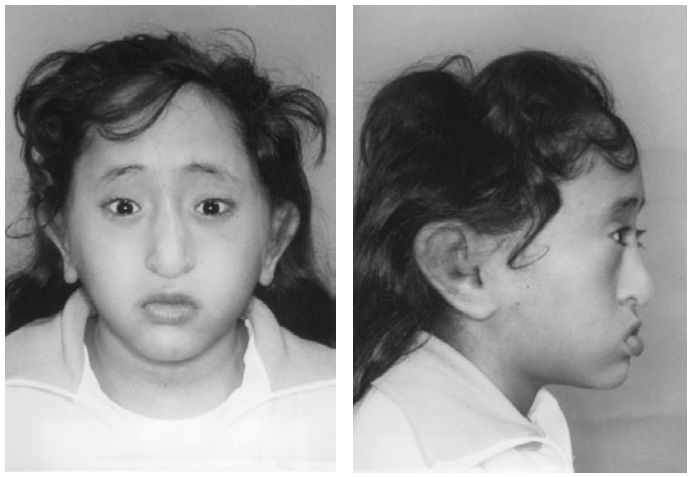
Marden-Walker-like syndrome without psychomotor retardation

Van den Ende et al (2) and Gupta et al (1) described children born to consanguineous couples. The unrelated children, one Brazilian, the other Pakistani, exhibited blepharophimosis, narrow beaked nose, hypoplastic maxilla, cleft palate or short palate, and everted lower lip (Figs. 18–21 and 18–22).

There is normal mentation and growth and development. Arachnodactyly and self-limiting joint contractures were noted.



A B

Fig. 18–21. *Marden-Walker-like syndrome without psychomotor retardation.* (A,B) Triangular-shaped face, malar hypoplasia, downslanting eyebrows, upslanting palpebral fissures, blepharophimosis, narrow beaked nose, everted lower lip, and cleft palate. (A,B from JJ van den Ende, Am J Med Genet 42:467, 1992.)

References (Marden-Walker-like syndrome without psychomotor retardation)

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2. Van den Ende JJ et al: A Marden-Walker-like syndrome without psychomotor retardation: Report of a Brazilian girl born to consanguineous parents. Am J Med Genet 42:467–469, 1992.

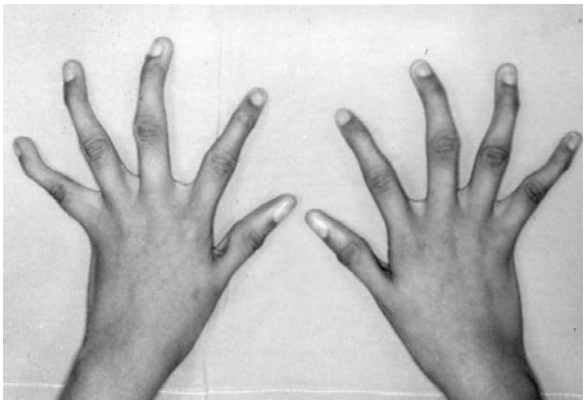
Craniocarpotarsal dysplasia (whistling face syndrome, Freeman-Sheldon syndrome, windmill vane hand syndrome)

In 1938, Freeman and Sheldon (14) described a syndrome characterized by microstomia, flat midface, talipes equinovarus, and ulnar deviation of the fingers. Unaware of this report, Burian (6), in 1963, described the same complex, utilizing the term "whistling face syndrome." Hall et al (18) and Bamshad et al (5) consider it to be a form of distal arthrogryposis most closely related to distal arthrogryposis, type 1. The disorder has also been suggested to be one of congenital myopathy (40). Confusion has been experienced in a large family regarding classification (27). A number of authors have tabulated and analyzed cases (2,4,10,29,33,41,48,54). Over 75 patients have been reported (2,33,36,37).

Although most cases have been sporadic, there are numerous examples of the disorder in two or more generations (2,4,10,12,15,18,25, 31–33,37,39,40,42,46,52,55). The condition has also been described in sibs with normal, in some cases, consanguineous parents (3,11,13,23, 28,35,43,53). Hashemi (20) found parental consanguinity in an isolated example. This suggests genetic heterogeneity but separation of phenotypes has not been possible with the exception of a milder variant (29,30) that has been mapped to 11p15.5–pter (vide infra). Sauk et al (44) pointed out the possible depiction of the condition in a pre-Columbian vase.

Facies. The stiff immobile, flat midface, full cheeks, small nose, long philtrum, puckered mouth, and H-shaped defect on the chin are striking but extremely variable features. Microstomia and long philtrum are constant, but such features as small nose with broad bridge, pronounced supraorbital ridges, deep-set eyes, micrognathia, and short broad neck are less frequent. The typical facies is present in only approximately 50% (4,12) (Figs. 18–23 and 18–24).

Eyes. Strabismus, epicanthus, and hypertelorism have been noted in over 60% (4,8,17,19,33,35,37,42). Approximately half of the



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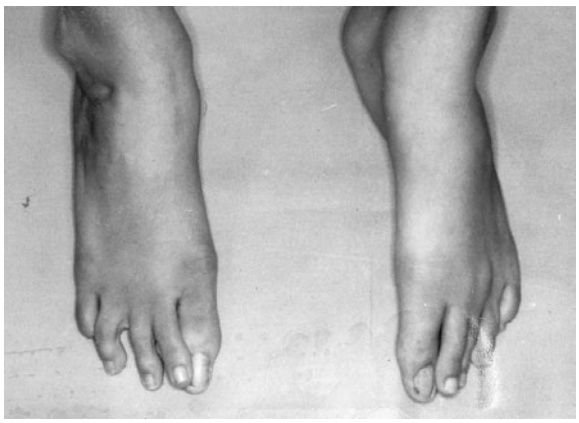

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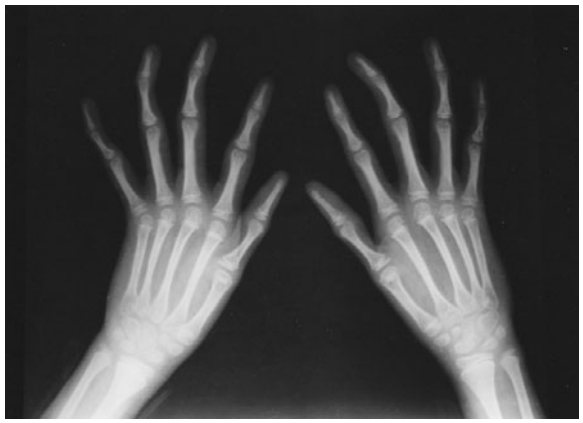

C

Fig. 18–22. *Marden-Walker-like syndrome with normal intelligence*. (A,B) Long fingers and toes, clinodactyly, and mild camptodactyly. (C) Slender metacarpals and phalanges. (From JJ van den Ende et al, Am J Med Genet 42:467, 1992.)

patients have exhibited downslanting palpebral fissures and ptosis (9,46,54) (Fig. 18–23B).

Nose. The nose is usually small. The nostrils are narrow, the alae being bent in approximately half the cases, simulating nostril colobomas. Near the tip, the alae are of normal thickness, but they thin dorsally to be inserted close to the columella. The nasolabial folds are evident only near the sides of the nose. The philtrum is long (Fig. 18–23).

Musculoskeletal system. Growth has been retarded below the third centile in approximately 30% of the cases (18). There is ulnar deviation of the fingers without bony abnormalities. Flexion contractures of the fingers are a common feature, the thumbs being adducted at the metacarpophalangeal joints. It should be emphasized, however, that the hands may be normal (38,47,51), and may improve with age (32).

Talipes equinovarus, occasionally unilateral, has been found in approximately 80% (Fig. 18–23). Moderate to severe kyphoscoliosis has been documented in approximately 60% (21). Frequently there is atrophy of the forearm and leg muscles, especially below the knees (6,39,40,45,52,54) (Fig. 18–23). Other less frequent anomalies include spina bifida occulta (45,49,54,55) and inguinal hernia (6,13,14,35,42).

The facial skeleton is small. The anteroposterior lengths of both base and cranium are short whereas facial height is relatively great. Most patients have exhibited a steep cranial base (42,54). In a few, the ribs have been broad and tapering near the costovertebral angle (38).

Other joints have occasionally shown limitations. Hall et al (18) found approximately 15% had limited movement at the hips and 5% at the elbow. Dislocation of the radial heads has been noted (13). Pterygia of the neck (31,54) or axillae (13) have also been described.

Other findings. A few children have suffered aspiration pneumonia or respiratory death (42), and a few were mentally retarded (4,13,42). A few experienced muscle rigidity following halothane anesthesia (24).

Oral manifestations. Microstomia may be marked, the intercommissural distance being approximately 65% of that for a child of the same age (9). The lips are pursed or held as in whistling in approximately half the cases. The hard palate is often highly arched and the mandible and tongue tend to be small. Frequently there is nasal speech. Rarely, there is cleft palate (32). Extending from the middle of the lower lip to the chin is a fibrous band or elevation that is demarcated by two paramedian grooves forming an H- or V-shaped scar-like structure in approximately 30%.

Differential diagnosis. Krakowiak et al (29) reported a large family in which 21 individuals in 5 generations exhibited a variant of Freeman-Sheldon syndrome: triangular facies, downslanting palpebral fissures, attached earlobes, prominent nasolabial folds, small mouth, and micrognathia. In addition, there were short stature, marked camptodactyly with ulnar deviation, and calcaneovalgus. Features that distinguished this variant from classic findings included feeding difficulties during early infancy and a different shaped mouth and chin. Chin grooves were not present. There was resemblance to the cases of Kawira and Bender (26), Moore and Weaver (34), and case 2 of Freeman and Sheldon (14). It was the variant that was mapped to 11p15.5. Differential diagnosis includes arthrogryposis, *Schwartz-Jampel syndrome*, and *Burton syndrome*. The Burton syndrome is an autosomal recessive condition characterized by microstomia, pursed lips, ectopia lentis, and skeletal changes similar to those of *Kniest syndrome* and *dyssegmental dysplasia, Rolland-Desbuquois type*. However, no coronal clefts were noted. Scattered dense patches of extremely broad collagen fibers were found scattered throughout the cartilage matrix (7). We believe the constellation of anomalies seen here is sufficiently characteristic to cause little confusion with other entities. It should be pointed out that ulnar deviation of the fingers (windmill fingers) may have autosomal dominant inheritance (1,16,24,30). However, it is possible that windmill fingers are the same as craniocarpotarsal dysplasia in which craniofacial expression has been minimal. A severe form of Freeman-Sheldon syndrome has been described with brain anomalies and sensorineural hearing loss (22,56). This is probably the same as *cleft palate, whistling face, distal arthrogryposis and mental retardation*.

Laboratory aids. Electromyography has shown hypoplasia of the musculature of the buccinator and some of the hand and foot muscles (6,18,44,45). Biopsy of the buccinator muscle has shown fibrous connective tissue replacement of muscle bundles (44,49).

References [Craniocarpotarsal dysplasia (whistling face syndrome, Freeman-Sheldon syndrome, windmill vane hand syndrome)]

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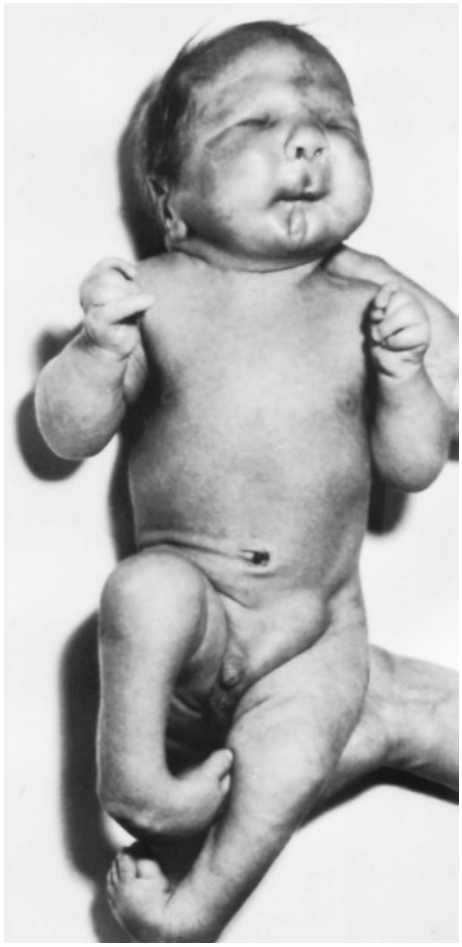

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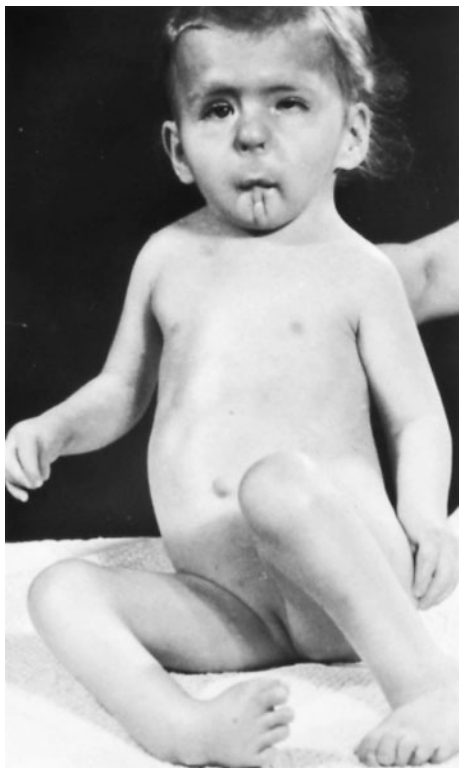

B

Fig. 18–23. *Craniocarpotarsal dysplasia*. (A) Sunken eyes, chin grooves, overlapping fingers, talipes equinovarus, and inguinal hernia. (B) Deep-set eyes, lid ptosis, convergent strabismus, H-shaped chin grooves, overlapping fingers, and talipes. (A from AE Rintala, Acta Paediatr Scand 57:553, 1968. B courtesy of J Külz, Rostock, East Germany.)

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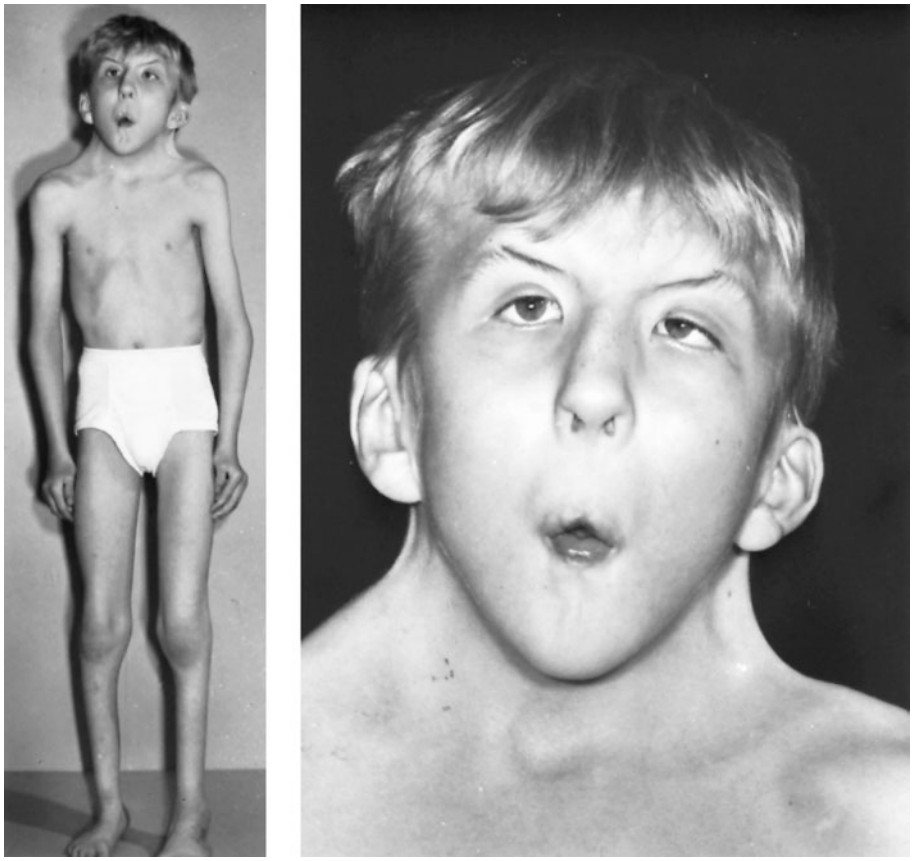

A B

Fig. 18–24. *Craniocarpotarsal dysplasia*. (A,B) Whistling facies is produced by small puckered mouth. Note pterygium colli and notched nostrils.

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Trismus-pseudocampylodactyly syndrome (Hecht-Beals syndrome)

The syndrome of limited oral opening and curvature of the fingers at all interphalangeal joints on dorsiflexion of the wrists (pseudocampylodactyly) because of shortened flexor muscle-tendon units was described independently in 1969 by Hecht and Beals (6) and by Wilson et al (22). The family originated in the Netherlands (2,10,17,21). The disorder has autosomal dominant inheritance with variable expressivity (1,2,6–8,13,14,17–19,22,23). Hall et al (5) classified the disorder as a form of distal arthrogryposis. Linkage studies (14) done on the family reported by Yamashita and Arnet (23) were not fruitful.

The patients are normally proportioned, but stature is often reduced to between the 3rd and 25th centiles (3).

Facies. De Jong (2), Mercuri (12), and Fukumori et al (3) described blepharochalasis in older individuals, and a quilted appearance of the cheeks (Fig. 18–25).

Musculoskeletal alterations. In addition to mildly reduced stature and limited oral opening, the distinguishing features of the syndrome are limited to abnormalities of the extremities that result from shortness of various skeletal muscles or flexor tendons.

The hands may be clenched at birth but loosen during infancy and childhood (21). On dorsiflexion of the wrist, because of shortening of the

Fig. 18–25. *Trismus-pseudocampylodactyly syndrome*. Kindred of affected father and several affected and normal children showing attempt to open mouth fully. [From *F Hecht* and *RK Beals*, Birth Defects 5(3):96, 1969.)

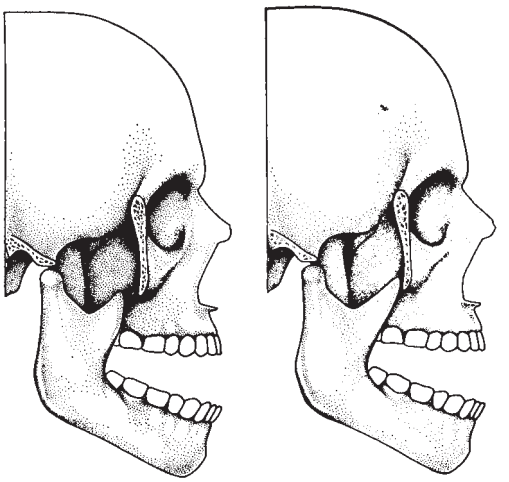


Fig. 18–27. *Trismus-pseudocampylodactyly syndrome*. Left, normal relationship. Right, enlarged coronoid process that prevents normal opening of jaws. (Courtesy of *RF Van Hoof*, Leiden, The Netherlands.)

flexor tendon-muscle unit, curvature of all fingers at each interphalangeal joint is noted. Upon volar flexion, all fingers are completely extended (Fig. 18–26). There is no associated muscular weakness, but there is mild limitation of dorsiflexion and supination at the wrist.

Leg or foot problems are found in at least 10%. Short leg muscles result in a variety of mild foot deformities: talipes equinovarus or calcaneovalgus, metatarsus varus, etc. Shortened hamstring muscles produce pelvic tilt with straight leg raising (16). Pes planus, hammer toes, and torticollis have also been noted (8,22).

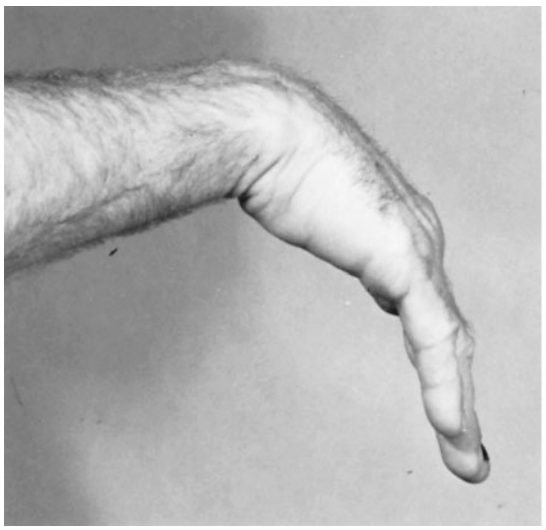
Oral manifestations. The maximum aperture between the incisal edges of the upper and lower incisors ranges from 3 to 13 mm. This inhibits mastication, an affected individual requiring approximately twice as much time to consume a meal. Some infants cannot use a conventional nipple to feed. There may be difficulty with endotracheal intubation during general anesthesia.

The temporomandibular joints have been shown to be normal (8). The coronoid processes may be enlarged or distorted, unilaterally or bilaterally, and are often responsible for the inability to open the mouth widely because of their impingement on the zygomatic bones (Fig. 18–27). Fibrous bands extend from the maxilla to the mandible in the retromolar areas. The decreased opening may be secondary to shortening of the muscles of mastication, which in turn causes elongation of the coronoid processes (17). A hardened nodular cord has been noted in the region of the nasolabial furrow. Some patients have micrognathia (17).

Differential diagnosis. Inability to open the mouth must be differentiated from microstomia seen in a variety of disorders [*craniocarpotarsal dysplasia, chondrodystrophic myotonia* (*Schwartz-Jampel syndrome*), etc.]. Abnormalities, either congenital or acquired, of the temporomandibular joint may result in reduced jaw opening. Patients with the temporomandibular joint dysfunction syndrome cannot open their mouths widely, but this disorder can easily be differentiated from the syndrome under discussion.

Hall et al (4) reported a dominantly inherited disorder of small mouth with limited opening, outstanding pinnae, and flexion contractures of the hands.

Fig. 18–26. *Trismus-pseudocampylodactyly syndrome*. (A) On volar flexion, all fingers can be completely extended. (B) On dorsiflexion of wrist, there is flexion of fingers at interphalangeal joints. [From *F Hecht* and *RK Beals*, Birth Defects 5(3):96, 1969.]



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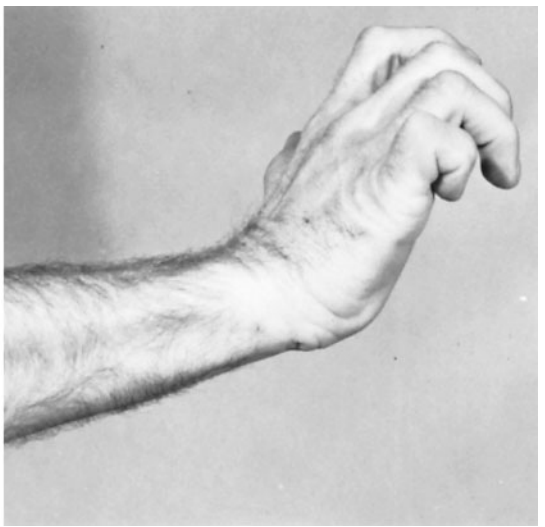

B

Laboratory aids. Average opening between edges of incisor teeth is 49 mm (range 30–70 mm) in normal adults. From 8 to 12 years of age, the normal vertical distance is approximately 40 mm (range 25–55 mm) (6,9–11). This has also been our experience, but not that of Sheppard and Sheppard (15).

References [Trismus-pseudocampylodactyly syndrome (Hecht-Beals syndrome)]

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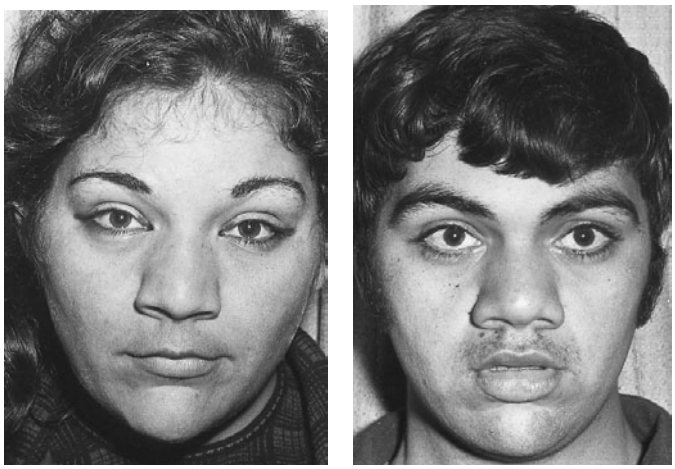
Unusual facies, camptodactyly with fibrous tissue hyperplasia, knuckle pads, and skeletal dysplasia

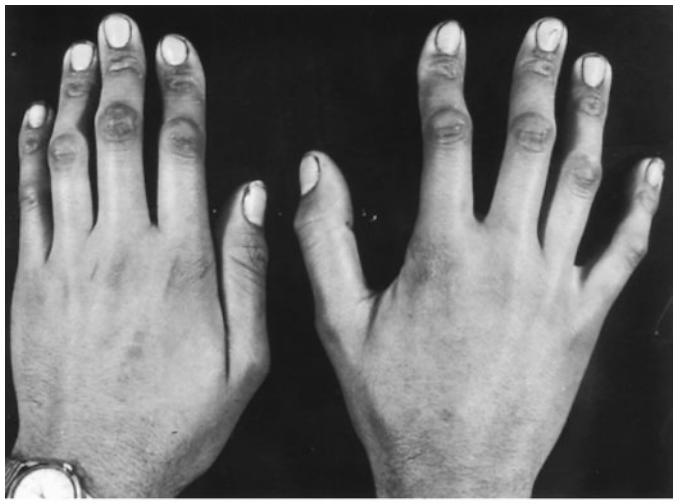
Goodman et al (1) described a consanguineous kindred of Jewish Iranian ancestry. Three sibs, two female and one male, manifested a broad nose with flared nostrils (Fig. 18–28). The hands and feet were especially large for stature. All digits of the hand except the thumbs were camptodactylous, the onset of which began around 10 years. Knuckle pads were noted on the second, third, and fourth fingers bilaterally (Fig. 18–29).



A B

Fig. 18–28. *Unusual facies, camptodactyly with fibrous tissue hyperplasia, knuckle pads, and skeletal dysplasia*. Note similar broad nose with round nostrils in sibs.

Fig. 18–29. *Unusual facies, camptodactyly with fibrous tissue hyperplasia, knuckle pads, and skeletal dysplasia*. Note camptodactyly and knuckle pads. (From *R Goodman et al*, J Med Genet 9:203, 1972.)



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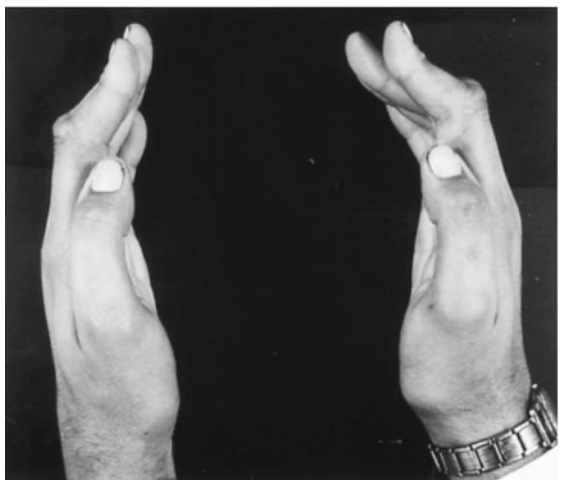

B

Hammertoes were bilateral. All had mild thoracic scoliosis. Each presented dull expression with low normal intelligence. Inheritance appears to be autosomal recessive.

Knuckle pads may be an isolated finding, associated with Dupuytren contractures, camptodactyly (3), or hypodontia.

Knuckle pads, leukonychia, hearing loss, and palmoplantar hyperkeratosis is known as Bart-Pumphrey syndrome (2). A dominant digitotalar dysmorphism has similar camptodactyly and rocker bottom feet (4).

References (Unusual facies, camptodactyly with fibrous tissue hyperplasia, knuckle pads, and skeletal dysplasia)

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Chapter 19
Branchial Arch and Oral-Acral Disorders

Oculo-auriculo-vertebral spectrum (hemifacial microsomia, Goldenhar syndrome)

In the 1960s, hemifacial microsomia was defined as a condition affecting primarily aural, oral, and mandibular development. The disorder varies from mild to severe, and involvement is limited to one side in many cases, but bilateral involvement is also known to occur, with more severe expression on one side. Goldenhar syndrome is considered a variant of this complex, characterized additionally by vertebral anomalies and epibulbar dermoids (55). The condition is now known to be extremely complex and heterogeneous. Thus, in the present edition we have employed the term oculo-auriculo-vertebral (OAV) spectrum.

The first recorded cases may have been those of Canton (21), in 1861, and von Arlt, in 1881 (6). An excellent early review is that of Geissmar (47). There are numerous important reviews in modern times (5,9,13, 20,26,27,42,57,88,91,100,126–128,143).

The many terms used for this complex indicate the wide spectrum of anomalies described and emphasized by various authors. The complex has been known as hemifacial microsomia, oculo-auriculo-vertebral dysplasia, facio-auriculo-vertebral dysplasia, Goldenhar syndrome, Goldenhar-Gorlin syndrome, first arch syndrome, first and second branchial arch syndrome, lateral facial dysplasia, unilateral craniofacial microsomia, otomandibular dysostosis, unilateral mandibulofacial dysostosis, unilateral intrauterine facial necrosis, auriculo-branchiogenic dysplasia, and facio-auriculo-vertebral malformation complex (73). These terms have been reviewed elsewhere (27). Systems of classification, OMENS-plus and others, have been advocated by Horgan et al (70), Vento et al (164), and Cousley (31).

Although there are no agreed upon minimal diagnostic criteria, the facial phenotype is characteristic when enough manifestations are present. In some instances, isolated microtia or auricular or preauricular abnormality may represent the mildest manifestation (12,57,90,128,155). Unilateral microtia or ear abnormality, including preauricular tags, has been suggested as a mandatory feature by some authors (128). Involvement is not limited to facial structures; cardiac, renal, skeletal, and other anomalies may also occur. In particular, the so-called "expanded Goldenhar complex" has demonstrated a wide spectrum of central nervous system malformations not previously appreciated (2–5,111,165). It has been suggested by several authors that invalid nosologic splitting, on the one hand, and inappropriate lumping on the other, complicate our understanding of this complex (26,27,68,105,110,156). Those with the Goldenhar end of the spectrum constitute only approximately 10% of the cases (128).

Poswillo (118) suggested a frequency of 1/3500 births, although he presented no data to support his conjecture. Grabb (57) estimated 1/5600 births. Stoll (147) noted a prevalence of 1/19,500 consecutive births. Melnick (91) recorded a frequency of 1/26,550 live births in a prospective newborn study. Our impression is that the true frequency is near that offered by Grabb (57). The male:female ratio is at least 3:2 (127,165); there is also a 3:2 predilection for right-sided ear involvement (25,127).

Poswillo (117–119), using an animal model, showed that early vascular disruption with expanding hematoma formation *in utero* resulted in destruction of differentiating tissues in the region of the ear and jaw. The severity appeared to be related to the degree of local destruction. Other theories involve disturbances in branchial arches or in various populations of neural crest cells that impede development of adjacent medial or frontonasal processes. The constellation of anomalies suggests their origin at approximately 30–45 days of gestation. This has been confirmed in humans by demonstration of disruption of vascular supply (55,124,146). Disturbance in chondrogenesis has also been espoused as a theory (32,54). A common pathway for CHARGE association and OAV spectrum has been suggested (163).

First and second branchial arch anomalies often combined with facial palsy have been observed in infants born to pregnant women exposed to thalidomide (95,130), primidone (63), and retinoic acid (83). The OAV phenotype has also been noted in infants with *diabetic embryopathy* (59). A transgenic mouse model has been created (104).

Several chromosomal anomalies have been associated including del(5p) (82,105), del(6q) (58), trisomy 7 mosaicism (69), del(8q) (161), trisomy 9 mosaicism (166), trisomy 18 (14,58), recombinant chromosome 18 (149), del(18q) (33), ring 21 chromosome (58), del(22q) (67), dup(22q) (65), trisomy 22 (78), 49,XXXXX (140), 49,XXXXY (81), and 47,XXY (116).

Discordance in monozygotic twins has been reported frequently (16,17,22,29,30,37,53,57,107,112,128,142,147). Rarely, concordance with variable expression including mirror imaging has been documented in monozygotic twins (126,133,138,156). Discordance has been reported in dizygotic twins (57,65,121,144), in twins of undetermined zygosity (15,52,108), and in triplets (154). The rarity of reports of concordance of the defect in twins supports the suggestion that the condition is sporadic in most families. The interested reader is referred to the excellent analysis of Burck (20).

Most cases are sporadic, but familial instances may also be observed. Within families, expression varies. For example, there are reports of ear and mandibular involvement in two first-degree relatives, and reports of isolated microtia or preauricular tags in one first-degree relative of a patient with ear and mandibular involvement (128). These reports support the suggestion that isolated microtia or preauricular tags may represent the mildest expression in some families (57,90,127,128,155). Affected individuals in successive generations have been observed (26,57,68,98,109,121,123,129,142,150,154,157). Affected sibs with normal parents have also been reported (57,77,79,136). Consanguinity was noted in a single sporadic instance (110). Although autosomal dominant and autosomal recessive inheritance have been suggested to explain the rare familial occurrence, etiologic heterogeneity is a more likely explanation for most cases. Using segregation analysis, Kaye et al (76) opted for autosomal dominant inheritance. Overall, it would be compatible with a low empiric recurrence risk of 2%–3% (57,128), and the usual discordance and rare concordance (13%) between monozygotic twins (171). Some families (50,68,121,148,150), probably representing 1%–2% of the cases, clearly manifest an autosomal dominant form with variable penetrance. Involvement tends to be bilateral, but without eye or vertebral involvement. D Kelberman (personal communication, 2000) indicated that the gene maps to 14q32 (76a). RJ Gorlin (2001) documented a large family that does not map to 14q32.

A branchial arch anomaly should be regarded as a nonspecific symptom complex that is etiologically and pathogenetically heterogeneous. Evaluation of first-degree relatives is important to exclude mild facial manifestations of the defect and various extracranial anomalies. Recurrence risk counseling should be provided on an individual family basis.

Extreme variability of expression is characteristic (Figs. 19–1 to 19–3). Approximately 50% have been noted to have other anomalies in addition

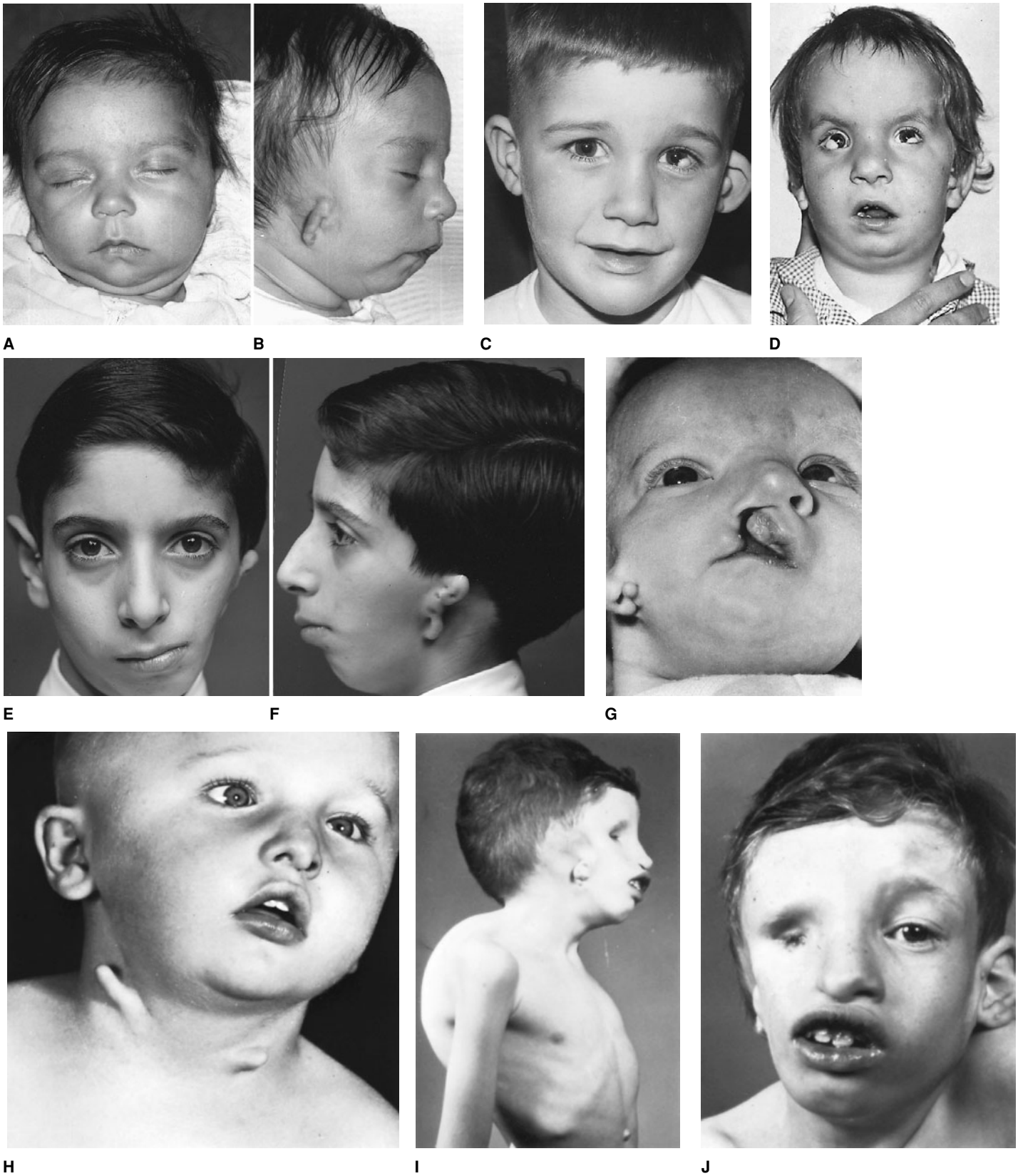
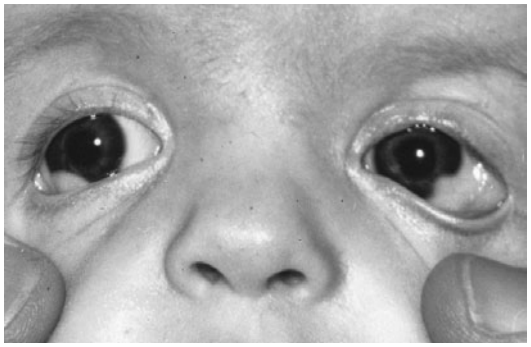


Fig. 19–1. *Oculo-auriculo-vertebral spectrum*. (A–J) Variable degrees of severity. Compare facies. Note cleft lip-palate, ear anomalies, and epibulbar dermoid in G. Note unusual cervical structures containing cartilage, epibulbar dermoids and strabismus in H. Note bilateral epibulbar dermoids in D. Note anophthalmia in I and J. (A,B from MM Cohen Jr, The Child with Multiple Birth Defects, Raven Press, New York, 1982. C courtesy of M Lejour, Brussels, Belgium. E,F courtesy of WC Grabb, Ann Arbor, Michigan. G courtesy of of BGA ter Haar, Nijmegen, The Netherlands. H courtesy of S Budden, Vancouver, British Columbia. I,J from CH Ide et al, Arch Ophthalmol 84:427, 1970.)



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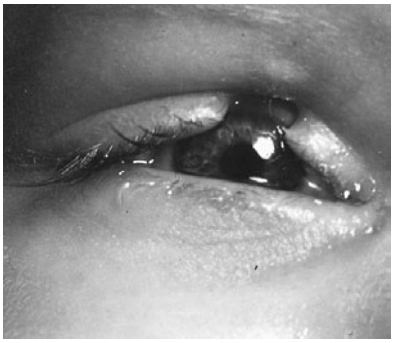

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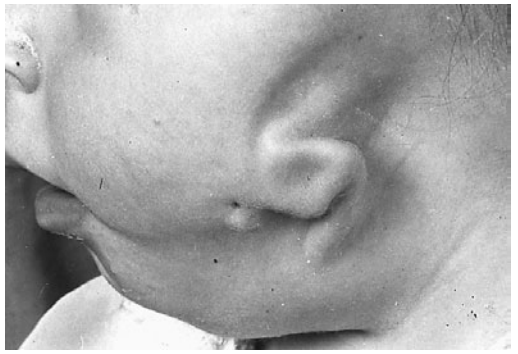

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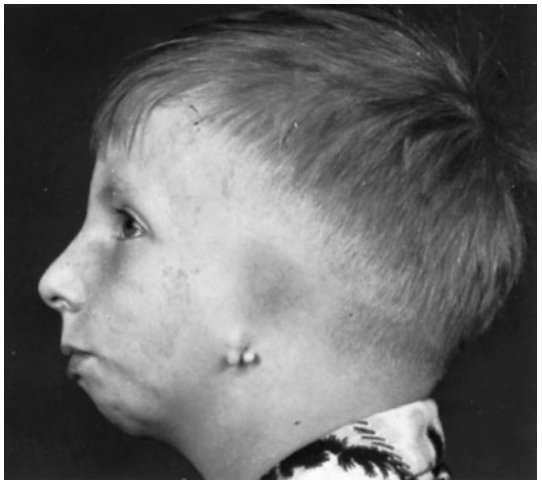

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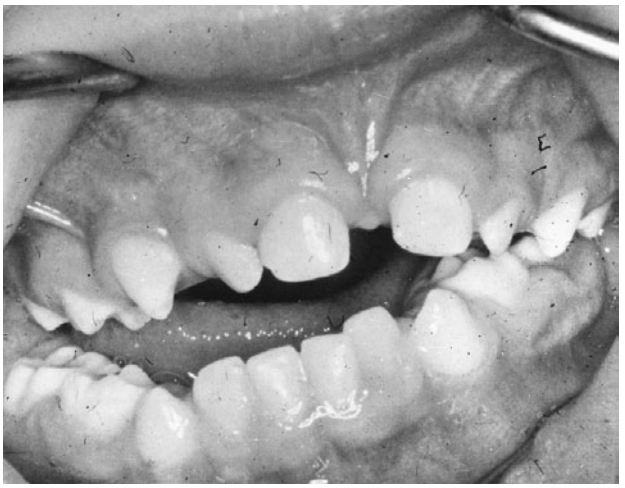

E

Fig. 19–2. *Oculo-auriculo-vertebral-spectrum*. Closeups. (A) Bilateral epibulbar dermoids. (B) Coloboma of upper eyelid. (C,D) Variable degrees of ear involvement. (E) Malocclusion. (D from WC Grabb, Plast Reconstr Surg 36:485, 1965.)

to the principal features of the defect (127). Not uncommonly the infants are small for their ages and may have feeding difficulties that may be related to cleft lip and/or cleft palate or an anatomically narrow pharyngeal airway. Obstructive sleep apnea diagnosed by all-night polysomnography and nasopharyngoscopy has been described (144). Scrupulous medical and nursing care in the first few weeks can often prevent the need for surgical gastrostomy (143).

Facies. Marked facial asymmetry is present in 20% but some degree of asymmetry is evident in 65% (146). This is because of both displacement and/or abnormality of the pinna and also to underlying abnormalities of skeletal support. The asymmetry may not be apparent in the infant or young child but can surface with growth, usually becoming apparent by age four. Adequate overlying soft tissues may mask the skeletal asymmetry (Fig. 19–1). Conversely, a deficient soft tissue mass overlying adequate bony structures may result in facial asymmetry (42). The exact relationship between bone and muscles of mastication is still hotly debated (163a).

The maxillary, temporal, and malar bones on the more severely involved side are somewhat reduced in size and flattened (131). Asymmetry may result from aplasia or hypoplasia of the mandibular ramus and condyle. Some patients manifest mild pneumatization of the mastoid region. Approximately 10%–33% of patients have bilateral involvement (22,57,127). The disorder is nearly always more severe on one side. Among 193 unilaterally affected patients studied by Rollnick et al (127), the right side was involved in over 60%. Frontal bossing can be noticeable at birth but becomes less apparent with time (55). The reader is referred to various anthropometric studies (39,40,74,145).

Eye. Blepharoptosis or narrowing of the palpebral fissure occurs on the affected side in approximately 10%. Unilateral palpebral shortening was noted in 6 of 57 patients studied by Mansour et al (88). Elevated orbit is seen in 7% (106). Clinical anophthalmia or microphthalmia has been described in several patients who also manifested severe mental retardation (2,9,25,26,89,143,165). Various retinal abnormalities have been

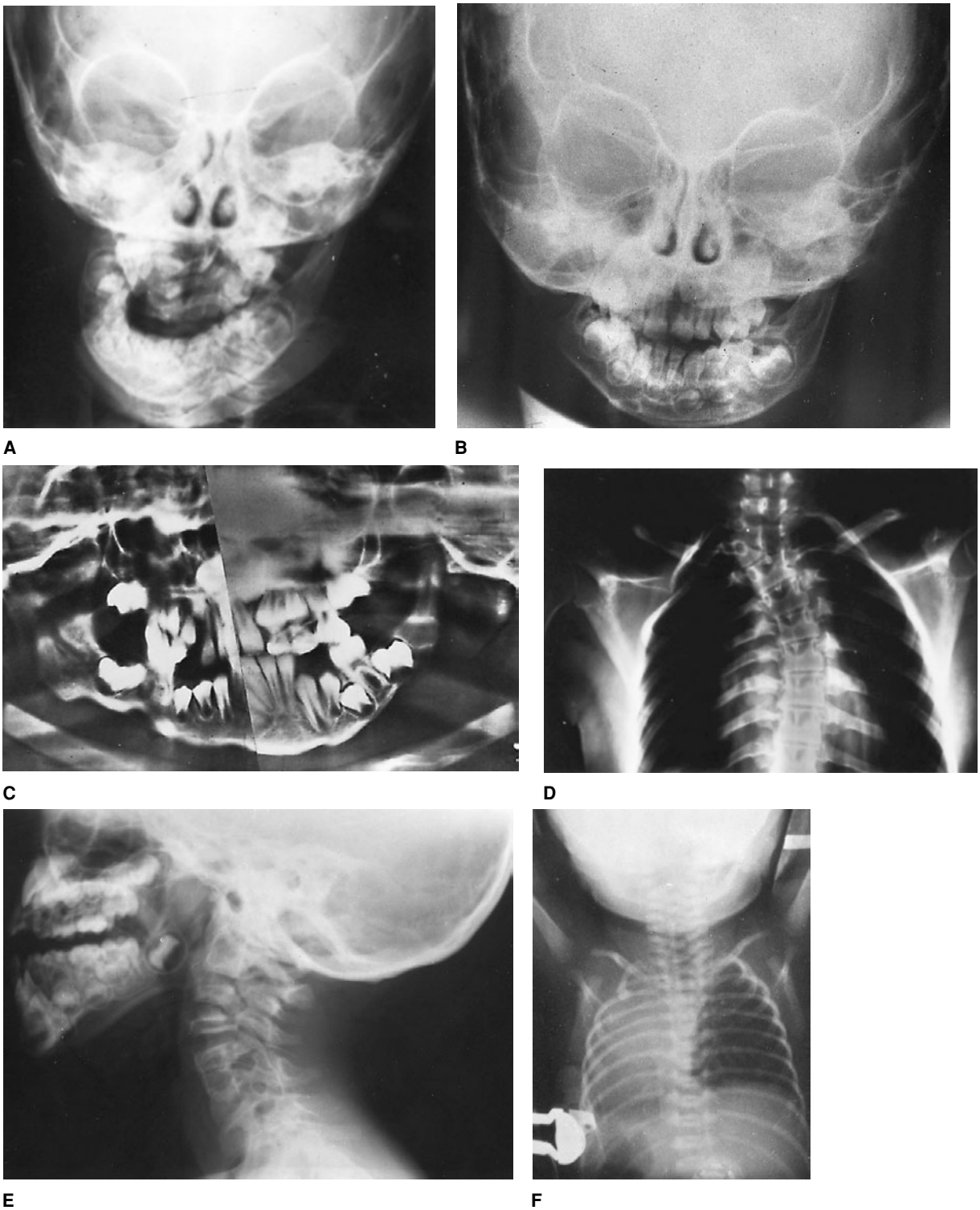

Fig. 19–3. *Oculo-auriculo-vertebral-spectrum*. Radiographs. (A) Asymmetry and unilateral hypoplasia of mandibular ramus. (B) Absent ramus and condyle on affected side. (C) Panorex X-ray showing more severe involvement on one side. Compare mandibular angle and ramus on both sides. (D) Hemivertebra in thoracic spine. (E) Note fusion in cervical area. (F) Unilateral absence of lung.

reported (89). Epibulbar tumors (Fig. 19–2A) are found in approximately 35% (9,52,88). They appear as solid yellowish or pinkish white ovoid masses varying in size from that of a pinhead to 8–10 mm in diameter. They occur most often at the inferotemporal quadrant at the limbus. The surface is usually smooth and frequently has fine hairs. They can occur at any location on the globe or in the orbit and can be dermoid (white solid masses), lipo-dermoid (yellow, movable, conjunctival), or dermis-like or complex (mesoectodermal). Unilateral epibulbar dermoids are seen in 50% (9). Bilateral lesions occur in 25% and have a tendency to be symmetrically placed in both eyes. However, multiple lesions can occur in the same eye. Lipodermoids are less common (25%), more often bilateral (20%), and more often superotemporal or inferotemporal (9). Vision may be impaired by encroachment on the pupillary axis, by lipid infiltration of the cornea, or as a result of astigmatism (9).

Removal of the masses can lead to scar formation with resultant leukoma.

Patients with epibulbar dermoids have a higher frequency of eyelid, extraocular, and lacrimal drainage abnormalities (9,62,88), microcornea, blepharoptosis (9), microphthalmia, and clinical anophthalmia (88,127). Unilateral colobomas of the upper lid are noted in approximately 20%, bilateral in possibly 3% (9) (Fig. 19–2B). Other ocular motility disorders, found in up to 25%, include esotropia, exotropia, and Duane syndrome (3,9,96,114). Choroidal or retinal colobomas, congenital cystic eye, Peters anomaly, and various other anomalies may be found occasionally (9,48).

Skin tags are the only characteristic of the syndrome that correlates with epibulbar dermoids for laterality (88). This association/localizing significance might be related to the fact that both are histologically choristomas.

Ear. Abnormalities ranging from anotia to an ill-defined mass of tissue that is displaced anteriorly and inferiorly, to a mildly dysmorphic ear are found in over 65% (Fig. 19–2C,D) (25). Farkas et al (39) showed no direct relationship between the degree of microtia and the extent of facial defect, whereas other authors have shown moderate correlation (42). Occasionally, bilateral anomalous pinnae are noted. Preauricular tags of skin and cartilage are extremely common, and may be unilateral or bilateral. Supernumerary ear tags may occur anywhere from the tragus to the angle of the mouth. They are more commonly seen in patients with macrostomia and/or aplasia of the parotid gland and epibulbar dermoids. Preauricular sinuses and/or tags are noted in greater than 40%. Narrow external auditory canals are found in more mild cases; atretic canals are seen in more severe cases. At times, small auricles with normal architecture are seen. Isolated microtia is considered a microform of OAV spectrum (12). Rollnick et al (127) require at least some ear involvement to confirm the diagnosis. Many previous studies included patients without ear involvement (57,134,155). Both conductive and, less frequent (15%), sensorineural hearing loss because of lesions of the middle and external ears, hypoplasia or agenesis of ossicles, aberrant facial nerves, patulous or absent eustachian tube, and skull base anomaly have been reported in greater than 50% (8,9,83a,97,135,164,170).

Central nervous system. A wide range of central nervous system defects may be associated with the OAV spectrum, and reported frequencies of mental deficiency appear to have ascertainment bias. For example, series preselected for severe central nervous system malformations have an inordinately high frequency of mental retardation, whereas those reported as treated patients from various craniofacial centers tend to have a low frequency. Most estimates range from 5% to 15% (143). Higher frequencies are those reported by Tenconi and Hall (37%) (155) and Wilson (82%) (165). Cohen (26) suggested an association between microphthalmia or clinical anophthalmia and mental retardation, as the eye is an outpouching of the primitive brain.

Neurodevelopmental studies (28) have shown that those with lower muscle tone, bilateral involvement, and cervical vertebral involvement have increased risk for delay.

Nearly all cranial nerves have occasionally been involved (5,120). Lower facial weakness occurs in 10%–20%, probably being related to bony involvement in the region of the facial canal (8,57). Abnormal course of the seventh cranial nerve (170) and unilateral aplasia of the trigeminal nuclei and the facial nerve (5,37) have been described, as well as trigeminal anesthesia (37,167). Other cranial nerves involved have included I (2), II (89), III, IV, and VI (3), and VIII, IX, and X (5).

The range of skull defects includes cranium bifidum, microcephaly, dolichocephaly, and plagiocephaly (5).

For the expanded oculo-auriculo-vertebral spectrum, brain malformations have been discussed especially well by Aleksic et al (5). Intracranial anomalies may include occipital and frontal encephaloceles, hydrocephaly, lipoma of corpus callosum, dermoid cyst, teratoma, Arnold-Chiari malformation, lissencephaly, arachnoid cyst, holoprosencephaly, porencephalic cyst, unilateral arhinencephaly, and hypoplasia of the corpus callosum (2,4,10,26,62,63,68,94,101,111,139,143,158,162,165). This group tends to be retarded or to suffer early death (139).

When flattened frontal encephalocele occurs, the patient appears to have frontonasal malformation together with ear tags, other ear anomalies, and even epibulbar dermoids (44,62). Since encephalocele is more common in the occipital region than in the frontal region, we suggest that cases of so-called frontonasal malformation with epibulbar dermoids and ear tags may represent oculo-auriculo-vertebral spectrum with the encephalocele expressed anteriorly (27).

Trachea and Lung. Approximately 5% have tracheo-esophageal fistula (19,92,115,125,151). Pulmonary anomalies range from incomplete lobulation to hypoplasia to agenesis, unilateral or bilateral, the absent lung usually being ipsilateral to the facial anomalies (Fig. 19–3F) (18,19,64,115).

Heart. A range of from 5% to 58% of patients with various forms of heart anomalies have been reported (46,80,99,115,143,155,165). Ventricular septal defect and tetralogy of Fallot with or without right aortic arch account for 65% of the anomalies, although no single cardiac lesion is characteristic. A wide variety of associated cardiac findings including transposition of the great vessels, tubular hypoplasia of the aortic arch associated with mild coarctation of the aorta, cardiomegaly, rare isolation of the left innominate artery with bilateral PDA (isolated or in combination with other anomalies), pulmonary stenosis, dextrocardia, double outlet right ventricle, and other aortic arch abnormalities have been described (115,127). Hypoplasia of the external carotid artery and situs ambiguus also have been noted (55).

Skeletal alterations. Facial anteroposterior and vertical dimensions are reduced on the affected side, especially in the lower face toward the otocephalic center (Fig. 19–3A–C). Approximately 10% have ipsilateral frontal plagiocephaly (106). The temporomandibular joint is anteroinferiorly displaced. Often the orbit is reduced in size and elevated in approximately 7% (106,146). Cervical spine, cranial base anomalies and torticollis occur with increased frequency. Skull defects also have been noted (26,62,94,101). This group seems to have a worse prognosis (165). Cervical vertebral fusions (Fig. 19–3E) occur in as many as 60%, whereas platybasia and occipitalization of the atlas are found in approximately 30% (7,41,56). Spina bifida, hemivertebrae, butterfly, fused and hypoplastic vertebrae, Klippel-Feil anomaly, MURCS association, scoliosis, and anomalous ribs (agenesis, bifidity, fusion, supernumerary) occur in at least 30% (Fig. 19–3D) (7,39,66,125,162). Talipes equinovarus has been reported in approximately 20% (38). Radial limb anomalies have been noted in approximately 10%. These may take the form of hypoplasia or aplasia of radius and/or thumb and bifid or digitalized thumb (55,92,98,165). Poland anomaly has been reported but may be aleatory (24). Caudal regression has also been noted (132).

Kidney. A variety of renal abnormalities have been reported: absent kidney, double ureter, crossed renal ectopia, anomalous blood supply to the kidney, hydronephrosis, hydroureter, and other defects (22,27,143).

Gastrointestinal anomalies. Imperforate anus with or without rectovaginal fistula has been described. Situs inversus has been described (54a).

Oral manifestations. At least 35% with agenesis of the mandibular ramus have associated macrostomia or pseudomacrostomia, that is, lateral facial cleft, usually of mild degree. In the presence of epibulbar dermoids, the frequency of macrostomia may be somewhat higher. It is nearly always unilateral and on the side of the more affected ear. Occasionally, there may be agenesis of the ipsilateral parotid gland, displaced salivary gland tissue, or salivary fistulas. Intraorally, there is decreased palatal width from the midline palatal raphe to the lingual surface of the teeth on the affected side. The palatal and tongue muscles may be unilaterally hypoplastic and/or paralyzed. Unilateral or bilateral cleft lip and/or cleft palate occurs in 7%–15% of patients (43,127). Cleft palate is twice as common as cleft lip with or without cleft palate (91). Tooth maturation is not affected significantly on the involved side (38,85). Canting of the occlusal plane and malocclusion are common (Fig. 19–2E). The

occurrence of a tongue-like structure projecting from the tonsillar pillar in place of a tonsil has been reported by several authors (93,137,141). In some cases there was partial aplasia of the soft palate, ear atresia, and facial palsy.

Approximately 35% have velopharyngeal insufficiency (86). Shprintzen (144) reported 12 patients with velopharyngeal insufficiency, and 2 of the 12 had cleft palate. Among the 10, the insufficiency resulted from asymmetry of movement of the lateral pharyngeal wall and dyssynchrony of palatal motion. Tongue restriction and hypernasality have been studied (134).

Differential diagnosis. The OAV spectrum is phenotypically variable and causally heterogeneous (126). It is essential to exclude various chromosome disorders and several syndromes with overlapping features. *Townes-Brocks syndrome* (72,160) consists of dysplastic ears, ear tags, and hearing loss in addition to thumb anomalies, anal defects, and renal anomalies. It has autosomal dominant inheritance. The *branchio-oto-renal (BOR) syndrome* is associated with mixed hearing loss, preauricular pits, branchial fistulas or cysts, anomalous pinnae, malformed middle or inner ear, lacrimal duct stenosis/aplasia, and/or renal dysplasia. There is autosomal dominant inheritance with high penetrance and variable expression. Families have been described in which first-degree relatives have varying features of hemifacial microsomia and/or BOR, suggesting that in some instances hemifacial microsomia may constitute a component toward the severe end of the spectrum of the BOR syndrome (129). Epibulbar dermoid may be an isolated finding. Corneal dermoids are usually isolated (61). Preauricular skin tags or nodules occur in approximately 1% of the normal population and may be familial (127,152).

The characteristic features of OAV spectrum are distinguishable from *mandibulofacial dysostosis*, *maxillofacial dysostosis, Nager acrofacial dysostosis*, and *postaxial acrofacial dysostosis*. Facial involvement in the OAV spectrum is usually asymmetric, with one side of the face more severely involved (127). Furthermore, there is far less hypoplasia of the malar bones present. Partial to total absence of the lower eyelashes has not been reported in the OAV spectrum. Preauricular tags occur less often in mandibulofacial dysostosis.

Colobomas in OAV spectrum affect the upper eyelid; in mandibulofacial dysostosis and Nager acrofacial dysostosis the notch is in the outer one-third of the lower lid. Upper eyelid colobomata may occur very rarely as an isolated finding (1).

Characteristics of the VATER association (vertebral anomalies, ventricular septal defect, anal atresia, T-E fistula with esophageal atresia, and radial and renal dysplasia), the *CHARGE association* (*c*oloboma, *h*eart disease, *a*tresia choanae, *r*etarded growth and development, *g*enital anomalies, and *e*ar anomalies and/or hearing loss), and the MURCS association (*Mü*llerian duct aplasia, *r*enal aplasia, and *c*ervicothoracic *s*omite vertebral dysplasia) overlap with the OAV spectrum. It has been pointed out that some patients share stigmata of both OAV spectrum and *frontonasal malformation*, *oculoauriculofrontonasal dysplasia*, and *ophthalmofrontonasal dysplasia* (23,26,34,44,45,51,60,62,63,102, 103,155,159). Duncan and Shapiro (36) discussed overlap with VATER association. Several authors have described OAV spectrum with complex malformations of left–right asymmetry (22,84,87).

Laboratory aids. Prenatal diagnosis by ultrasonography in severe hypoplasia of mandible, severe abnormality of the auricle, and cleft lip and/or cleft palate may be helpful in some cases (11,35,153). Polyhydramnios may be present. CT to see the middle ear bones when evaluating hearing. Radiographic analysis for skeletal findings is also indicated. The descent of the tegmen may, in association with microtia, be the most reliable clinical marker of OAV spectrum. The level of the tegmen below the base of the middle cranial fossa appears to bear a direct relationship to the severity of the disorder (113).

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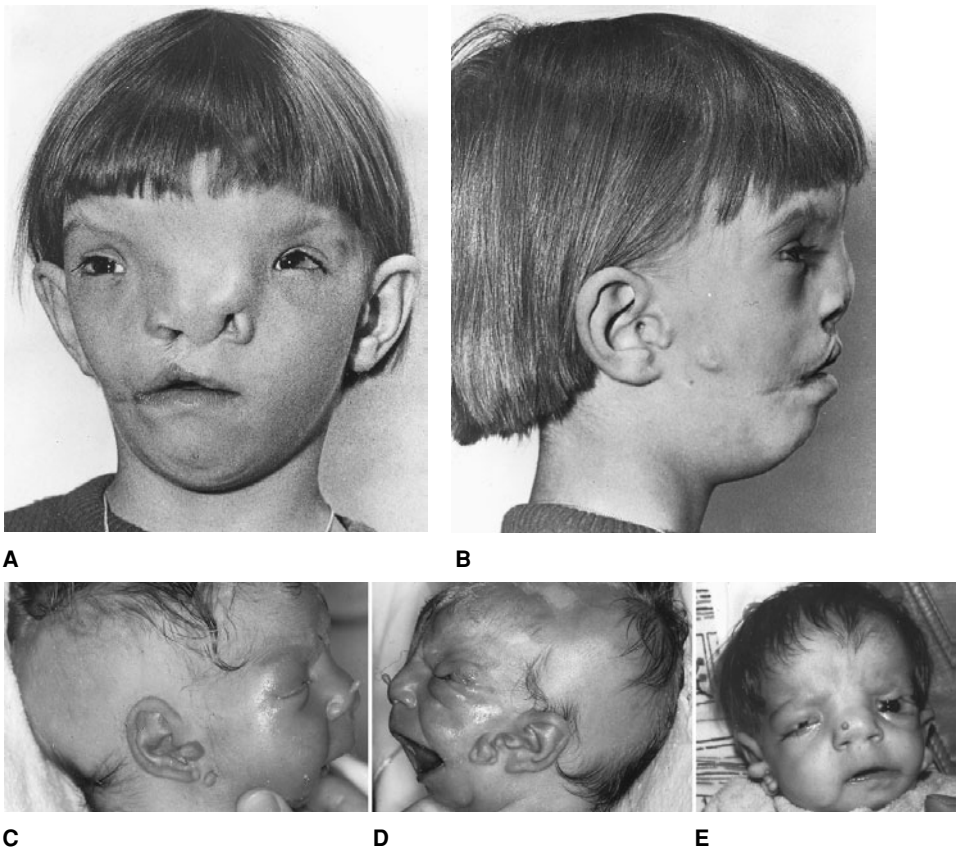

Fig. 19–4. *Oculoauriculofrontonasal dysplasia*. (A,B) Patient had normal intelligence, marked hypertelorism, very broad nose. Observe scars from lateral facial cleft (macrostomia), epibulbar dermoid, ear tags. (C–E) Increased severity in different child. (A,B from A Fleischer-Peters. Dtsch Zahnarztl A 24:545, 1969. C–E from MA Musarella and ID Young, Am J Med Genet Suppl 2:135, 1986.)

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Oculoauriculofrontonasal spectrum (ophthalmofrontonasal dysplasia, Golabi-Gonzales-Edwards syndrome)

Some patients share the stigmata of both OAV spectrum and frontonasal malformation. Variously this has been termed oculoauriculofrontonasal dysplasia, ophthalmofrontonasal dysplasia, and Golabi-Gonzales-Edwards syndrome (1–15). It is debatable whether this hybrid condition merits a separate classification but cases will be summarized for the reader (1). At least 15 examples have been reported.

Since encephalocele is more common in the occipital region than in the frontal region, we suggest that cases of so-called frontonasal malformation with epibulbar dermoids and ear tags may represent oculo-auriculo-vertebral spectrum with the encephalocele expressed anteriorly (2).

As in *frontonasal dysplasia*, there is no single gene inheritance. Golabi et al (6) reported affected sibs. Toriello et al (15) suggested heterogeneity.

In addition to the usual facial stigmata of frontonasal dysplasia (ocular hypertelorism, wide nasal bridge) and oculo-auriculo-vertebral spectrum (microtia, skin tags, epibulbar dermoids, cleft lip, macrostomia), various other findings have been demonstrated. Only rarely are epibulbar dermoids absent (2,14) (Fig. 19–4).

Central nervous system. Four encephaloceles have been documented. Two were posteriorly located (4,14), two anteriorly placed (9,10). Mental retardation was noted (2,14).

Heart. Congenital heart anomalies have been reported rarely (5,14).

Skeletal anomalies. Fusion of the posterior aspects of C_2-C_3 has been found (6).

Diagnosis. A fetal example was reported by Kennedy et al (11). The child described by Guion-Almeida and Richieri-Costa (8) has many of the stigmata seen in oculoauriculofrontonasal spectrum.

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Mandibulofacial dysostosis (Treacher Collins syndrome, Franceschetti-Zwahlen-Klein syndrome)

Mandibulofacial dysostosis (Figs. 19–5 to 19–7) involves structures derived from the first and second pharyngeal arch, groove, and pouch. Although the syndrome was probably first described by Thomson (63) and Toynbee (64) during 1846-1847, credit for its discovery is usually given to Berry (5) or, especially, to Treacher Collins (65) who described the essential components of the syndrome. Franceschetti and co-workers (15,16), during the 1940s, published extensive reviews of the disorder and coined the term *mandibulofacial dysostosis*. An excellent review is that of Dixon (8). The reader should enjoy the article by Winter (71).

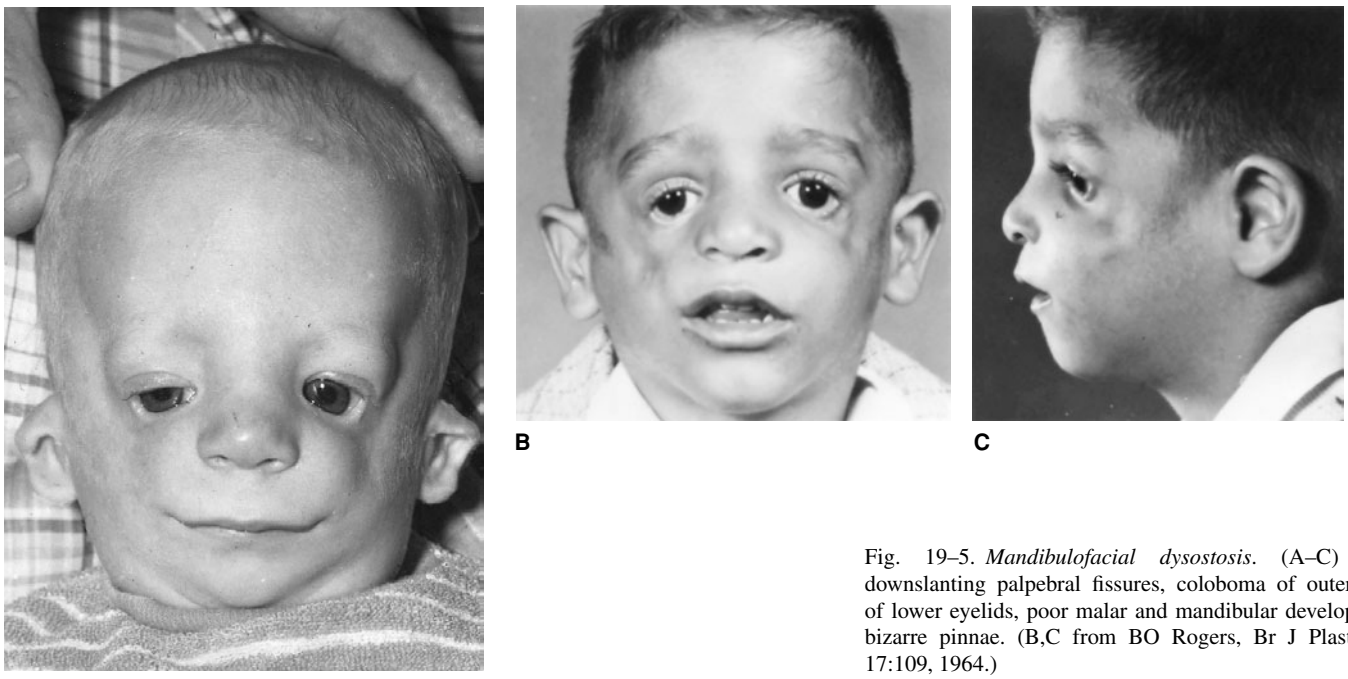
The syndrome has autosomal dominant inheritance with variable expressivity (10,57,60,68). Nonpenetrance is rare (39). Roughly 60% represent new mutations (16,28). Among these, the fathers tend to be older (28). Perhaps 450 or more cases have been published. The frequency is approximately 1 per 50,000 live births (57). The gene for the syndrome (Treacle or TCOF1) has been mapped to 5q32–33.1 (10–13,25,26,59a). The gene encodes a putative nucleolar phosphoprotein (71). The mutation leads to premature termination of the coded protein (8–12,14,20,66,72). A mild example has been found in association with an interstitial deletion, del(3)(p23;p24.12) (1). We assume that the severe example shown by Hansen et al (22) is the result of uniparental disomy producing homozygosity for the gene.

Poswillo (50), Sulik et al (61), and Wiley et al (69) employing mouse, rat, and hamster models gave teratogenic doses of vitamin A and isotretinoin and produced malformations of the craniofacial skeleton that closely resembled the syndromic features of human mandibulofacial dysostosis. Histological studies indicated that abnormalities of neural crest development occurred in these phenocopies but whether the principal defect is in migration or differentiation of the ectomesenchymal cells or their death in the condensing trigeminal ganglia or results from the effects on the first and second arch placodal cells following their release from the neural folds of neural crest cells into the developing cranial regions remains unclear (3,23,61). Apoptosis in the prefusion neural folds seems to play a critical role (12a).

Facies. The facial appearance is characteristic. Abnormalities are bilateral and usually symmetric (Fig. 19–5), but not always (70). The nose appears large but really is not (29); the appearance is secondary to hypoplastic supraorbital rims and hypoplastic zygomas. The face is narrow. Downward-sloping palpebral fissures, depressed cheekbones, malformed pinnae, receding chin, and large down-turned mouth are characteristic. Approximately 25% manifest a tongue-shaped process of hair that extends toward the cheek (56).

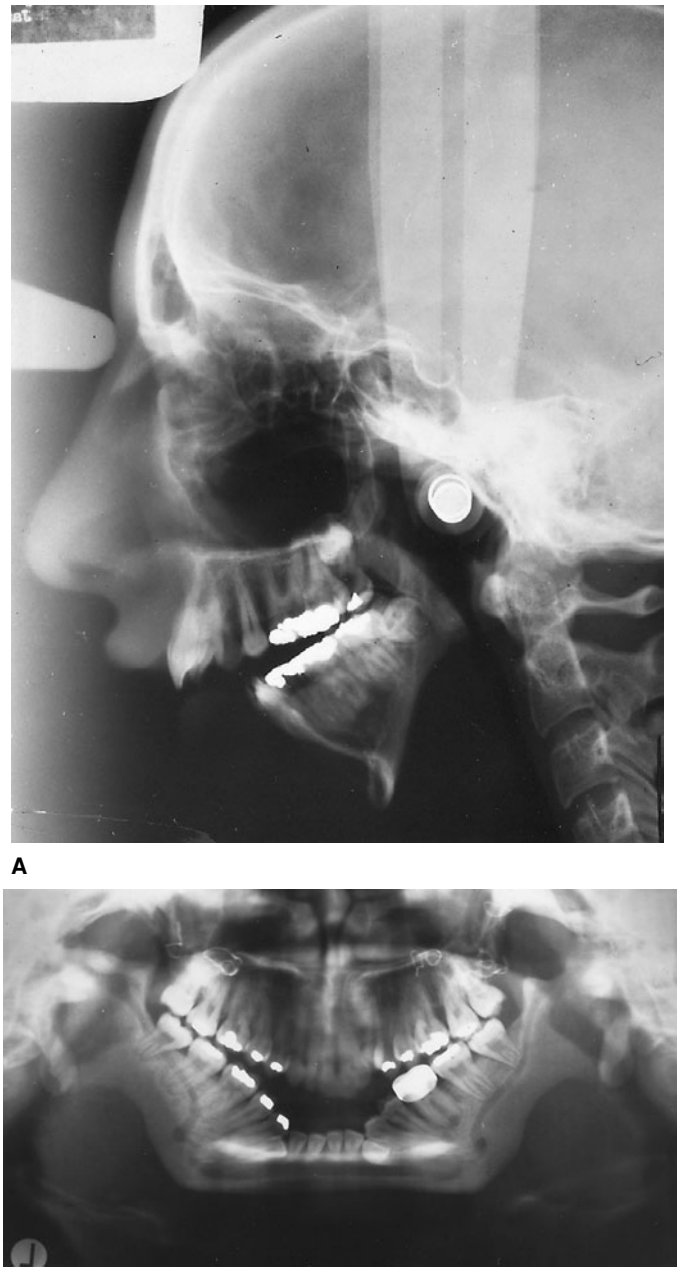
Skull. The calvaria is essentially normal, but radiographic studies reveal that the supraorbital ridges are poorly developed (40,45,60). The body of the malar bones may be totally absent but more often is grossly and symmetrically underdeveloped, with nonfusion of the zygomatic arches. The zygomatic process of the frontal bone is hypoplastic as are the lateral pterygoid plates and muscles. The mastoids are not pneumatized and are frequently sclerotic (62). The paranasal sinuses are often small and may be completely absent. The orbits are hyperteloric (29). The lower margin of the orbit may be defective and the infraorbital foramen is usually absent. The cranial base is progressively kyphotic (30,47) resulting in airway difficulties. The mandibular condyle and coronoid process are severely hypoplastic, flat, or even aplastic (Fig. 19–6). The undersurface of the body of the mandible is quite concave. The angle is more obtuse than normal, and the ramus is deficient. The condyle is covered with hyaline cartilage rather than fibrocartilage. The condylar neck is short. There is no articular eminence, and the articular area is atypically medial (19,21,42,55). There have been several excellent anatomic studies (3,6,23,33,41) and detailed craniofacial measurements (2,9).

Eyes. The palpebral fissures are short and slope laterally downward and, often (75%), there is a coloboma in the outer third of the lower



A B C

Fig. 19–5. *Mandibulofacial dysostosis*. (A–C) Note downslanting palpebral fissures, coloboma of outer third of lower eyelids, poor malar and mandibular development, bizarre pinnae. (B,C from BO Rogers, Br J Plast Surg 17:109, 1964.)



A

B

Fig. 19–6. *Mandibulofacial dysostosis*. Radiographs. (A) Lateral cephalogram showing extremely steep mandibular plane angle, antegonial notching, and mandibular deficiency. Soft tissue demonstrates prominent nasal contour, acute nasolabial angle, and lip incompetence. (B) Panorex X-ray showing prominent antegonial notching and open bite.

lid (Fig. 19–7). We have seen several patients in whom the downward slope is asymmetric. Approximately half of the patients have deficiency of cilia medial to the coloboma. Iridial coloboma may also occur. The lower lacrimal points may be absent as well as the Meibomian glands and intermarginal strip (22,37). The eye anomalies have been especially well reviewed by Franceschetti et al (17).

Ears. The pinnae are often malformed, crumpled forward, or misplaced toward the angle of the mandible. In the survey of Stovin et al (60), 51 of 63 patients had anomalous pinnae with meatal atresia and over one-third had absence of the external auditory canal or ossicle defect accompanied by bilateral conductive hearing loss in at least 55% (36). Pron et al (51), in a CT study, found normal, stenotic, and atretic external canals associated with 44,54, and 62 dB loss, respectively. Those without ossicles had flat conductive loss, whereas those with ankylosed or hypoplastic ossicles had flat (60%) or sloping (40%) audiograms. Kolar et al (29) found microtia in 60%. The auditory ossicles and cochlear and vestibular apparatus have been observed to be absent or severely malformed (24,32,37,41,49,62,67) and often asymmetric in severity (67). Radiographic and surgical studies have shown agenesis or hypoplasia of the mastoid, absence of the external auditory canal, narrowing or agenesis of the middle ear cleft, agenesis or malformation of the malleus and/or incus, monopodial stapes, absence of stapes and oval window, ankylosis of stapes in the oval window, deformed suprastructure of stapes, complete absence of middle ear and epitympanic space (36). The space may be filled with connective tissue. The inner ears are normal (24,32,37,41).

Extra ear tags and blind fistulas may occur anywhere between the tragus and the angle of the mouth. In one case, blind fistulas were found behind the ear lobes (21).

Nose. The nasofrontal angle is usually obliterated, and the bridge of the nose raised. The nose appears large (29) because of the lack of malar development and hypoplastic supraorbital ridges. The nares are often narrow, and the alar cartilages hypoplastic. Choanal atresia has been reported (35,42,58). Obstructive sleep apnea is not rare (27).

Mental status. Intelligence is usually normal. However, Stovin et al (61) reviewed 63 patients and found four who were mentally deficient. Other investigators have also noted mild mental retardation in their patients (21). We suspect that the "retardation" may be secondary to hearing loss.

Oral findings. The palate is cleft in approximately 35% (11,45, 48,60). Congenital palatopharyngeal incompetence (agenesis of soft palate, foreshortened soft palate, submucous palatal cleft, immobile soft palate) has been found in an additional 30%–40% (48). Rarely cleft lip-palate has been noted. Macrostomia, observed in approximately 15%, may be unilateral or bilateral. The elevator muscles of the upper lip are deficient (23). The parotid salivary glands may be absent or hypoplastic (23,38,41). Pharyngeal hypoplasia, a constant finding, may explain cases of neonatal death (59).

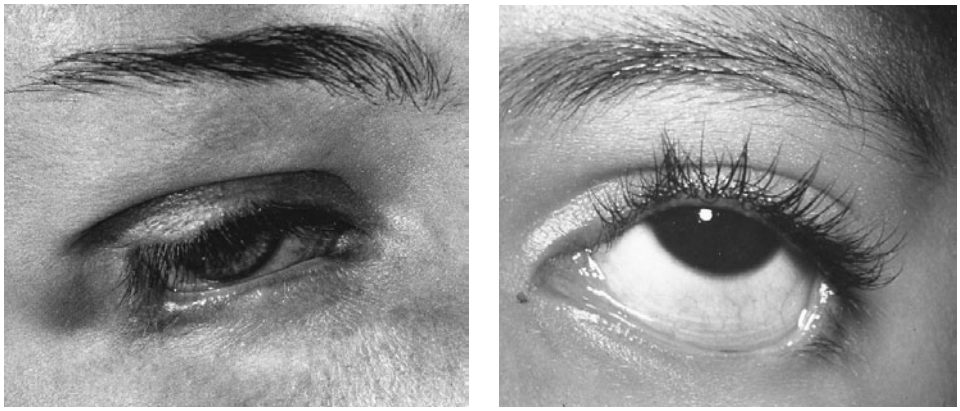
Differential diagnosis. *Oculoauriculovertebral spectrum* is easily excluded. The facies is so characteristic that little difficulty in diagnosis should be experienced. However, affected relatives may have minimal signs of the syndrome and must be closely examined. A sporadic case with minimal involvement can present difficulties in diagnosis.

Nager acrofacial dysostosis closely resembles mandibulofacial dysostosis. The thumbs are hypoplastic or absent, the radius and ulna may be fused or there may be absence or hypoplasia of the radius and/or one or more metacarpals. Lower lid colobomas are rarer, cleft palate more frequent, and the mandible more severely retarded in growth than in mandibulofacial dysostosis.

Dominantly inherited and X-linked maxillofacial dysostosis consists of bilateral hypoplasia of malar bones, downward-slanting palpebral fissures without colobomas, maxillary hypoplasia, open bite, and relative mandibular prognathism.

A similar facies has been seen in an autosomal recessive disorder found in Hutterites (34), in an autosomal dominant osteosclerotic disorder (31), and in a father and son with ectrodactyly (see EEC syndrome). Richieri-Costa (53) and Stovin et al (60) described autosomal recessive mandibulofacial dysostosis. Richieri-Costa et al (52) reported a woman with mandibulofacial dysostosis and tibial hemimelia. Robb et al (54) found mandibulofacial dysostosis with tracheoesophageal fistula, rectovaginal fistula, and anal atresia.

Laboratory aids. Midtrimester sonographic diagnosis has been accomplished (3,4,6,43). Fetoscopy has also been employed (46).



A B

Fig. 19–7. *Mandibulofacial dysostosis*. (A,B) Close-up of eye in different patients showing absence of cilia on lower eyelid. Note coloboma of lower lid in A.

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Autosomal dominant mandibulofacial dysostosis (Bauru type)

Marçano and Richieri-Costa reported a Brazilian family with 5 affected members having malar hypoplasia, cleft lip/palate, micrognathia, mild down-slanting palpebral fissures, and abnormal pinnae (Fig. 19–8).

Inheritance is autosomal dominant.

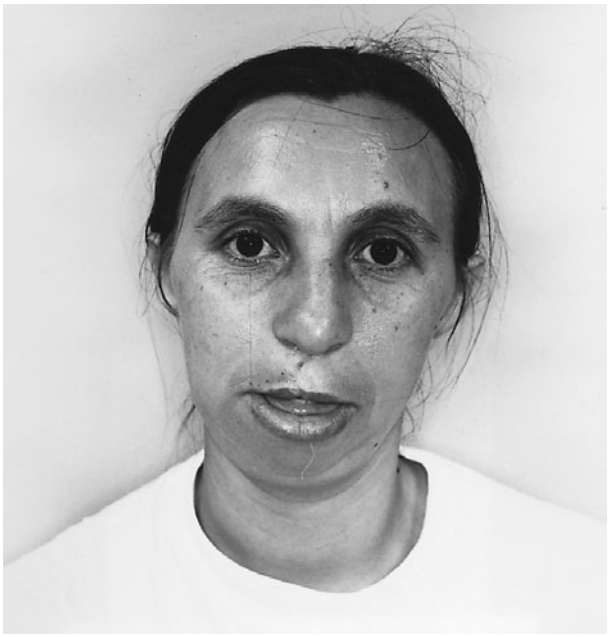

Fig. 19–8. *Mandibulofacial dysotosis (Bauru type)*. Thirty-one-year old woman with mild downslanting palpebral fissures, malar hypoplasia, repaired cleft lip and micrognathia. She also had hypoplastic tragus and ear lobes. (From ACB Marçano and A Richieri-Costa, Braz J Dysmorphol Speech Hear Dis 2:37–41, 1998.

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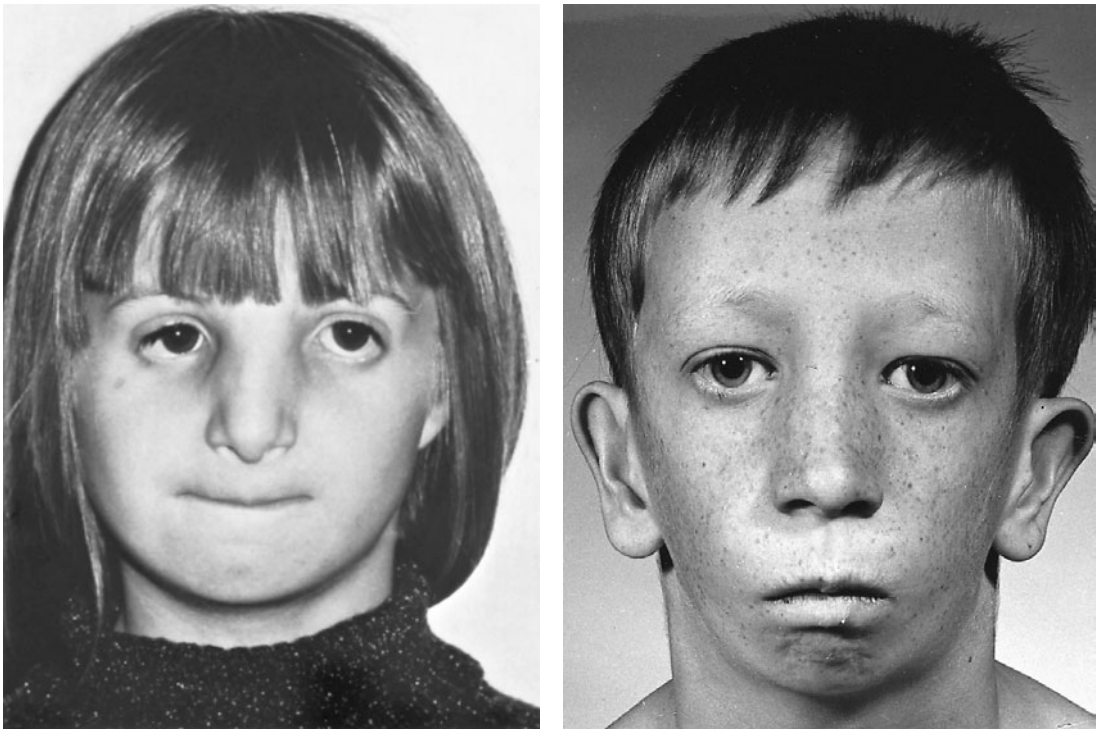
Acrofacial dysostosis, type Nager (preaxial acrofacial dysostosis)

Nager acrofacial dysostosis is a mandibulofacial dysostosis associated with radial defects. Since the original description of the syndrome by Nager and DeReynier (38) in 1948, over 85 cases have been reported (1–11,14–17,19–26,28–32,34–36,38–45,48,51,52,54–56a,58–60).

Growth retardation is noted in 10% (5,6,16,59). Death during the neonatal period is documented in 20% (6,7,21,22,25,26,30,34,52,55,56a).

Most cases of Nager acrofacial dysostosis have been sporadic. Mildly to moderately affected sibs with apparently normal parents have been described (6,7,22,40,48,58), suggesting autosomal recessive inheritance. Single cases with consanguineous parents have lent some support to this concept (5,26,45,56a). Transmission from parent to child has been reported (1,21,28,31,35,59). One family with six affected individuals covering four generations was briefly presented (59). Advanced paternal age in sporadic cases has supported autosomal dominant inheritance (4,32,34). Manifestations within a family may be markedly consistent, as in the mildly to moderately affected father and son reported by Aylsworth et al (1). In contrast, Hall (21) described extreme intrafamilial variability: a mildly to moderately affected mother, whose son died minutes after birth with severe phocomelic Nager acrofacial dysostosis. Palomeque et al (43) described an extremely severe example. Bonthron et al (3) reported minor changes in parents. Genetic heterogeneity clearly challenges both diagnosis and counseling. Apparent recessive inheritance could represent nonpenetrance or gonadal mosaicism. Alternatively both autosomal dominant and recessive forms of the disorder may exist. One cannot assume that mild to moderate cases are more likely to be recessive whereas severe cases are dominant. After the birth of one affected child, a couple



A B

Fig. 19–9. *Preaxial acrofacial dysostosis (Nager).* (A,B) Note malar hypoplasia, slight downslanting of palpebral fissures, almost total absence of eyelashes, low-set, cup-shaped ears, and micrognathia. [A from FA Walker, Birth Defects 10(8):135, 1974. B from P Bowen and F Harley, Birth Defects 10(5):109, 1974.]

should be offered high resolution ultrasonography in a subsequent pregnancy. In one patient, a probably balanced chromosome 9q32 translocation was found (62). Another had deletion 1q12–q21 (56b).

Craniofacial findings. Abnormalities of the cranium have been described in 25% (14,16,21). Hypoplasia of the zygomata, maxilla, and mandible are almost constant features (Fig. 19–9). The palpebral fissures are down-slanting in approximately 100%. An estimated 80% have absence of the medial third of the lower eyelashes (4,11,20,25,26,29,32,36,40,58,59) with coloboma of the lower lid being noted in almost 50% (16,20,26,58,59). A high nasal bridge with upturned nasal tip is a constant feature. A tongue-like extension of hair onto the cheek is seen occasionally (20,25,26). Limited jaw movement secondary to functional ankylosis of the temporomandibular joints is present in approximately 25% (4,16,20,24,25,29,36,40). Greater than 20% have macrostomia (17,25,26,29,45,52), occasionally in association with lateral facial clefts (17,26). Abnormalities of the palate are frequent, and include cleft palate in over 60%, agenesis or partial agenesis of the soft palate (10,24), short soft palate (4,7,32), highly arched palate (11,26), submucous cleft palate (20), and bifid uvula (20,58). Cleft lip has been reported in 10%. Bilateral lateral palatine fistulae (32), broad palatine ridges (1), and hypoplasia of the epiglottis (7,30) have also been reported. Dental anomalies include enamel hypoplasia and oligodontia (32). Facial asymmetry is rare (36).

The auricles are dysplastic in 80%. Hypoplasia of the anthelix (20), tragus (4,20), antitragus (20), and helix (14,32) have been described. The pinnae are occasionally simple and small (16,21) with a preauricular tag (21,26,32,59), and are frequently low set and posteriorly angulated (6,22,30,36). In almost 85%, there is narrowing or atresia of the external auditory canal.

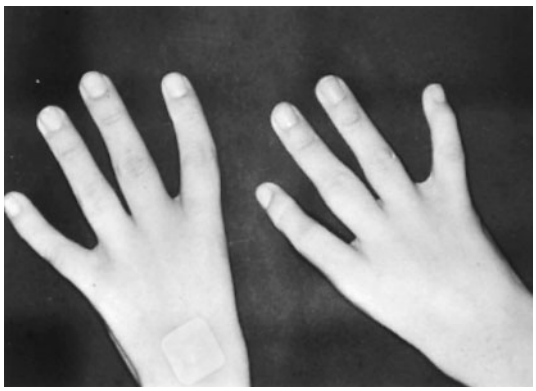
Conductive hearing loss of 50–70 dB, frequently congenital (21) and usually moderate (20), is noted in 85% of patients. Unilateral mixed hearing loss was described by Burton and Nadler (5). Even with normal pinnae, one may find ossicular abnormalities.

Musculoskeletal system. Radial ray abnormalities are a common feature of Nager syndrome (14,21). Varying degrees of asymmetric thumb hypoplasia or aplasia are seen in 75% (Fig. 19–10). Other thumb anomalies include stiff metacarpophalangeal joint (20), triphalangeal thumb (6,31,49), symphalangism (44), double thumb (15,19), and syndactyly between thumb and index finger with associated thumb hypoplasia (4,22). Radial hypoplasia or aplasia has been described in nearly all patients, with proximal radioulnar synostosis in 25% (35). These malformations frequently lead to reduced extension at the elbow. Marked reduction in size of the forearm is rare (56), but when present is usually associated with hypoplasia of humerus and ulna (5,22,45). Total absence of the forearm has rarely been reported (17,21,26). Other upper limb anomalies include synostosis of carpal bones (4,5,20), hypoplasia of thenar eminence (4,20,44), camptodactyly (26,30,36,55), and clinodactyly (7,26,36,44). Mild abnormalities of the lower limb include talipes (16,20,21,28), duplication of proximal hallucal phalanx (45), hypoplastic hallux (21), absent or hypoplastic toe (20,24,36,43), metatarsus varus (1), and absence of the distal interphalangeal creases of the toes (36). A few patients have been described with more significant lower limb anomalies, including absence of tibia and fibula (2,17,26,31) and frank phocomelia with hypoplasia of pelvis (26). Scoliosis (20,58), tightness of trapezius muscles leading to pseudopterygium colli and Sprengel deformity (12,20), hip dislocation (16,30,36), pes cavus (20), pectoral muscle hypoplasia (21), and pectus excavatum (16) are rare features.

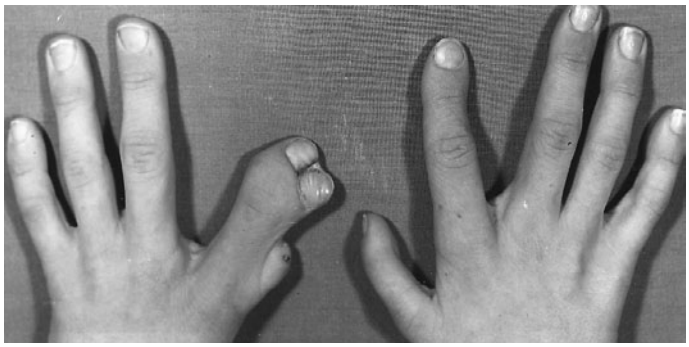
Cardiovascular system. Tetralogy of Fallot (17,55), ventriculoseptal defect (26), and patent foramen ovale (52) occur rarely.

Genitourinary system. Vesico-ureteric reflux (20), unilateral renal agenesis (45), duplication of ureter (26), and bicornuate uterus (26) have each been noted in one patient.

Central nervous system. Intelligence is usually normal but intellectual handicap has been reported (6,20,43).



A



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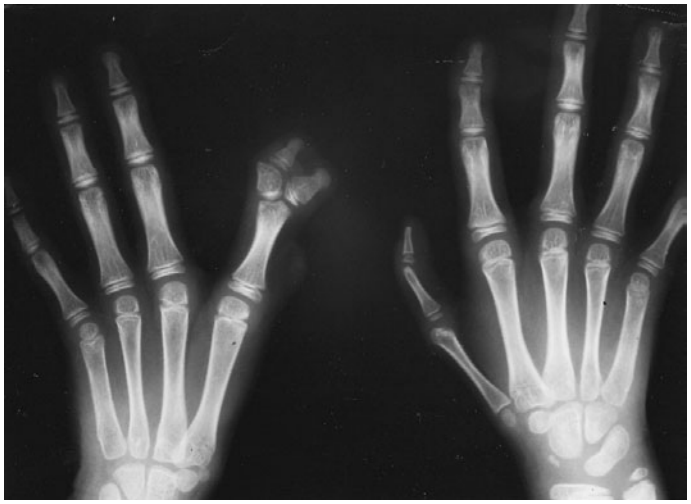

C

Fig. 19–10. *Preaxial acrofacial dysostosis (Nager).* (A) Absence of thumbs. (B,C) Preaxial involvement with missing phalanges and syndactyly. [A from FA Walker, Birth Defects 10(8):135, 1974. B,C from P Bowen and F Harley, Birth Defects 10(5):109, 1974.]

Ossicular defects have been confirmed at autopsy. These have included deformation of ossicles (4), absent incus with fused ossicular mass (32), stapedial footplate fixed to oval window (30), and absence of ossicles with rudimentary semicircular canals (17).

Miscellaneous findings. Autopsy has also revealed hypoplasia of the larynx and epiglottis (30) and abnormal septation of lungs (26,30). Cutaneous mastocytosis has been reported in two patients (39,60).

Diagnosis. Several entities must be considered in the differential diagnosis of Nager acrofacial dysostosis. In *Miller syndrome*, acrofacial dysostosis is associated with post-axial limb defects, and both upper and lower limbs are usually involved (37). Distinctive features include cup-shaped ears, cleft lip and/or palate, and accessory nipples. Although postaxial limb defects are most common, preaxial defects may be seen to a lesser degree, and abnormal thumbs, shortness of radius and ulna with or without radioulnar synostosis have all been described. Reynolds et al (47) reported an autosomal dominant acrofacial dysostosis syndrome with both pre- and postaxial involvement. There was mild congenital mixed hearing loss. Patients with *Fontaine syndrome* (12) have abnormal ears, retromicrognathia, cleft palate, and split foot with normal upper limbs. They do not show downward-slanting palpebral fissures, coloboma of the eyelids, or hearing loss. *Distal 2q duplication* syndrome shares some of the features of Nager acrofacial dysostosis such as down-slanting palpebral fissures, dysplastic external ears, and micrognathia (57,60). However, malar hypoplasia and defects of the external ear canal are absent, and hypertelorism and nystagmus, which are not seen in Nager acrofacial dysostosis, are frequent. Acral anomalies in the distal 2q duplication syndrome are usually limited to clinodactyly and camptodactyly of the fifth digit. No thumb defects have been described. We remain skeptical regarding the patient described by Fryns et al (13). *Oculo-auriculo-vertebral spectrum* may occasionally include radial defects but can usually be differentiated by the unilateral involvement of the ear, eye, face, and mandible, and the presence of epibulbar dermoids and vertebral anomalies. Sugiura (53) described a 6-year-old boy with hemifacial microsomia, absence of left radius and thumb, ventricular septal defect, and crossed renal ectopia. Gorlin et al (18) described a female infant with oculo-auriculo-vertebral spectrum phenotype and absence of the first left metacarpal with hypoplasia of the corresponding thumb. In 1971, Mandelcorn et al (33) reported a boy with hemifacial microsomia and acral anomalies, consisting of short ulna, four metacarpals, and four fingers on the left side, with hypoplastic humerus, short ulna, and three metacarpals, and two fingers on the right side. The facial features of Nager acrofacial dysostosis are similar to those in isolated *mandibulofacial dysostosis (Treacher Collins syndrome)*. The presence of preaxial limb defects distinguishes the two. External ear defects and cleft palate are more common in Nager syndrome, whereas lower lid colobomata are more frequent in mandibulofacial dysostosis.

In 1977, Kelly et al (27) described three males, two of them brothers, with preaxial limb anomalies with mild mandibulofacial hypoplasia. In addition, they showed intrauterine growth retardation with subsequent short stature, mental retardation, and genitourinary anomalies. All had sensorineural hearing loss. Autosomal recessive or X-linked recessive inheritance seems likely. The acrofacial dysostosis triphalangeal thumb syndrome described by Richieri-Costa et al (49) can be distinguished from Nager acrofacial dysostosis by the rarity of cleft lip and triphalangeal thumb in Nager syndrome. In 1983, Poissonnier et al (46) described a single male whose facial features were consistent with mandibulofacial dysostosis. In addition, there was hypoplastic scapulae and right humerus, hypoplastic or absent ulnae and fibulae, and absent fifth digito-metacarpal rays, in association with aplasia of the left hemidiaphragm and atrial and ventricular septal defects. In 1990, Rodriguez (50) described an apparently new autosomal recessive syndrome in three sibs with acrofacial dysostosis, predominantly preaxial limb deficiencies, rare postaxial limb anomalies, and cardiac and CNS malformations. The third sib showed marked similarity to Nager syndrome (50) as did that of Fryns and Kleckowska (12a).

Prenatal diagnosis. Ultrasonographic diagnosis has been reported (2).

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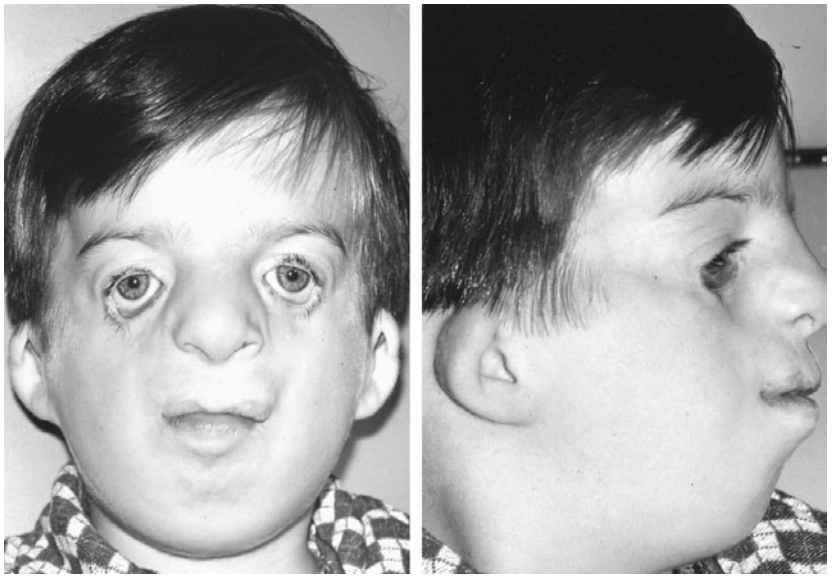
Postaxial acrofacial dysostosis, cupped ears, and conductive hearing loss (Miller syndrome, Genée-Wiedemann syndrome, Wildervanck-Smith syndrome)

Genée (10), in 1969, reported an infant with postaxial limb deficiency, cup-shaped ears, and malar hypoplasia. Wiedemann (25), in 1973, and Wildervanck (26), in 1975, noted similar patients. Miller et al (14), in 1979, presented details of three similar unrelated patients, one of which was previously reported by Smith et al (23) in 1975. An affected sib of a patient described by Miller et al (14) was briefly reported by Fineman (8). At least 25 patients have been described (2–6,8–21,23,26). A severe example was described by Poissonnier et al (18a).



A B

Fig. 19–11. *Postaxial acrofacial dysostosis (Miller or Wildervanck-Smith)*. (A,B) Characteristic facial appearance with downslanting palpebral fissures, ectropion of lower lids, repaired cleft lip, and malformed ears. (From MM Cohen Jr, Dysmorphic syndromes with craniofacial manifestations, in Oral Facial Genetics, RE Stewart and GH Prescott, eds, C.V. Mosby, St. Louis, 1976.)

Sibling pairs with normal parents have been reported (8,11,14–16). The parents of a sporadic patient were fifth cousins (21); thus it appears that the syndrome is transmitted in an autosomal recessive manner.

Craniofacial findings. Malar hypoplasia and lower lid ectropion are extremely common. Ectropion tends to become more obvious with age. Eyelid colobomata and eyelash anomalies were occasionally noted. Micrognathia is a constant finding (Fig. 19–11). Cleft lip and/or cleft palate was found in several cases (21). Other patients appeared to have a long philtrum. Supernumerary nipples were seen in almost 50% (6,13,16).

The ears, remarkably similar in reported cases, are small, simple, and cupped. Stenosis of the external auditory canal and hypoplasia of the middle ear were noted in two cases. Hearing loss was found in several patients (8,15,21).

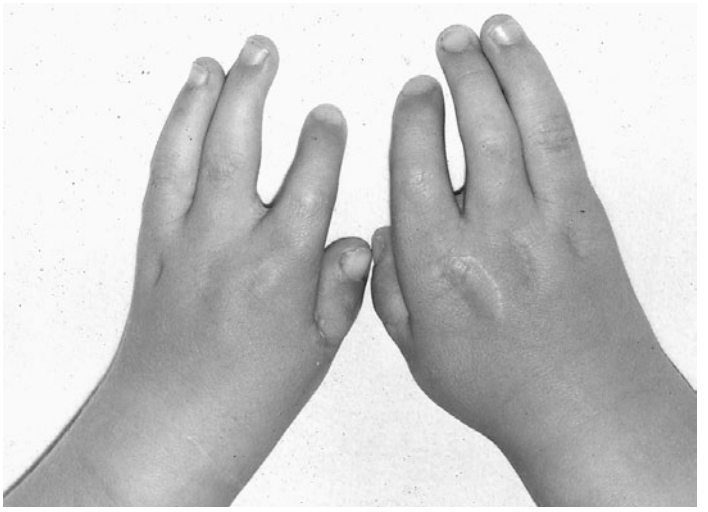
Musculoskeletal system. Almost all patients have bilateral absence of the fifth finger including the fifth metacarpal. Varying degrees of hypoplasia of the thumbs and syndactyly are occasionally noted. Forearm anomalies are extremely common, with ulnar hypoplasia being the most characteristic (Fig. 19–12A). Radioulnar synostosis has also been reported (15). It is possible that some patients have no digital anomalies (18). Absence of the toes on the lateral border of the feet was observed with rare exception (4,18) (Fig. 19–12B). The fifth toe was always involved, with occasional hypoplasia or absence of the third and fourth toes. Severe limb anomalies, rarely described, have included absent fibula, phocomelia, and hypoplasia of the pectoral girdle. Supernumerary vertebrae, vertebral and sternal segmentation anomalies, cervical ribs, and pectus excavatum have also been noted.

Sulik et al (24) postulated involvement of the apical ectodermal ridge of limb buds.

Other findings. Ogilvy-Stuart and Parsons (15) described midgut malrotation, gastric volvulus, and renal tract anomalies (reflux, hydronephrosis).

Diagnosis. Several disorders must be distinguished from this acrofacial malformation syndrome. The facial appearance is similar to that described in *Treacher Collins syndrome*, but distal limb anomalies are not part of that autosomal dominant condition. *Nager acrofacial dysostosis* includes preaxial hand deficiencies, normal feet, and a Treacher Collins-like face (3,22). The distal limb anomalies in Nager syndrome are most frequently hypoplasia or absence of the thumb and/or radius, as opposed to the predominantly postaxial limb anomalies in this condition. *De Lange syndrome*, *Weyers syndrome*, femur-fibula-ulna syndrome, and

Fig. 19–12. *Postaxial acrofacial dysostosis (Miller* or *Wildervanck-Smith*). (A,B) Postaxial agenesis of digits. (From MM Cohen Jr, Dysmorphic syndromes with craniofacial manifestations. In: Oral Facial Genetics, RE Stewart and GH Prescott (eds), C.V. Mosby, St. Louis, 1996.)



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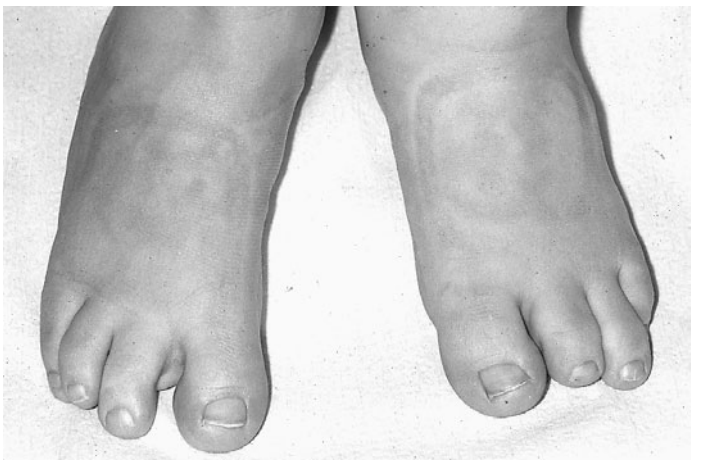

B

Schinzel-Giedion syndrome have ulnar ray defects, but differ in facial appearance and other clinical features. Allanson and McGillivray (1) and Falace and Hall (7) reported autosomal dominant inheritance of a syndrome of ectropion, facial clefting, and dental anomalies. The patient with four digits reported by Ruedi (22) appears to have Nager syndrome. The child reported by Danziger et al (5) has features of both Miller and Nager syndrome.

References [Postaxial acrofacial dysostosis, cupped ears, and conductive hearing loss (Miller syndrome, Genée-Wiedemann syndrome, Wildervanck-Smith syndrome)]

1. Allanson JE, McGillivray BC: Familial clefting syndrome with ectropion and dental anomaly with limb anomalies. Clin Genet 27:426–429, 1985.
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26. Wildervanck LS: Case Report 28. Syndrome Ident 3(1):11–13, 1975.

Acrofacial dysostosis, type Arens or Tel Aviv

Arens et al (1), in 1991, described a female child born to uncle/niece parents. There was intrauterine growth retardation, mandibulofacial dysostosis, low-set pinnae with narrow auditory canals, absence of the fifth rays in all extremities, camptodactyly of fingers, asymmetric syndactyly of fingers 3–5, and rudimentary polydactyly between digits 3–4. In addition, there was congenital hip dislocation, talipes, absence of distal phalanges of toes 2–3, and death at two months.

Inheritance may be autosomal recessive.

Reference (Acrofacial dysostosis, type Arens or Tel Aviv)

1. Arens R et al: A new form of postaxial acrofacial dysostosis? Am J Med Genet 41:438–443, 1991.

Acrofacial dysostosis, type Catania

Opitz et al (1), in 1993, reported a mother and four sons from Catania, Sicily with autosomal dominant inheritance of a previously undescribed acrofacial dysostosis. Wulfsberg et al (2) reported an affected mother and daughter (Fig. 19–13A).

Mild intrauterine growth retardation and short stature were constant features as was mild microcephaly.

The hair was coarse and curly with a low posterior hairline and widow's peak. The forehead was high with somewhat sparse lateral eyebrows. There was short nose, relatively long upper lip with thin vermilion and smooth philtrum, overjet or overbite, small posteriorly angulated pinnae, and small chin.

The hands exhibited brachydactyly (especially the thumb), transverse palmar creases, short fifth fingers with or without clinodactyly, fetal finger pads, and low total ridge count.

Mild mental retardation was evident in several of the patients. Inguinal hernia, hypospadias, and cryptorchidism were seen in the males.

Autosomal (less likely X-linked) dominant inheritance was noted.

References (Acrofacial dysostosis, type Catania)

1. Opitz JM et al: Acrofacial dysostosis: Review and report of a previously undescribed condition: The autosomal or X-linked dominant Catania form of acrofacial dysostosis. Am J Med Genet 47:660–678, 1993.
2. Wulfsberg EA et al: Confirmation of the Catania brachydactylous type of acrofacial dysostosis: Report of a second family. Am J Med Genet 63:554–557, 1996.

Acrofacial dysostosis, type Palagonia

Sorge et al (1), in 1997, reported a family of four patients with a new type of acrofacial dysostosis characterized by short stature, pili torti, aplasia cutis verticis, oligodontia, mild soft tissue syndactyly of digits, malar hypoplasia, micrognathia, and normal intelligence (Fig. 19–13B). One patient had cleft lip. The family lived in Palagonia, Italy.

Skeletal changes included short fourth metacarpal, large atlas, small odontoid, and mild scoliosis.

Inheritance was either autosomal or X-linked dominant.

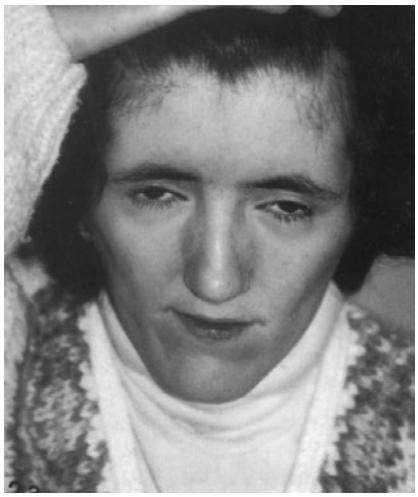
Reference (Acrofacial dysostosis, type Palagonia)

1. Sorge G et al: Another "new" form, the Palagonia type of acrofacial dysostosis in a Sicilian family. Am J Med Genet 69:388–394, 1997.

Acrofacial dysostosis, type Reynolds

Reynolds et al (1) described a family manifesting autosomal dominant inheritance of a previously undescribed acrofacial dysostosis syndrome. The craniofacial manifestations were those of mild mandibulofacial dysostosis and included prominent forehead, ptosis, downslanting palpebral fissures, malar hypoplasia, highly arched palate with dental malocclusion, and micrognathia (Fig. 19–13C,D). The pinnae were normal. However, mild congenital mixed type hearing loss was a feature.

The variable acral abnormalities predominantly affected the radial ray, manifesting as mild hypoplasia of the first metacarpal and first proximal



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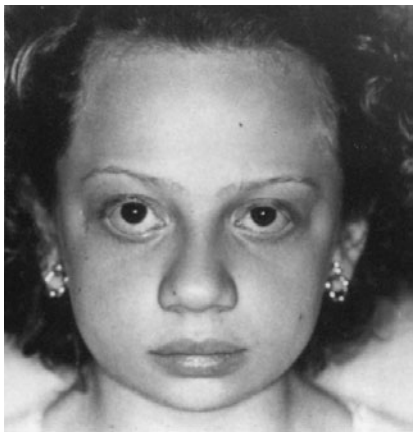

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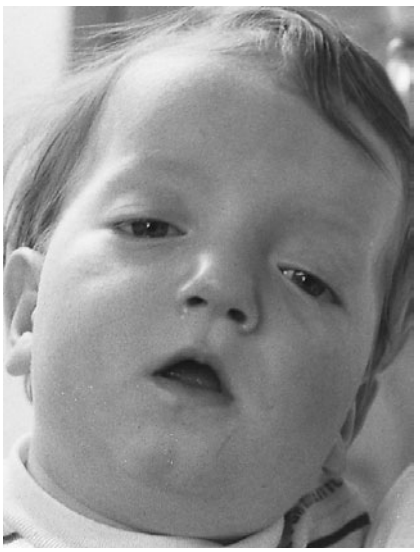

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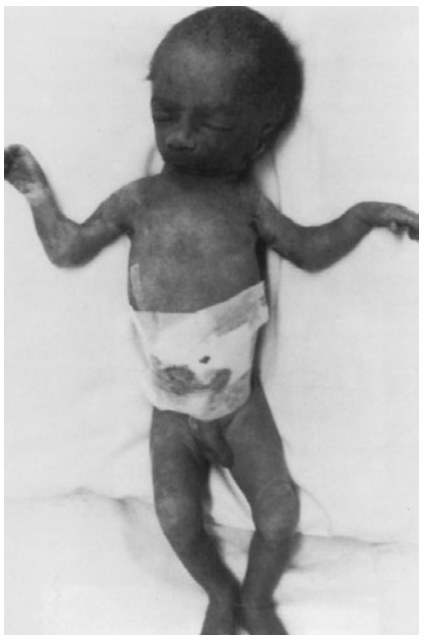
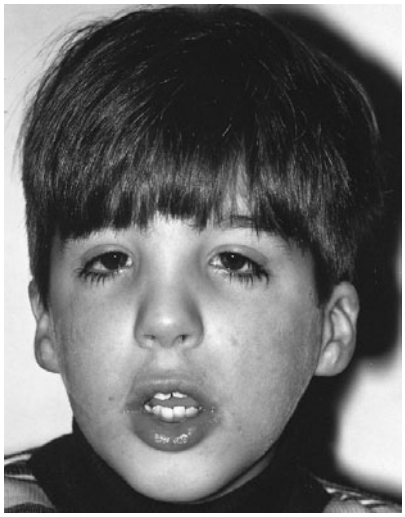


F

Fig. 19–13. *Acrofacial dysostosis*. (A) *Type Catania*. Coarse curly hair with widow's peak, high forehead, triangular face, small chin. (B) *Type Palagonia*. Pili torti, bilateral ectropion of lower lids, sparse brows, malar hypoplasia, micrognathia. (C,D) *Type Reynolds*. Affected grandfather and grandson. Craniofacial features are those of mild mandibulofacial dysostosis and include prominent forehead, eyelid ptosis, downslanting palpebral fissures. Note normal ears in both and micrognathia in D. (E,F) *Lethal acrofacial dysostosis, type Rodriguez*. Note malformed pinnae with atretic canals, prominent nasal bridge, severe micrognathia. Variable anomalies include absent forearm bones and predominantly preaxial digital anomalies. The lower limbs are similarly variable in extent of defect. (A from EA Wulfsberg et al, Am J Med Genet 6:554, 1996. B from G Sorge et al, Am J Med Genet 69:388, 1997. C,D from JF Reynolds et al, Am J Med Genet Suppl 2:143, 1986. E from JP Fryns and A Kleckowska, Am J Med Genet 39:223, 1991. F from JI Rodriguez et al, Am J Med Genet 35:484, 1990.)



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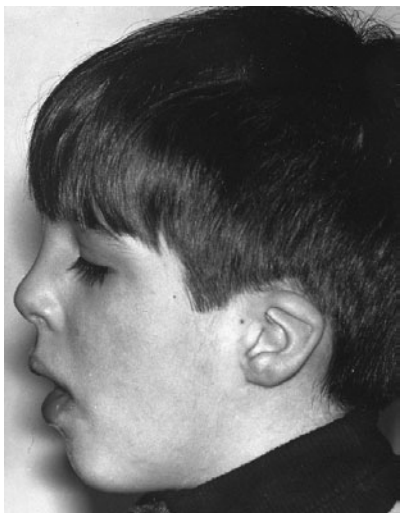

B

Fig. 19–14. *Maxillofacial dysostosis*. (A,B) Maxillary hypoplasia, downslanting palpebral fissures, minor ear anomalies. [From M Melnick and JR Eastman, Birth Defects 13(3B):39, 1977.]

phalanx. This was more evident on metacarpal-phalangeal pattern profile than on clinical examination in some affected individuals.

There is some resemblance of the facies to that of *maxillofacial dysostosis*.

Reference (Acrofacial dysostosis, type Reynolds)

1. Reynolds JF et al: A new autosomal dominant acrofacial dysostosis syndrome. Am J Med Genet Suppl 2:143–150, 1986.

Acrofacial dysostosis, type Rodriguez

In 1990, Rodriguez et al (4) reported three male sibs with a lethal acrofacial dysostosis. Death occurred in the neonatal period for respiratory problems secondary to severe mandibular underdevelopment. Other examples have been described (1,3). A 100-year-old example has been reported (2).

In addition to severe micrognathia, there are malar hypoplasia, malformed pinnae with atretic canals, prominent nasal bridge and, in most cases, cleft palate (Fig. 19–13E,F).

Skeletal alterations are variable but include short or absent humerus, absent forearm, preaxial (predominantly) and/or postaxial digital anomalies, lower limb defects, including digital deficiencies, shoulder and pelvic girdle hypoplasia, and rib defects.

Cardiac malformations, CNS malformations, and absent lung lobation can also be seen.

To be excluded are *Genée-Wiedemann syndrome* and *Nager syndrome.*

References (Acrofacial dysostosis, type Rodriguez)

1. Fryns J-P, Kleckowska A: New lethal acrofacial dysostosis syndrome. Am J Med Genet 39:223–224, 1991.

2. Oostra RJ et al: Severe acrofacial dysostosis with orofacial clefting and tetraphocomelia in the plaster cast of a 100-year-old anatomical specimen. Am J Med Genet 78:195–197, 1998.

3. Petit P et al: Acrofacial dysostosis type Rodriguez: A new lethal MCA syndrome. Am J Med Genet 42:343–345, 1992.

4. Rodriguez JI et al: New acrofacial dysostosis syndrome in 3 sibs. Am J Med Genet 35:484–489, 1990.

Maxillofacial dysostosis, autosomal dominant

Peters and Hövels (3), in 1960, described autosomal dominant inheritance of maxillary hypoplasia, downward-slanting palpebral fissures, minor changes in the pinnae, and abnormal and retarded speech (Fig. 19–14). They employed the term maxillofacial dysostosis to differentiate the condition from mandibulofacial dysostosis. An earlier report by Villaret and Desoille (4) probably represents the same disorder. Other more recent reports (1,2) have confirmed the existence of the syndrome. Our combined experience suggests that the disorder is more frequent than the sparse number of reports indicates.

References (Maxillofacial dysostosis, autosomal dominant)

1. Escobar V et al: Maxillofacial dysostosis. J Med Genet 14:355–358, 1977.

2. Melnick M, Eastman JR: Autosomal dominant maxillofacial dysostosis. Birth Defects 13(3B):39–44, 1977.

3. Peters A, Hövels O: Die Dysostosis maxillo-facialis, eine erbliche, typische Fehlbildung des 1. Visceralbogens. Z Menschl Vererb Konstit Lehre 35:434–444, 1960.

4. Villaret M, Desoille H: L'hypoplasie primitive familiale du maxillaire supérieur. Ann Med (Paris) 32:378–381, 1932.

Maxillofacial dysostosis, X-linked (Toriello syndrome)

Toriello et al (5) reported two male sibs and their male first cousin with somewhat short stature, microcephaly, mild mental retardation, down-slanting palpebral fissures due to malar hypoplasia, sparse lateral eyebrows, outstanding pinnae, mild micrognathia, slightly webbed neck (Fig. 19–15), and cryptorchidism. All had mixed hearing loss of sufficient degree to warrant hearing aids. One had stenotic external ear canals. Inheritance may be X-linked. Ensink et al (2) described two brothers. Intelligence was normal. Zelante et al (6) also reported a single affected male. There is some resemblance to *maxillofacial dysostosis, autosomal dominant* (4).

References [Maxillofacial dysostosis, X-linked (Toriello syndrome)]

1. Brunner HG et al: Molecular genetics of X-linked hearing impairment. Ann New York Acad Sci 630:179–190, 1991.

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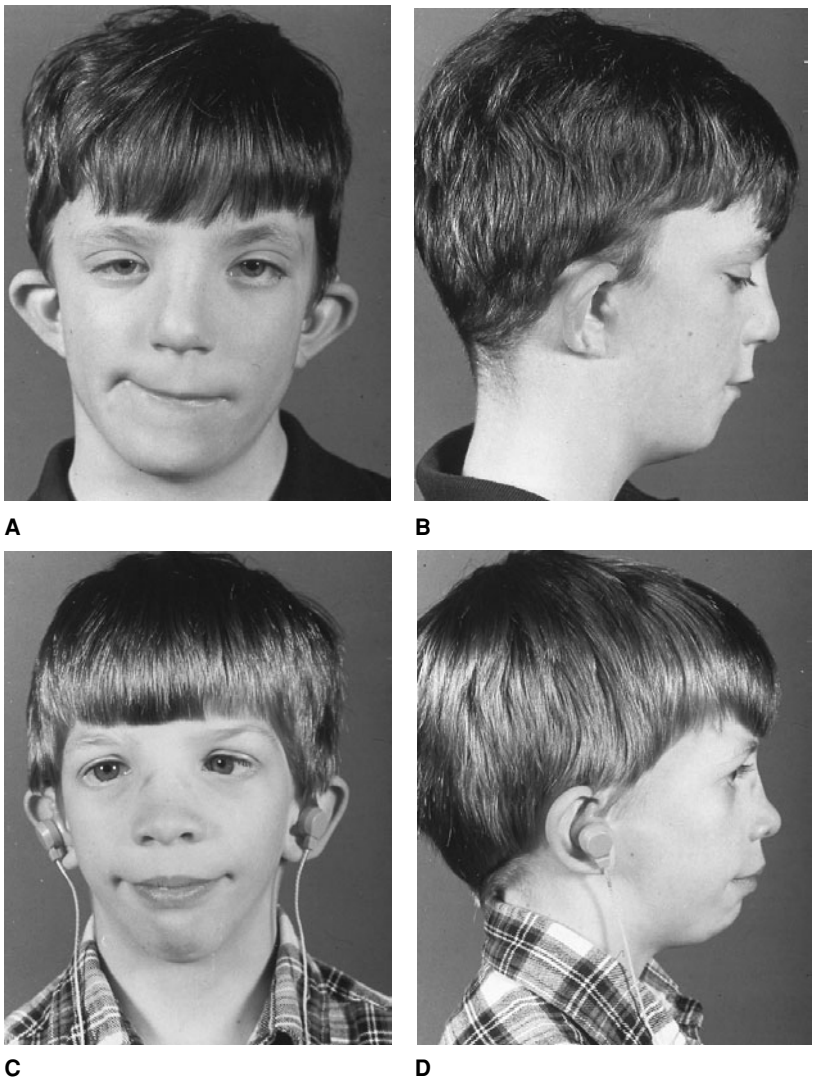

Fig. 19–15. *Maxillofacial dysostosis, X-linked.* (A–D) Two male sibs with microcephaly, downslanting palpebral fissures, sparse eyebrows laterally, outstanding pinnae, mixed hearing loss, mild micrognathia, and slightly webbed neck. (From HV Toriello et al, Am J Med Genet 21:137, 1985.)

Branchio-oto-renal syndrome (BOR syndrome)

Melnick et al (45), in 1975, first used the term branchio-oto-renal syndrome (BOR) to refer to patients with *b*ranchial cleft, fistulas or cysts, *o*tologic anomalies, including malformed pinnae, preauricular pits or sinuses, and hearing loss; and *r*enal anomalies of various types. Many other clinical features have subsequently been noted. Its prevalence is approximately 1/40,000 (20). The first summary descriptions were published in the nineteenth century (4,28,54,55). Early examples were reviewed by Anand et al (3). Excellent summaries by Fraser et al (19), Cremers and Fikkers-van Noord (12), and Allanson (2) are available.

The branchio-oto (BO) syndrome (44,47) has been thought to be distinct from the BOR syndrome based on molecular considerations (vide infra). The earpit-hearing loss syndrome had been considered a distinct entity (42). We suspect that the syndrome of renal pelviocalceal dysmorphism and sensorineural hearing loss is the same as BOR syndrome (50).

The BOR syndrome has autosomal dominant inheritance with variable expressivity (19,30,32,46,51). Penetrance is very high (12,19,20,26,52) but not complete (27). The gene has been mapped to 8q13.3 (1,31, 34,64,68). There is heterogeneity (64a), a second gene having been mapped to 1q31 (36). Kumar et al (35) stated that BOR syndrome and BO syndrome were not allelic whereas Vincent et al (67) demonstrated that they were allelic. The gene for BOR is the homologue for *Drosophila eyes absent* (1). In the mouse, expression of the gene occurs in all phases of the developing inner ear and in metanephric cells surrounding the ureteric branches that have just divided (1).

Craniofacial findings. Facial shape is frequently long and narrow with a constricted palate and deep overbite (10,19,45,46). Facial nerve paralysis (12,27,58) has been described in approximately 10% of cases and aplasia or stenosis of the lacrimal duct in 25% (8,12,19,47). Rarely, clinical features suggestive of lacrimal duct stenosis are actually due to misdirected seventh cranial nerve enervation leading to gustatory lacrimation (56). Occasionally, facial or mandibular asymmetry is found (27,51,58).

Ears. Anomalies of the external ear, noted in 30%–60%, range from severe microtia to minor anomalies of the pinnae, variously described as cup, flap, lopped, flattened, or hypoplastic (19,49) (Fig. 19–16). The external canal may be narrow, "malformed," or slanted upward in 30% (8). Helical or preauricular pits are present in 70%–80% (8,19). The pits are shallow, pinhead sized, with blind depressions in the helix of the ear near its upper attachment, or in the skin anterior to this site (12,27,46). Rarely, the pits communicate with the tympanic cavity (11).

Hearing loss has been reported in approximately 75%–95% (8,12,19): conductive, 30%, sensorineural, 20%, and mixed, 50% (12,13,23). Age of onset ranges from early childhood to young adulthood. Only rarely is there acute deterioration (22). All three types have been observed in different members of the same family (12,17,19,27,70).

Malformations of the ossicles include unconnected or fused stapes and incus (12,13,27). Inner ear malformations include bulbous internal auditory canal (8) and unilateral or bilateral malformed cochlea (12,16,17,19,46,53,62). The cochlea is often hypoplastic, with an acutely

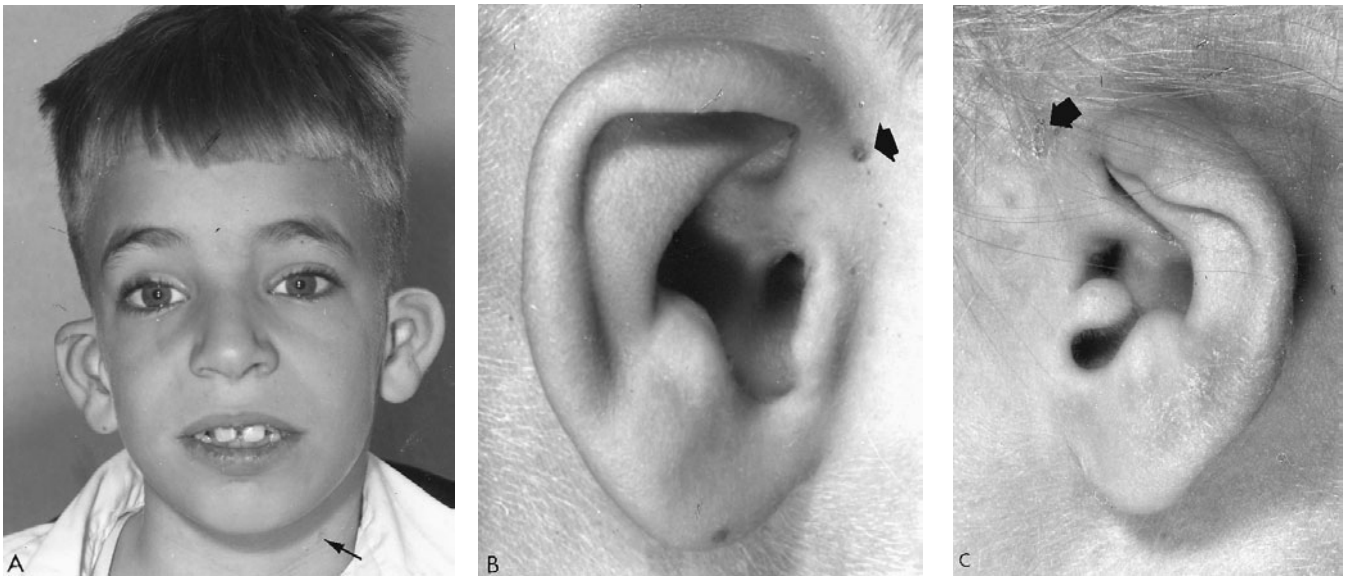

Fig. 19–16. *Branchio-oto-renal syndrome*. (A) Outstanding malformed pinnae. (B) Preauricular pit, marked by arrow. (C) Auricular appendage, grossly malformed ear, and preauricular pit.

angled basal turn, and a reduced number of coils (1 1/2 or 2, in comparison to the usual 2 1/2) (8,32,53,62,73). This is similar to but not characteristic of Mondini defect. However, Mondini dysplasia of the inner ear has been reported in this condition (17,22,46).

There is no vestibular alteration.

Branchial cysts/fistulas. Branchial cleft cysts or fistulas are reported in approximately 50%–60% (12,19). Branchial cleft cysts, fistulas, or sinuses, usually bilateral, are present on the external lower third of the neck, usually at the median border of the sternomastoid muscle. The fistulas may rarely open internally into the tonsillar fossa; they may drain fluid or become infected. Nipple-like cartilage rests can also be found.

Genitourinary system. Between 12% and 20% of affected individuals reported in the literature had diagnosed structural anomalies of the renal system (12,19). This is probably underreporting, as the renal anomalies may be so subtle that they can be missed on intravenous pyelography (20,27).

For accurate readings it is advisable to inform the radiologist of potential manifestations of the syndrome (27). One systematic study of 19 patients by intravenous pyelography showed 75% had a structural anomaly and 33% had functional anomalies of the renal system (12). Another study of 16 patients found 100% to have structural or functional renal manifestations (70). Some renal anomalies can remain asymptomatic (12); most are minor. Only approximately 6% have severe symptomatic renal involvement (7,16,17,20,47,57). If renal agenesis or severe hypoplasia is not present in infancy, the anomalies are not progressive (70).

Severe renal anomalies include bilateral renal agenesis (7,16,17,24,47) and polycystic kidneys (12,46). Structural anomalies can range from mild to severe and include hypoplastic kidneys (9,16,44,70), vesicoureteric reflux (10,27), crossed renal ectopia (7), bilateral bifid renal pelvis (27), uretero-pelvic junction obstruction (27), extra-renal pelvis (27), fetal lobulation (27), abnormal rotation of the kidney (70), and calyceal diverticuli or distorted calyceal system (19,46,70).

Mild structural anomalies include slight blunting of the calyces, blunted calyceal fornices without pyelonephritis or papillary necrosis, segmented hypoplasia of the superior pole, reduced renal parenchymal volume (12), and outpouching of the renal pelvis on the medial border of the kidney (12,46).

With regard to renal function, a small number of patients have disturbed concentration capacity and proteinuria, or reduced clearance of creatinine and diminished glomerular filtration rates (12,70). Histological studies may reveal prominent glomerular lesions (14,70) and irregularly shaped tubuli with swollen tubular epithelial cells (70). Segmental and focal hyalinization with dense immunoglobulin deposits of IgG, IgM, IgA, and C_3 along the basement membrane and in the mesangium have been observed (14).

Neither the presence/absence nor the severity of the renal defect may run true within families (7,16,17,24).

Diagnosis. Preauricular tags occur in 0.2% of live births and preauricular pits or sinuses in 0.8% of the normal population. Nonsyndromic preauricular pits or sinuses are far more common in blacks than in whites (44). Approximately 1/200 children with a preauricular pit has profound hearing loss (20,41). Autosomal dominant inheritance of isolated preauricular pits with approximately 85% penetrance (25) is well described (33,40). Preauricular pits and renal disease have been reported in a family in which there was no evidence of branchial anomalies or other features of the BOR syndrome (37). Some individuals had only preauricular pits, others only renal disease, while a third group had a combination of the two.

Branchial cleft sinuses are relatively common congenital anomalies that usually occur as isolated defects but may have autosomal dominant transmission (5,25,38,60,63,65,69). Several families have been reported in which the combination of preauricular pits and branchial fistulas is dominantly inherited without mention of hearing loss (6,48,51,59), although this was not ruled out audiometrically. Autosomal dominant preauricular pits and sensorineural hearing loss (18), autosomal dominant malformed auricules, preauricular tags or preauricular pits, and moderate conduction hearing loss (71) and branchial fistulas, malformed auricles, and hearing loss (43) have been reported. These may represent variable expressions of the BOR syndrome rather than distinct entities.

The branchio-oto-ureteral (BOU) syndrome (21) may also represent variable expressions of the BOR syndrome, particularly as Heimler and Lieber (27) have described a family in which some affected individuals have duplication of the collecting system and others have renal anomalies more characteristically associated with BOR syndrome. Still others have overlap with *OAV spectrum* (27,61). Fraser et al (21) proposed *duplication of the renal collecting system, external ear anomalies, and sensorineural hearing loss* as a separate entity, There is marked overlap between BOR syndrome and *otofaciocervical syndrome* (15), which is discussed later in this chapter. The latter lacks preauricular tags and lacrimal duct stenosis and has, in addition to features of BOR syndrome, unusual sloping

shoulders, short stature, and characteristic facies. There is some overlap with *Wildervanck syndrome.*

Several syndromes have been described with ear and renal anomalies including autosomal dominant dysmorphic pinnae-polycystic kidney syndrome (29), autosomal dominant dysmorphic pinnae-hypospadias-renal dysplasia syndrome (29), and autosomal recessive oto-renal-genital syndrome (72). We suspect that the syndrome described in 1994 by Marres et al (39) is really the BOR syndrome in chance association with commissural lip pits. Vincent et al (66) suggested a contiguous gene syndrome of BOR, *Duane syndrome*, a dominant form of hydrocephalus and aplasia of the trapezius.

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Wildervanck syndrome (cervico-oculo-acoustic syndrome, Klippel-Feil anomaly plus)

The major clinical features of Wildervanck syndrome are fused cervical vertebrae, abducens palsy with retracted globe (Duane syndrome), and sensorineural hearing loss (55,56). Different phenotypic definitions are evident (34,53,56).

All cases with this triad of abnormalities are sporadic. The overwhelming majority of affected individuals reported are female, although a few males with the condition have been described (15). Several modes of inheritance have been proposed (11,28,29,56) and nongenetic causes cannot be excluded (7).

Facial and ocular findings. Facial asymmetry (4,15,16) and nonprogressive hemifacial weakness, present since birth, have been described (8). Unilateral or bilateral Duane syndrome is a major feature (6,8,14,16,29,34,35,39,50,55). Duane syndrome consists of abducens paralysis that prevents external rotation of the affected eye. On adduction, the lid fissure of the affected eye narrows, and the globe retracts (Fig. 19–17). Abducens paralysis without retraction has also been reported (4,13). Pseudopapilledema, unilateral epibulbar dermoid (8,15), and bilateral temporal subluxation of the lens (50) have been observed. Cleft palate may be present (4,16,29) and an anterior glottic web has been noted. Some have abnormal bony masses in the mandibular ramus region that have occasionally been reported as duplication phenomena (2,12,30).

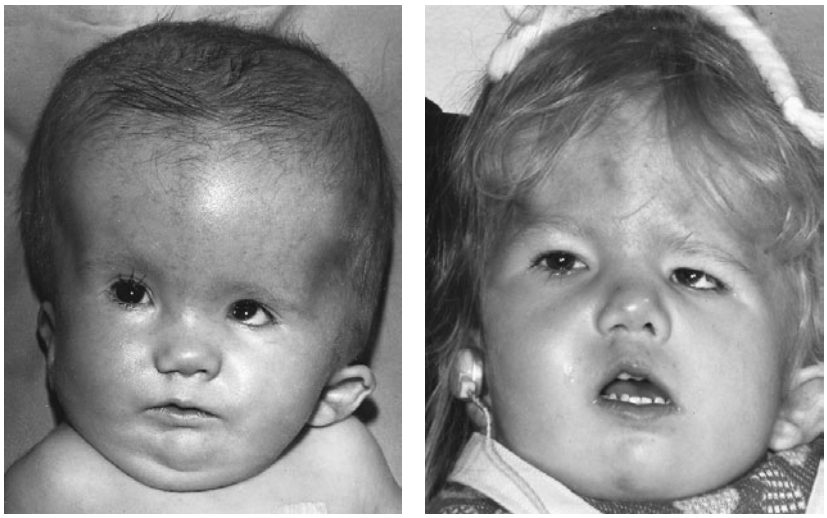
Auditory system. Among patients having just Duane's anomaly (44), hearing loss, both sensorineural and conductive, has been found in approximately 15%. However, in Wildervanck syndrome, hearing loss is found in at least 30%. It may be sensorineural (15–17,24,29,35,37,50), conductive (4,10,13,26,44,45,48,49,51), or mixed (7,15,37). Although age of onset is usually in the first decade (7,47,54,55) and may be profound (29), the severity and age of onset have not been well documented. The loss may be unilateral (8,14,53). In addition, preauricular tags (8,15,37), cheek skin tags, malformation of the pinna (4), atresia or absence of the external auditory canal (8,13), abnormal and absent ossicles (8,32), ossified stapedial tendon (8), stenotic or short internal auditory meatus (14), stapes fixation (7), stapes gusher (9), abnormal semicircular canals (14,32), and underdevelopment of the bony labyrinth (Mondini deformity) (3,14,27,37,43,46,52,53,57) have also been described. Caloric areflexia is usually found (3,14,25,54).

Musculoskeletal system. Klippel-Feil anomaly, consisting of fusion of one or more cervical and sometimes thoracic vertebrae, is characteristic (4,7,8,13,15,18,29,55). The neck is short, thick, and webbed, and the head appears to sit directly on the trunk (4,8,14,16,50). Flexion, extension, and lateral mobility of the neck are severely restricted (4,13,14,16,29) and there may be torticollis (15). Spina bifida occulta (13,15,16), Sprengel deformity, hemivertebrae (8), fusion of ribs (8), absent ribs (8), kyphosis (8), scoliosis (8,14,15), and basilar impression (4,13–15) have been reported.

Central nervous system. A few authors describe mild (4,6) or severe (16) mental retardation. Facial paralysis and mirror movements (13) have been reported as has brainstem hypoplasia (5a).

Diagnosis. Differential diagnosis is complicated because many patients with Klippel-Feil anomaly have been incompletely described; some may have Wildervanck syndrome. Klippel-Feil anomaly and associated abnormalities have been particularly well reviewed by Helmi and Pruzansky (23). There is overlap with *oculo-auriculo-vertebral spectrum* (8,15). A number of unusual cases with some Wildervanck syndrome features are difficult to classify (5,6,29,33,50). Okihiro syndrome consists of autosomal dominant inheritance of Duane anomaly with congenital hypoplasia of the thenar eminence and sensorineural hearing loss (22,40). The hand anomalies resemble those seen in Stewart-Bergstrom syndrome (19). MURCS association (Rokitansky-Küster-Hauser syndrome) consists of *M*üllerian duct aplasia, *R*enal aplasia, *C*ervicothoracic *S*omite dysplasia. Vertebral defects occur from C_5 to T_1. Clinical manifestations include Klippel-Feil anomaly, absent uterus and vagina, renal agenesis, and conductive hearing loss (20,24,31,36,38,41,42).

The *unusual smiling face, cleft palate, and absence of middle ear space syndrome*, mislabeled by Wiedemann, consists of bilateral grooves, as if



A B

Fig. 19–17. *Wildervanck syndrome (cervico-oculo-acoustic syndrome)*. (A,B) Same patient at different ages showing asymmetry of head, severe cervical vertebral involvement, strabismus, arrested hydrocephaly, and sensorineural hearing loss.

smiling when the mouth is closed. Some of these patients have cleft palate, hearing loss, and partial duplication of the upper jaws as well as cervical vertebral fusion (53a). We have seen similar cases reported by C Morris (personal communication, 1998).

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Townes-Brocks syndrome (lop ears, imperforate anus, triphalangeal thumbs, and sensorineural hearing loss, REAR syndrome)

Townes and Brocks (36), in 1972, described a family in which a father and five of his seven children displayed a syndrome of "satyr" ears with sensorineural hearing loss, imperforate anus, and triphalangeal thumbs. Similarly affected families have subsequently been described (2,4–7,9,15–17, 22,25,28,29,31,32,38) and the spectrum of anomalies expanded to include renal and cardiac defects. At least 65 cases have been published. An excellent review is that of Powell and Michaelis (20). The acronym, REAR (*r*enal-*e*ar-*a*nal-*r*adial) syndrome, has been used (17).

The syndrome has autosomal dominant inheritance with variable expressivity (21). The gene has been mapped to 16q12.1 (14,31). Mutations in *SALL1*, a putative zinc finger transcription factor gene, cause the syndrome (3,5,14,14a,19).

Ears. The satyr form of lop-ear anomaly with folding of the superior helix has been found in 25%–35% (23) (Fig. 19–18A–C). Additional ear anomalies include preauricular skin tags (40%), preauricular pits (5%),

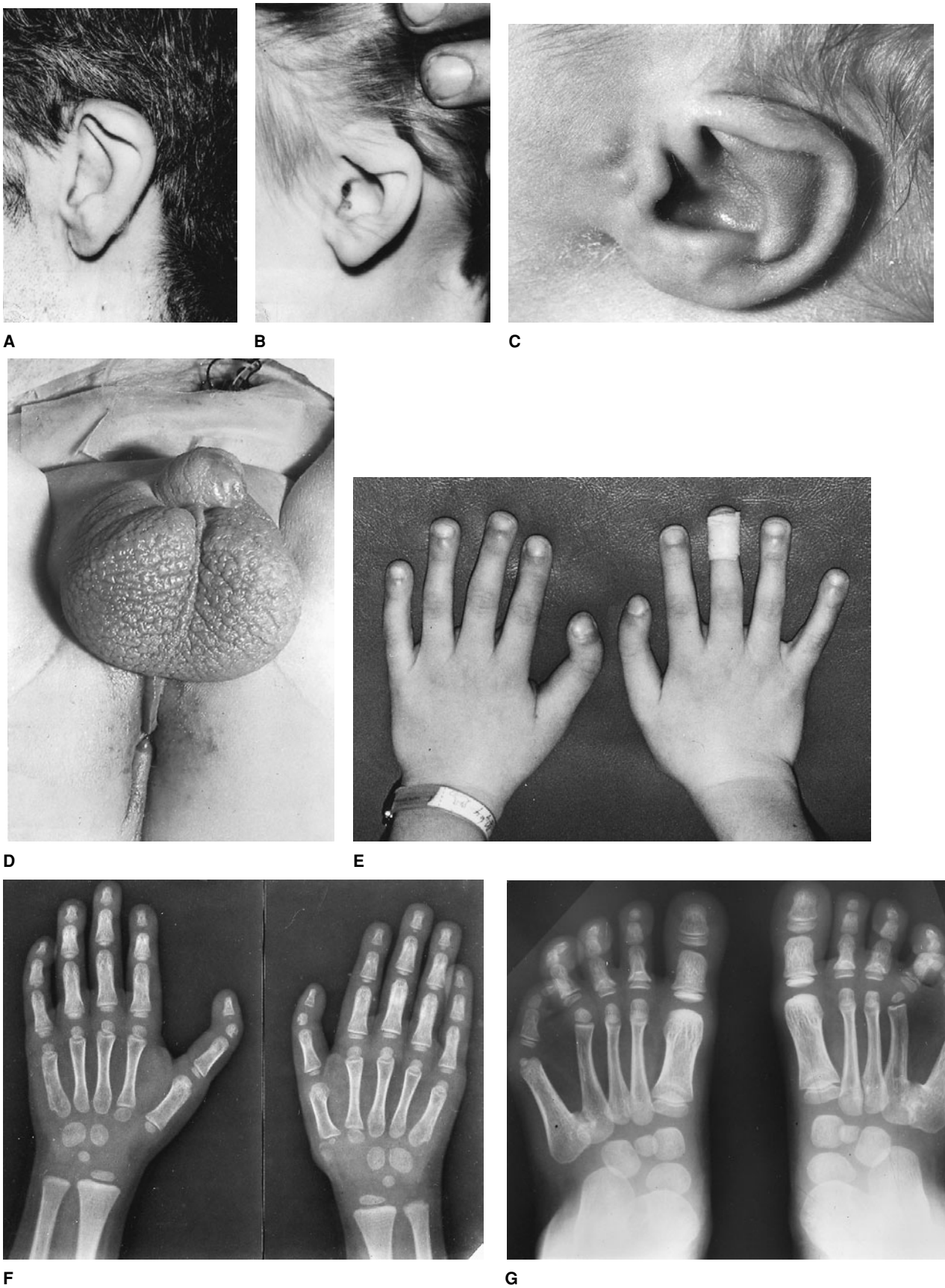

Fig. 19–18. *Townes-Brocks syndrome*. (A) Lateral view showing satyr form of lop-ear anomaly. (B) Another lateral view presenting similar abnormality. (C) Small satyr ear with preauricular protuberances. (D) Imperforate anus, prominent perineal raphé, scrotum bifidum, and glandular hypospadias. (E) Deviation of distal phalanges of thumb. (F) Note triphalangeal thumbs. Supernumerary thumbs had been surgically excised. Note accessory carpal bone and absence of triquetral bones. (G) Radiograph of feet. Note lateral displacement and fusion of proximal ends of fourth and fifth metatarsals. Also observe cone-shaped epiphyses at proximal end of first metatarsals and at proximal phalanges of second and third toes. (A,B,E–G from PL Townes and ER Brocks, J Pediatr 81:321, 1972; C,D from MACS de Vries-Van der Weerd et al, Clin Genet 34:195, 1988.)

and microtia (2,18,24), findings similar to those in *oculo-auriculo-vertebral spectrum*.

Among those with dysmorphic pinnae, 14 of 48 (30%) patients had congenital unilateral or bilateral sensorineural hearing loss. In childhood, it is mild (20–40 dB) and slowly progresses to 40–60 dB in adulthood (24,29). Ossicular anomalies can be found (6).

Gastrointestinal system. Anorectal anomalies constitute the most constant feature of this condition, having been found in 39 of 40 patients (5). Imperforate anus (usually high) has been found in 43% of 54 patients. It is associated with rectoperitoneal or rectovaginal fistula in 65% of cases (24). A midline peroneal raphe may extend from the site of the anal orifice to the scrotum (5,28). Anal anomalies may also include anterior placement (seven females), anal stenosis (15%) (24), or excess perianal skin without functional disturbance (six males) (23).

Musculoskeletal system. The skeletal anomalies are variable, but radial ray anomalies are present in more than 50% with triphalangeal thumbs (25%), bifid thumbs, broad thumbs, hypoplastic thumbs, supernumerary thumbs (25%), and distal ulnar deviation of thumbs all described (Fig. 19–18E–G).

Variable syndactyly of the second to fourth fingers has been seen (5,6). Absence of third toes, syndactyly of third and fourth toes, overlapping of second to fourth toes, clinodactyly of fifth toes, and pes planus have been noted in approximately 25%.

Hand radiographs have demonstrated broad bifid thumb with ulnar deviation, hypoplastic thumb, slender or bifid first metacarpal, pseudoepiphysis of the second metacarpal, absent triquetral and/or navicular bones, fused triquetrum and hamate, cone-shaped epiphyses, and short or fused metatarsals (5,6,9,36,38). Foot radiographs may exhibit duplication of tarsal bone, fused metatarsals, rocker bottom feet, and absent or small third toe.

Scoliosis has also been documented (3,11). These same patients had mental retardation.

Genitourinary system. Although renal anomalies were not part of the original description, 15% have been reported with a variety of findings including renal hypoplasia, unilateral renal agenesis, polycystic kidney, posterior urethral valves, ureterovesical reflux, meatal stenosis, and glandular hypospadias (5,7,9,29) (Fig. 19–18D). End stage renal failure has been noted (2,3,5,22,29).

Cardiovascular system. Congenital heart defects, seen in 10%, include tetralogy of Fallot, atrial septal defect, truncus arteriosus, and ventricular septal defect (2,6,9).

Central nervous system. Mental retardation has been noted in a few patients (3,11,38).

Diagnosis. The incidence of anal/rectal malformations varies from 1/1500 to 1/5000 live births (35). Most isolated malformations are sporadic although, in rare instances, autosomal dominant, autosomal recessive, and X-linked recessive inheritance have been reported (13,33,37,39). In approximately 50% of affected individuals, associated congenital anomalies can be found (6,8). Imperforate anus may be part of a complex association of vertebral defects, cardiac defects, tracheoesophageal fistula with esophageal atresia, and radial and renal defects known as VATER or VACTERL association (23). Auricular defects are rarely present in VATER association. However, anal malformations (55%), renal dysplasia or agenesis (45%), congenital heart anomalies (75%), ear anomalies (40%), and thumb anomalies (30%) show considerable overlap with Townes-Brocks syndrome (39). Quan and Smith (27) proposed that defective differentiation of mesoderm, prior to 35 days gestation, might be the pathogenetic mechanism in VATER or VACTERL association. Such a mechanism may be the basis for the clinical manifestations of Townes-Brocks syndrome as well.

Triphalangeal and/or bifid thumb may be inherited as an isolated dominant trait (34), in Fanconi anemia, or in association with cardiovascular anomalies in the Holt-Oram syndrome (10), Blackfan-Diamond syndrome (19), and *Baller-Gerold syndrome*. Aase and Smith (1) described a combination of congenital anemia and triphalangeal thumbs as an autosomal recessive syndrome. Triphalangeal thumbs have also been reported in association with hearing loss. What appears to be autosomal dominant *oculo-auriculo-vertebral spectrum* with anal stenosis has been labeled Townes-Brocks syndrome (12,20). The association of anorectal malformation with end stage renal disease and sensorineural hearing loss in several members of a three-generation family was reported by Lowe et al (18) but the association may have been one of chance. Finally, many of the features of Townes-Brocks syndrome, including preauricular tags, anal atresia, cardiac and renal malformations, are also seen in partial duplication 22 (*cat eye syndrome*), so careful chromosome studies are indicated, particularly if ocular anomalies are present (30).

Laboratory aids. Sensitivity testing to diepoxybutane should be done to rule out Fanconi anemia (26).

References [Townes-Brocks syndrome (lop ears, imperforate anus, triphalangeal thumbs, and sensorineural hearing loss, REAR syndrome)]

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Oral-acral syndrome, type Verloes-Koulischer

Verloes and Koulischer (3), in 1992, described a woman with absence of the medial part of the upper alveolar ridge, including gingiva, frenulum, and tooth buds for the maxillary incisors and canines. Cohen (1), in the same year, described a boy with absent maxillary incisors and canines and asymmetric defects of hands and left first and second toes. de Silva and Verloes (2) added still another example in 1998. The child had absent fourth fingers of one hand and bilateral fifth finger clinodactyly. In all three cases, the upper lip receded because of the absence of the upper median alveolar ridge. Pathogenesis is unclear. Perhaps there is a vascular etiology, causing secondary disruption of an area of the maxilla and tooth buds. Digital development is similar to that in amniotic disruption syndrome.

References (Oral-acral syndrome, type Verloes-Koulischer)

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Meier-Gorlin (ear-patella-short stature) syndrome

Meier et al (13), in 1959, reported a male with micrognathia, microtia, midface hypoplasia, ankylosis of knees, cryptorchidism, and agenesis of the patellae. Gorlin et al (7,8) described a male with microtia, absent patellae, and micrognathia. As an infant, his "knees bent backwards." There was unilateral cryptorchidism. Blount osteochondritis dessicans and bilateral aseptic necrosis of the lateral femoral condyles were found on radiologic examination. Subsequently, several additional examples have confirmed the syndrome (3–6,9,15,16).

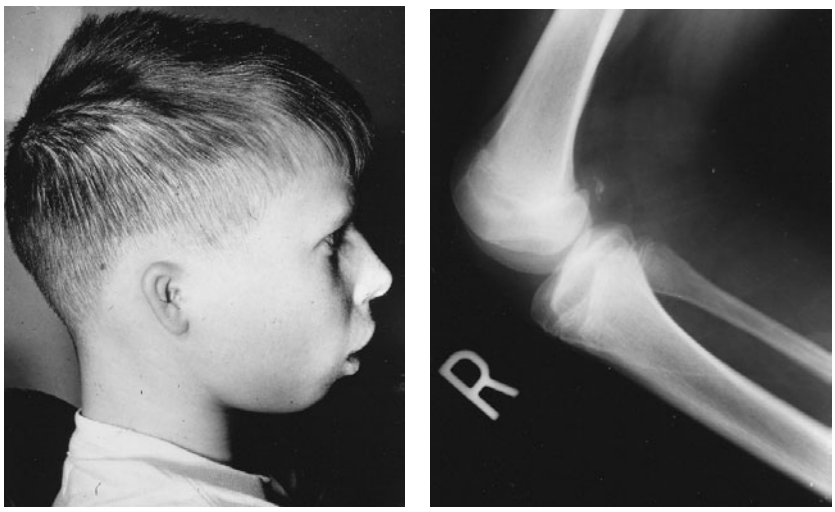
Inheritance is clearly autosomal recessive. In addition to parental consanguinity (11), there have been several pairs of affected sibs (3,5, 6,9,12,14a). Lacombe et al (11) postulated that the syndrome is similar to the short ear mouse phenotype. The murine disorder is an osteochondrodysplasia caused by a mutation within the bone morphogenetic protein 5 gene (BMP5).

Birth weight, length and head circumference have been below the 3rd centile in most cases. Height has been below the 3rd centile, but there may be catch-up growth during adolescence (6). Early closure of sutures (8,9), craniosynostosis (9,12), or prominent sutures (3) have been noted. Postnatal growth retardation can be marked (3,5). All had small pinnae and small mandibles; some also had small maxillae (Fig. 19–19). Several had full lips and small mouth. Hearing loss due to Mondini malformation has been noted (12). The nose is somewhat pointed.

Joint restriction (9), laxity (3,5,16), or aseptic necrosis (7,9) were observed as was clinodactyly of the fifth finger (3,5). The patellae were small or absent (Fig. 19–19). Long bones were slender and bone age delayed in all patients. The ribs may be short. Several patients had hooked clavicles (3,5,9,16). The glenoid fossa tended to be flat or absent and the epiphyses abnormal (3,5,9).

Clitoromegaly has been observed in two sisters (1).

The slight build may be confused with *3-M syndrome, Silver-Russell syndrome*, or *gloomy face syndrome*. The facies is mildly reminiscent of the symmetrical facial dysostoses (*mandibulofacial dysostosis, maxillofacial dysostosis*, and others in this group). The so-called small patella syndrome (coxo-podo-patellar syndrome) is an autosomal dominant



A B

Fig. 19–19. *Meier-Gorlin (ear-patella-short stature) syndrome*. (A) Microtia, micrognathia. (B) Agenesis of patellae. [From RJ Gorlin et al, Birth Defects 11(2):39, 1975.]

disorder characterized by small and subluxated patella, delayed patellar bone age or absent patella, occasional unusual facies (broad nasal bridge, anteverted nares, long philtrum, prominent lower lip, micrognathia), long tapered fingers, increased space between hallux and second toe, metatarsus adductus, ischiopubic rami defect with infraacetabular notch, abnormal scapulae, and short middle phalanges of second and fifth fingers (10).

A patient with a recessive form of small patella syndrome had absent ischia and inferior pubic rami as well as cleft palate. Also noted were hypotonia, macrocephaly, genu recurvatum, and delayed bone age. It was mentioned that the pinnae were small (1). Another recessive family has been poorly documented (2).

Various other small patella syndromes are discussed by Sandhaus et al (14). The autosomal recessive genito-patellar syndrome consists of absent patellae, scrotal hypoplasia, renal anomalies, unusual facies, and mental retardation. Among other findings are coarse facies, large nose, microcephaly, flexion deformities of the knees and hips with club feet, agenesis of corpus callosum, cryptorchidism, multicystic kidneys, hydronephrosis, and pulmonary hypoplasia. Radiographic changes are those of hypoplasia of the ischia and brachydactyly (5a).

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Carnevale syndrome

Carnevale (1) described two male sibs, the offspring of a consanguineous marriage, who manifested down-slanting palpebral fissures, ptosis of the upper eyelids, and convergent strabismus. They had limited extension of the forearms and hip dysplasia. Both exhibited mild mental deficiency, cryptorchidism, and partial agenesis of the abdominal musculature with diastasis (Figs. 19–20 and 19–21).

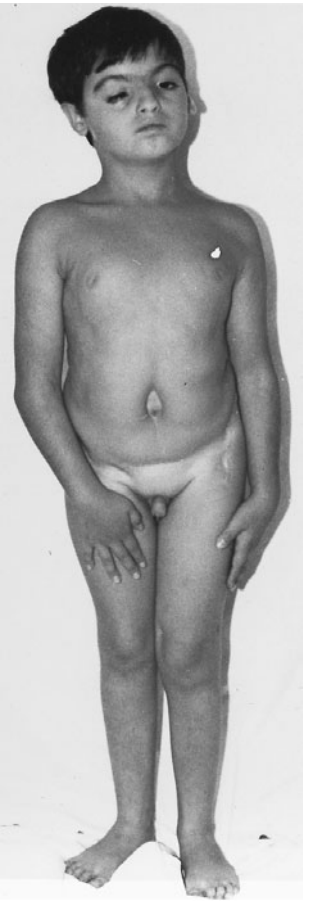
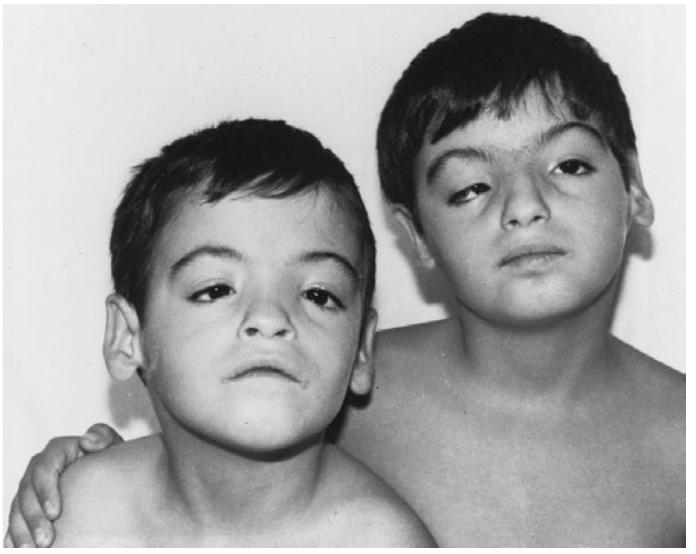


Fig. 19–20. *Carnevale syndrome*. Note ptosis, strabismus, limited extension at elbow, partial agenesis of abdominal musculature with diastasis, and cryptorchidism. (Courtesy of F Carnevale, Bari, Italy.)

Fig. 19–21. *Carnevale syndrome*. Two male sibs, the offspring of a consanguineous marriage. Note downslanting palpebral fissures, upper eyelid ptosis, and convergent strabismus. (Courtesy of F Carnevale, Bari, Italy.)



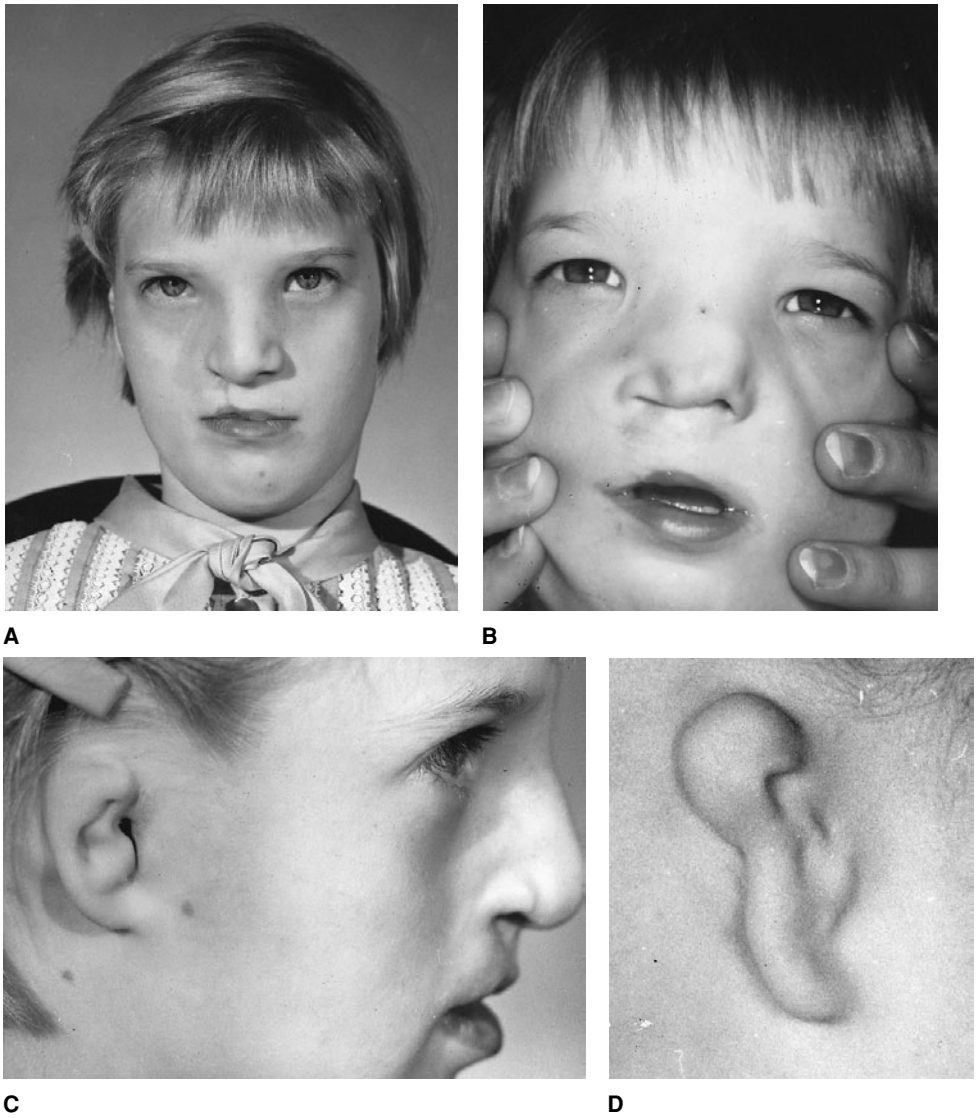


Fig. 19–22. *Hypertelorism-microtia-clefting syndrome*. (A,B) Note hypertelorism, repaired cleft lip in sisters. (C,D) Dysplastic pinna. [From D Bixler et al, Birth Defects 5(2):77, 1969.]

Reference (Carnevale syndrome)

1. Carnevale F et al: New syndrome: Ptosis of the eyelids, strabismus, diastasis recti, hip defect, cryptorchidism, and developmental delay in two sibs. Am J Med Genet 33:186–189, 1989.

Hypertelorism-microtia-clefting syndrome (Bixler syndrome, HMC syndrome)

*H*ypertelorism, *m*icrotia, and *c*left lip and palate (HMC syndrome) was described in two sibs by Bixler et al (2,3), in 1969 (Fig. 19–22). Schweckendiek et al (9), in 1976, reported identical twins with the same condition, and there have been several isolated case reports (1,5,8). A so-called Bixler syndrome variant is clearly an example of *oculo-auriculo-vertebral spectrum* (6).

Involvement of two of four sibs with normal parents in the original kindred strongly suggests autosomal recessive inheritance.

Four of six individuals with this condition had growth retardation. Broad nasal root with broadening of the nasal tip, which in extreme cases was bifid (1–3), was common. All six had ocular hypertelorism. Unilateral cleft lip and palate was present in five of six individuals, the older twin reported by Schweckendiek et al (9) being the exception. In four of five cases, the lip/palate anomaly was right-sided. Other facial anomalies included asymmetry, microstomia, and mandibular arch hypoplasia. The external ears in the original two sisters (2,3) were markedly abnormal, with bilateral absence of the tragus and anterosuperior helix. In both, one external auditory meatus was absent, whereas the other was atretic. Both male twins (9) exhibited right microtia. The second twin had ipsilateral atresia of the external auditory canal. In both twins the left ear was simple without folding of the helix. The boy described by Baraitser (1) had bilaterally malformed pinnae and stenosed external auditory canals. The patient of Fontaine et al (4) had bilateral dysplasia of the external ears with patent external auditory canals. The two original sisters (2,3) had bilateral conductive hearing loss, whereas one of the twins had unilateral conductive hearing loss (9).

Tomography has revealed bilateral atresia of the external auditory canals with hypoplasia of the left stapes and incus and of the right stapes and malleus. Mild limb anomalies, including bilateral thenar hypoplasia and shortening of the fifth fingers, were noted in the familial cases (2,3).

Sisters (2,3) had congenital heart disease with atrial septal defect in the older girl and endocardial cushion defect in the younger. Six other close maternal family members had congenital heart disease, suggesting this may represent an independent genetic defect, given that congenital heart disease was not noted in the other cases.

Renal anomalies found in several patients included left pelvic kidney (2,3), crossed ectopia of kidney (2,3), unilateral duplication of renal pelvis, and stenosis of ureter (9).

Skull radiographs showed a steep mandibular angle, short mandibular ramus, shortened upper facial height, depressed nasal floor, and decreased cranial flexure angle (2,3).

In *frontonasal malformation*, patients have a wide spectrum of anomalies that includes marked hypertelorism, bifid nose, cranium bifidum occultum, and occasionally cleft lip and/or palate (5). Some similar features are found in *oto-palato-digital I (OPD I) syndrome*, including conductive hearing loss, cleft palate, and growth retardation (5). However, the facial and skeletal alterations found in the OPD syndrome are not present in HMC syndrome. *Oculo-auriculo-vertebral spectrum* commonly has malformations of the pinnae, but cleft lip and palate are relatively uncommon (7%) and severe hypertelorism is not a feature. Motohashi et al (7) reported a boy with a chromosomal abnormality [46,XY,t(1;7)(1q31;7p15)] and features similar to those found in this condition, including hypertelorism, microtia, and cleft palate. However, the child lacked cleft lip and broad/bifid nose and had additional features that included distichiasis, hypoplastic eye lids, and absent lacrimal ducts.

References [Hypertelorism-microtia-clefting syndrome (Bixler syndrome, HMC syndrome)]

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DiGeorge anomaly

Depending on etiology, severity, and time of embryonic insult during the fourth to seventh week of gestation, DiGeorge anomaly can be minimally expressed as the III–IV pharyngeal pouch complex in which there is absence or hypoplasia of the thymus and/or parathyroid glands (Fig. 19–23) (32). However, it may be maximally expressed with cardiovascular anomalies, especially interrupted aortic arch and truncus arteriosus, and various craniofacial anomalies (11,36). The neural crest plays a critical role in the development of the thymus and parathyroid glands, aortic arches, and conotruncal part of the heart (6,7,29,57,60). DiGeorge (16), in 1965, first called attention to the association of absence of the thymus with aplasia of the parathyroid glands and described human thymic deficiency. Good (see 55) coined the term DiGeorge syndrome. Although we and others have used the term DiGeorge anomaly (19,25,29,42,57), the condition has also been known as III–IV pharyngeal pouch syndrome (46,48,49,55), DiGeorge syndrome (1–13,18,20,28,33,35,37,38,51,62), and DiGeorge sequence. An excellent history of the syndrome has been provided by Greenberg (19).

Etiology. Clinical and genetic aspects of DiGeorge anomaly are reviewed extensively by Lammer and Opitz (29), Müller et al (38), and Belohradsky (6). Conley et al (11) reported necropsy data on 25 patients. Miller et al (36) reviewed 156 patients with idiopathic hypoparathyroidism and found 40 different kinds of branchial arch and pharyngeal pouch anomalies. Thomas et al (57) have elegantly reviewed these variations.

Most instances of DiGeorge anomaly occur sporadically, but vertical (54) and horizontal (48,51,62) transmission have been documented. Monozygotic twins (35) have also been noted. Sporadic occurrence in most cases with occasional vertical and horizontal transmission is compatible with microdeletion 22q11 (50).

Clinical and pathologic evidence indicates that DiGeorge anomaly is etiologically heterogeneous (57) and may occur as part of a broader pattern of abnormalities. Various syndromes and associations have been reported (10,15,29) besides del(22q11): dup(1q), del(5p), dup(8q), del(10p), del(17p),del(18q), Zellweger syndrome, diabetic embryopathy, fetal alcohol syndrome, retinoid embryopathy, Kallmann syndrome, holoprosencephaly, arhinencephaly/DiGeorge anomaly, CHARGE/DiGeorge anomaly, and cardiofacial syndrome/DiGeorge anomaly (1,2,6,11,13,14,17,18–30,34,40–45,50–54,56–58). The nude mouse gene, syntenic at human 17p13, may not be accidental (19).

The DiGeorge critical region (22q11.2) associated with microdeletions has a clinical spectrum of abnormalities that includes "DiGeorge anomaly," "velocardiofacial syndrome," and "conotruncal anomalies-face syndrome" (9,17,61,63). A number of candidate genes have been found in the critical region and several appear to be particularly important at this writing. Yamagishi et al (64) suggested that UFD1L haploinsufficiency contributes to the craniofacial and heart defects seen with 22q11 deletion. Baldini (3) and Srivastava and Yamagishi (53) discussed *UFD1L* and *CDC45L* and the role of the *dHAND-UFD1L* pathway in which *dHAND* normally activates *UFD1L* in neural crest-derived cells. Novelli et al (39) expressed skepticism by finding no *UFD1L* mutations in 20 affected but nondeleted patients. They indicated that the gene

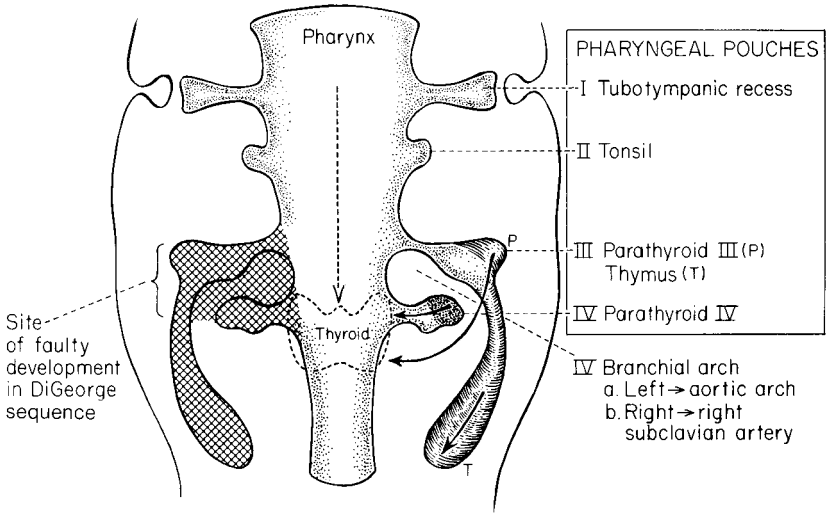

Fig. 19–23. *DiGeorge anomaly*. Schematic appearance of anterior foregut and its derivatives around fifth week of development showing site of DiGeorge defect. III–IV pharyngeal pouch complex. Thymus and inferior parathyroids develop from third pouch. Superior parathyroids develop from fourth pouch. Aortic arch from IV may also be involved. Left involvement results in type B interrupted aortic arch. Involvement of the right aortic arch results in aberrant right subclavian artery. (From DW Smith, Recognizable Patterns of Human Malformation, 3rd ed, W.B. Saunders, Philadelphia, 1982, p 470.)

responsible for the DiGeorge/velocardiofacial phenotype has not yet been isolated and that microdeletions per se might merely reflect genetic instability in the 22q11.2 region. Haplo-insufficiency of the GATA3 gene causes the condition (59a).

A second locus for DiGeorge appears to be at 10p13 (4,12,13,19,21, 27,31,51,59). We do not believe that the facies is reminiscent of velocardiofacial syndrome.

Clinical history. Infants with complete DiGeorge anomaly have a poor prognosis. Patients may have hypocalcemia with seizures, murmurs, or cardiac failure, or, after the first few weeks of life, may develop infections with purulent rhinorrhea, maculopapular rashes, failure to thrive, and development delay. Those with partial DiGeorge anomaly who survive infancy are moderately to severely mentally retarded (11,38).

Parathyroids. Hypocalcemia is a variable feature and patients with severe hypocalcemia are likely to have complete absence of the parathyroids. In most cases, one or two parathyroids or ectopic parathyroids are present (11).

Thymus. Defective cell-mediated immunity is attributable to deficiency of thymic tissue. The thymus gland may be absent (complete DiGeorge anomaly) or hypoplastic (partial DiGeorge anomaly). In the necropsy series of Conley et al (11), partial absence occurred in 58%. Three patterns were observed: cervical lobes only, median thymic tissue situated above the left innominate vein, or small lateralized accessory thymic lobules located in the neck (11). Moderate to almost normal T-cell function is found (4).

Cardiovascular anomalies. Only 5% have a normal heart. Symptomatic heart defects are common. Among 161 cases, type B interrupted aortic arch was found in 30% of clinically symptomatic cases and in 50% of necropsy cases (11,60). This may occur with or without aberrant right subclavian artery. Persistent truncus arteriosus was found in 24% (47,60). Pulmonary arteries in these patients are of variable size. Approximately 12% of cardiovascular anomalies are of other types, most commonly tetralogy of Fallot (6%) (10,36,60).

Craniofacial anomalies. Craniofacial anomalies occur in approximately 60%. The most frequent features include micrognathia, deep-set, low-set, small, posteriorly angulated ears that are sometimes pointed, anteverted nostrils, blunted nose, clefting or indentation of the nose, and hypertelorism (11). Short philtrum, cleft palate or bifid uvula, highly arched palate, choanal atresia, abnormalities of the middle ear, various eye anomalies, and central nervous system malformations have also been noted (11,32,36,38).

Other abnormalities. A variety of other abnormalities have been reported including absent thyroid lobe, accessory thyroid tissue, esophageal atresia, anomalous speech musculature, diaphragmatic defects, Meckel diverticulum, abnormal bowel rotation, imperforate anus, and hydronephrosis (11,36).

Diagnosis and differential diagnosis. DiGeorge anomaly includes patients with two of the three following findings: (1) cellular immune deficiency or demonstrated absence of all or part of the thymus gland or both, (2) symptomatic hypocalcemia or anatomic deficiency of the parathyroids or both, and (3) congenital heart defects. DiGeorge anomaly should be suspected in any neonate with interrupted aortic arch or truncus arteriosus, hypocalcemia, failure to thrive, chronic purulent rhinitis, or a mildly retarded child with manifestations of immunodeficiency (Table 19–1).

Several conditions have features in common with DiGeorge anomaly. *Oculo-auriculo-vertebral spectrum* has overlapping features with DiGeorge anomaly. However, to our knowledge, the finding of T-cell deficiency and/or hypoparathyroidism has not been reported to date. Characteristics of *trisomy 18 syndrome* include low birthweight, triangular facies, low-set pointed ears, micrognathia, congenital heart defects, renal anomalies, and central nervous system malformations. The thymus is frequently noted to be small on necropsy, and absence of the parathyroid glands has also been reported (11).

Table 19–1. Conditions with DiGeorge sequence

Condition	References
Chromosomal	
dup(1q)	59
del(5p)	56
dup(8q)	58
del(10p)	21,27
del(22q)	14,20,25,50
Monogenic	
Isolated autosomal dominant	26, 54
Isolated autosomal recessive[a]	40, 46
Velocardiofacial syndrome	
Zellweger syndrome	11,24,45
Teratogenic[b]	
Diabetic embryopathy	18
Fetal alcohol syndrome	1
Retinoid embryopathy	29
Associational	
Arhinencephaly/DiGeorge anomaly	11
CHARGE/DiGeorge anomaly	44,52
Cardiofacial/DiGeorge anomaly	40

[a] Affected male sibs have been reported on three occasions (2,62) suggesting that X-linked inheritance is still a theoretical possibility.

[b] Bisdiamine, a drug initially studied as a male contraceptive and not approved for human use in the United States, is known to produce a DiGeorge-like pattern of defects in experimental animals (41,43). From MM Cohen Jr and DEC Cole, J Pediatr 115:161, 1989.

Studies of calcium metabolism, cell-mediated immunocompetence, and cardiovascular function are indicated. Immunoregulatory disturbances (hypergammaglobulinemia, high titers of specific antibody production) prevail in partial DiGeorge anomaly (38).

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Oromandibular-limb hypogenesis syndromes

General aspects

Nosology. Syndromes of oromandibular-limb hypogenesis are confusing. Hall (31) called attention to the number of ambiguous and overlapping entities that exist in the literature on the subject. The problem is twofold. First, because almost all cases reported to date are seemingly sporadic, it has been extremely difficult to define syndrome boundaries among this group. Entities have been delimited on a somewhat arbitrary basis, and cases can be graded with various degrees of overlap between defined syndrome entities. Second, Hall (31) noted that the terminology used to describe these disorders shows many discrepancies, thus compounding the problem. He proposed a classification of syndromes with oromandibular-limb hypogenesis based on the presence of hypoglossia. It should be noted that mild degrees of hypoglossia are difficult to detect and may, in fact, go unnoticed.

This chapter considers six defined syndrome entities, including Moebius syndrome, hypoglossia-hypodactylia syndrome, Hanhart syndrome, glossopalatine ankylosis syndrome, limb deficiency-splenogonadal fusion syndrome, and Charlie M. syndrome. All are very uncommon except Moebius syndrome. After an extensive introductory section, each condition is discussed separately. However, this is done for convenience in documenting the vast literature on the subject. We do not recognize that all of the conditions are necessarily separate entities because of significant overlap among them. Furthermore, to speak of them as syndromes, as the literature does, may be misleading because some may represent sequences.

The etiology of this group of conditions is heterogeneous (12,14, 18,23,28,29,30,45). Because sporadicity is seemingly apparent in almost all cases and because the clinical features, especially limb anomalies, are remarkably variable, and, furthermore, because clinically graded overlap occurs between defined entities, it is not known how many entities there are or how etiologically heterogeneous or homogeneous this group is. Kaplan et al (41) considered them to be a syndrome community in which the overlapping phenotypes of the defined syndromes reflect underlying developmental relationships.

Documentation of phenotypic overlap is extensive. Spivak and Bennett (66) suggested that the glossopalatine ankylosis syndrome and the hypoglossia-hypodactylia syndrome were closely related. Cohen et al (16) reported a patient with a minute tongue, limb deficiency, and Moebius involvement; they suggested that hypoglossia-hypodactylia syndrome, Hanhart syndrome, and glossopalatine ankylosis syndrome might represent the same recurrent pattern syndrome. Bökesoy et al (9) reported a patient with features of hypoglossia-hypodactylia and glossopalatine ankylosis and called the condition Hanhart syndrome. Pauli and Greenlaw (56) and Barr (5) questioned whether Hanhart syndrome and limb deficiency-splenogonadal fusion might not be variants of the same condition. Tsingoglou and Wilkinson (75) and Watson (82) reported micrognathia and splenogonadal fusion; in the latter case, microstomia and cleft palate also occurred. Sieber (65) observed Moebius syndrome with splenogonadal fusion. Keymolen et al (41a) reported a variant with renal anomaly, micrognathia, and mild mental retardation in sibs. The association of Moebius syndrome with Poland anomaly has been documented by a number of authors (36,68).

Herrmann et al (36) analyzed 7 personally studied and 62 previously reported cases of oromandibular-limb hypogenesis. They found that severity of upper limb involvement and especially malformation of the feet, but not the presence of cranial nerve palsies, was significant in differentiating cases, and that the group of patients with cranial nerve palsies included some with limb defects similar to those observed in Hanhart syndrome and others with Poland anomaly. Finally, cases with cranial nerve palsies without limb involvement were documented. Herrmann et al (36) concluded that most reported cases of "aglossia-adactylia," "ankyloglossia superior," and Moebius syndrome represented instances of Hanhart syndrome. Second, they concluded that cases of Moebius syndrome combining a chest defect and/or symbrachydactyly represented Poland-Moebius syndrome. Finally, they noted that cranial nerve palsies obviously occurred in several etiologically distinct conditions.

Temtamy and McKusick (70) recognized three clinical entities within the Moebius syndrome category: (1) sixth and seventh cranial nerve palsy alone, (2) sixth and seventh nerve palsy with limb anomalies, and (3) sixth and seventh nerve palsy with arthrogryposis.

Etiology. Teratogenic etiology has been suspected by some authors, but reports to date have generally been anecdotal in nature. Gorlin and Pindborg (27) first suggested that cases of the hypoglossia-hypodactylia syndrome should be examined carefully for intrauterine environmental factors. Torpin (74) noted that rupture of the amnion during early pregnancy may produce membranous strands that constrict or amputate limbs and that may also lead to oral anomalies by ingestion of amnionic strands that interfere with orofacial development.

Hall (31) noted in his case that Tigan was given to the mother during the critical period of facial and limb development and cited another unpublished case in which the mother received Tigan. In the patient reported by Bökesoy et al (9), meclizine hydrochloride usage during pregnancy was noted. Putschar and Manion (59) postulated that limb deficiency-splenogonadal fusion syndrome is secondary to some environmental teratogen. Promethazine was prescribed during the sixth week of pregnancy in the case reported by Pauli and Greenlaw (56). In a case of glossopalatine ankylosis syndrome, Nevin et al (54) found that the mother had taken imipramine, diazepam, chlorpromazine, and meclizine throughout the pregnancy. Drug usage during gestation has also been recorded in other oromandibular-limb hypogenesis cases (36,66,76).

Graham et al (29) reported three cases of Moebius syndrome in which gestational hyperthermia toward the end of the first trimester or early second trimester may have been the etiology. Superneau and Wertelecki (69) reported a patient whose mother had a febrile illness during early pregnancy. They suggested similarities to the experimental effects of hyperthermia as a teratogen. In an animal model of the Moebius syndrome (47) when pregnant rats were subjected to hyperthermia (or uterine trauma), hemorrhage occurred in the distal limbs and brain stem. Human neuropathologic studies have demonstrated brain stem tegmental necrosis affecting multiple cranial nuclei (72).

In Brazil, misoprostol is used orally and vaginally as an abortifacient. Pastuszak et al (55) studied 96 infants with Moebius syndrome and concluded that attempted abortion with misoprostol was associated with an increased risk of Moebius syndrome in infants. The reader is referred to *misoprostol embryopathy*.

Bouwes-Bavinck and Weaver (12) hypothesized subclavian artery disruption sequence as a cause for Moebius syndrome. Possible causes for interruption or reduction of blood flow in the subclavian arteries and their branches include mechanical factors such as blood vessel edema, thrombi or emboli, hemorrhage, early intrauterine compression, delayed or abnormal formation of blood vessels, disruption of newly formed vessels, or premature disappearance of transient vessels (77). Uteroplacental vascular insufficiency has been postulated to cause the spectrum of oromandibular limb hypogenesis syndromes (49).

Chorionic villus sampling (CVS) has been associated with several cases of oromandibular limb hypogenesis (24,30). Firth et al (24) noted four cases in 289 CVS procedures.

David et al (18) reported a case of hypoglossia-hypodactylia with jejunal atresia in an infant of a diabetic mother.

Genetic causes have been postulated by a number of authors. However, almost all cases of oromandibular-limb hypogenesis have occurred sporadically. Genetic interpretations seem to depend on the presence of consanguinity or the rare presence of a relative of the proband with partial (never complete) manifestation of the condition or the presence of mendelian inheritance in a disorder that mimics oromandibular-limb hypogenesis syndromes but clearly differs from them.

In a case of hypoglossia-hypodactylia, Temtamy and McKusick (70) noted that the father and paternal aunt of the proband had hypodontia. They further observed in their study of several patients with the hypoglossia-hypodactylia syndrome or glossopalatine ankylosis syndrome that orofacial anomalies were observed in various relatives, but in no instance were limb abnormalities observed in a relative. They suggested either multifactorial inheritance or autosomal dominant transmission with reduced penetrance and extreme variability in expression. Since most cases are seemingly sporadic, the possibility that some examples represent autosomal dominant mutations with reduced genetic fitness could not be excluded. In Turkey, one case of hypoglossia-hypodactylia and two instances of isolated hypoglossia were each associated with parental consanguinity (76). However, the consanguinity rate is known to be high in the Turkish population and all three cases occurred sporadically within their respective families. Dellagrammaticas (21) reported two sporadic cases of hypoglossia-hypodactylia, referring to them as examples of Hanhart syndrome. Both sets of parents were Gypsies in whom the consanguinity rate is known to be high. In two published papers on Hanhart syndrome (31,32,50), distant consanguinity was noted, also suggesting autosomal recessive inheritance. However, affected sibs have never been reported.

Although autosomal dominant inheritance (25,51,79), autosomal recessive inheritance (6,42,73), affected first cousins (33), and instances of consanguinity [13,33,39 (case 3)] have been reported for some cases of the Moebius syndrome, critical review of such cases suggests strongly that they represent entities distinct from Moebius syndrome. In every instance, only the seventh cranial nerve was affected, and none of these patients had other manifestations of the Moebius syndrome (minimally sixth nerve palsy, in addition). Furthermore, patients in this genetically determined group also had a high frequency of hearing deficit and ear anomalies and were usually of normal intelligence. In the family reported by Becker-Christensen and Lund (6), only the proband had sixth and seventh nerve palsy. It is also clear that the dominantly inherited conditions described by Legum et al (45), Rubinstein et al (62), and Ziter et al (84) as Moebius syndrome represent other entities. Wishnick et al (83) reported bilateral sixth and seventh nerve palsies in six family members of two generations. However, affected individuals also had arthrogryposis and except for mild soft tissue syndactyly and talipes equinovarus, no limb defects were noted, especially reductive.

Using the original criteria of Moebius syndrome as sixth and seventh cranial nerve involvement with or without limb defects, almost all reported cases have occurred sporadically except for the dominantly inherited binary combination of abducens and facial paralysis reported by Krueger and Friedrich (43) and the mother–son involvement described by Hicks (38). Collins and Schimke (17) observed a Moebius syndrome

proband whose father had a transverse defect of one arm with absent radius and ulna just below the elbow but no cranial nerve involvement. Mitter and Chudley (53) reported a Moebius syndrome proband whose sister had isolated oligosyndactyly; the mother was noted to have bilateral facial weakness.

Pathogenesis. In the Moebius syndrome, combined palsy of the sixth and seventh cranial nerves occurs (31,67). The basic cause remains to be clarified and is probably heterogeneous. Postmortem studies have shown nuclear agenesis (36), prenatal encephalomalacic lesions with mineralized necrotic foci in brain stem nuclei (72), neuron hypoplasia (61), absence or hypoplasia of various cranial nerve trunks and nerves (2), and hypoplasia or absence of the facial muscles (57). Electromyograms and muscle biopsies have been of little value in determining etiology, although results have usually indicated a neural deficit (78). The most complete discussion of pathologic findings and theories of pathogenesis has been presented by Pitner and associates (57). Lammens et al (44) reported neuropathological findings in two presumed cases of Moebius syndrome. The first had splenogonadal fusion and the second lacked seventh nerve involvement.

In a detailed anatomic study of two infants with Hanhart syndrome, Bersu et al (8) indicated that phenotypic features probably resulted from incomplete rather than abnormal morphogenesis. They postulated that oral and limb anomalies resulted from deficient mesodermal proliferation caused by disturbances in ectoderm–mesoderm interactions beginning approximately the fourth week of intrauterine development. In glossopalatine ankylosis, the mechanism of fusion between intraoral structures such as tongue and palate is not yet clear. It is known that their epithelial coverings must come into contact, fuse, and disintegrate (64).

With regard to subclavian artery disruption as a postulated cause for Moebius syndrome, vascular compromise at specific locations around the sixth week of embryonic development could result in predictable patterns. Involvement of the subclavian artery distal to the origin of the internal thoracic artery could cause terminal transverse limb defects. Interruption of the subclavian artery proximal to the internal thoracic artery but distal to the origin of the vertebral artery could lead to Poland anomaly. Moebius involvement could result from premature regression of the primitive trigeminal arteries and/or delayed formation of, or obstruction in, the basilar and/or vertebral arteries (12). Vascular disruption was suggested by Preis et al (58) to explain the concurrent association of *OAV spectrum*, Moebius syndrome, and hypoglossia-hypodactylia.

In the limb deficiency-splenogonadal fusion syndrome, splenic and gonadal anlage may combine by adherence of the left surface of the dorsal mesogastrium (which becomes the dorsal border of the spleen following rotation) to the dorsal coelomic wall or ventral border of the developing mesonephric-gonadal structures. The presence of intraovarian splenic nodules found in some cases cannot be explained by adhesion, but by migrating splenic cells (28). Splenogonadal fusion may be of two types: the continuous variant type, in which a cord connects the spleen with the mesonephric-gonadal structures, and the discontinuous type, in which the splenogonadal fusion has no cord connected to the spleen itself (59). Fetal activity and mobility may be important in development of the two types (28).

Differential diagnosis. As we have already pointed out, there may be variable degrees of overlap between defined syndrome entities of oromandibular-limb hypogenesis. Limb defects have the same range of variability in all six syndromes, except for limb deficiency-splenogonadal fusion syndrome in which extensive lower limb defects may be found. Limb defects may be observed with isolated Poland anomaly, amnion rupture sequence, autosomal recessive acheiropody, and other syndromes with reductive limb anomalies.

Isolated hypoglossia is known to occur (19,22). Hypoglossia has also been observed in association with transposed viscera and dextrocardia (81). Hypoglossia has further been noted to occur with intraoral bands (13,23). Cleft palate has been reported in association with intraoral bands through three generations (35). Such bands have also been documented in some instances of the *popliteal pterygium syndrome*. Sato et al (63) reported a family with ankyloglossia (in which the lingual frenulum is attached to the tongue tip) associated with heterochromia irides and congenital clasped thumbs.

Superficially, syndromes of oromandibular-limb hypogenesis may be confused with *Robin sequence*, *oculo-auriculo-vertebral spectrum*, and *mandibulofacial dysostosis*.

Isolated seventh nerve palsy may result from birth trauma in some instances and has also been observed to follow autosomal dominant and autosomal recessive modes of inheritance. Familial juvenile onset of Bell's palsy (1) and familial palsy in Kawasaki disease (34) have been reported. Families with hereditary seventh nerve palsy without sixth nerve involvement with or without other cranial nerve palsies and with or without other types of anomalies (6,25,42,51,73,79) should not be confused with Moebius syndrome. Some Moebius-like cases eventuate as facioscapulohumeral dystrophy or as infantile *myotonic dystrophy*, both autosomal dominant disorders (3). Families with total external ophthalmoplegia and not abducens palsies (45) should not be confused with Moebius syndrome (4). Ziter et al (84) reported a three-generation pedigree of what they called a Moebius syndrome variant; patients had seventh nerve palsy, normal sixth nerve, finger contractures, mild mental deficiency, and a reciprocal translocation between chromosomes 1 and 13. Rubinstein et al (62) reported a patient with congenital paresis of the third, fourth, and seventh nerves, progressive peripheral neuropathy, anosmia, and hypogonadism. The *cardiofacial "syndrome"* (really an association) combines seventh nerve involvement as asymmetric crying facies with congenital heart defects, skeletal anomalies, and renal defects. Some cases of *thalidomide embryopathy* (39,52) have been noted to mimic Moebius syndrome.

Cohen (15) and Verloes and Koulischer (80) described a newly recognized oroacral syndrome consisting of absent maxillary incisors and canines together with asymmetric reduction defects of fingers and toes.

Splenogonadal fusion may occur as an isolated abnormality. When combined with extensive limb defects involving femora, fibulae, and upper limbs, there is overlap with femur-fibula-ulna dysostosis (FFU) discussed by Lenz et al (46). Splenogonadal fusion has also been noted in a case of *Roberts syndrome*.

Recurrence risk. Since syndromes of oromandibular-limb hypogenesis occur sporadically in almost all instances reported to date, recurrence risk is essentially negligible. Moebius syndrome should be separated from other syndromes of oromandibular-limb hypogenesis syndromes and should especially be separated from high-risk congenital myopathies, from seventh cranial nerve palsy without sixth nerve involvement, and from various other pseudo-Moebius syndromes (for differential diagnosis, vide supra). Several papers have dealt with recurrence risk of the Moebius syndrome (3,4,26). Baraitser (3) studied sibs and parents of 15 cases and concluded that when Moebius syndrome was accompanied by skeletal anomalies, recurrence risk was only approximately 2%, whereas bilateral facial palsy with or without abducens palsy without skeletal anomalies had a greater risk of recurrence. Defining skeletal anomalies as a feature of Moebius syndrome helped exclude high risk monogenic disorders of muscle and anterior horn cell, which facially appear Moebius-like in infancy.

Careful family history and examination are essential in Moebius syndrome patients. Although recurrence risk is negligible, rare familial full (38,43) or partial (17,53) instances have been recorded. Establishing a diagnosis of Moebius syndrome either with or without limb anomalies is important because assessment of psychomotor development tends to be erroneous. Early relative delay tends to disappear with age. Poor feeding during the first year of life, often resulting in poor growth, tends to improve. Some degree of mental deficiency occurs in only 10%–15%.

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Moebius syndrome. Moebius (22,23), in attempting to classify multiple congenital cranial nerve palsies, created a division in which palsies of the sixth and seventh cranial nerves were combined. Subsequent authors have broadened this classification to include involvement of other cranial nerves (15,32). Additional abnormalities may include reductive limb anomalies, defects of the chest wall, and mental retardation (Fig. 19–24).

If the minimal criteria for Moebius syndrome include palsies of the sixth and seventh cranial nerves, then almost all examples are apparently sporadic with few exceptions (8,16,18,21). Approximately 160 cases had been published by 1970 (13) and over 300 cases have been recorded to date. The ratio of affected males to females is 1:1. Extensive reviews include those of Henderson (15) and Danis (9). Various topics have already been addressed in the first section of this review: pathogenesis (1,25,34,36); pseudo-Moebius genetic entities with autosomal dominant inheritance (11,19,29,35,38), with autosomal recessive inheritance (3,4), with affected first cousins (14), and with consanguinity [6,14,28 (case 3)]; rare truly inherited cases (16,18,20); chromosome translocations and gene mapping (37); cases with partial manifestation in a first degree relative (8,21); recurrence risk (2), and Moebius sequence with hypogenitalism, and cerebral and skeletal changes in two brothers (8a). Poland syndrome, Moebius syndrome and Klippel-Trenaunay syndrome have been found in the same kindred (18a).

Mask-like facies may be obvious in the newborn, but may often go unrecognized at this time (10,12,15). Bilateral facial paralysis usually imparts a symmetric appearance to the face, but variance in the degree of involvement on each side of the face or upper and lower portions of the face can cause significant asymmetry. Occasionally, only unilateral facial nerve palsy is present (10). Sixth nerve palsy is the most common ocular finding (31). Nearly every remaining cranial nerve can be affected in addition, but of these, the third, fifth, ninth, and twelfth nerves predominate (10,30,32).

Most patients cannot abduct either eye beyond the midline. However, unilateral palsy does occur (17). Ptosis, nystagmus, or strabismus may accompany the above findings (5,13,15). Epicanthal folds are frequent. Some patients may be unable to close their eyes either during sleep or while awake, resulting in conjunctivitis or corneal ulceration (17,26).

The nasal bridge is often high and broad, particularly during infancy and early childhood (26). The broadness of the nasal bridge extends downward in a parallel fashion to include the nasal tip (15). Thus, an upper midfacial prominence usually results.

The mouth aperture is often small. The angles of the mouth droop and may allow saliva to escape (5,26). Attempts at opening the mouth further result in little change. As the child grows older, a definite but slow improvement can be observed in the ability both to open the mouth and to feed adequately (10,15). Poor feeding during the first year of life frequently results in poor growth.

Unilateral tongue hypoplasia is frequent (10), but bilateral hypoplasia can occur (10,13,26). The degree of hypoplasia may, on occasion, be extreme (7). Muscular fasciculations of the tongue may be present (12). Poor palatal mobility, inefficient sucking and swallowing, coarse voice, and speech impairment are often present (26).

Frequently, the mandible is mildly to moderately hypoplastic (10,26), and when combined with the small mouth aperture, imparts the appearance of a lower midfacial hypoplasia. The coronoid process may be enlarged (34a). Oligodontia has been described in one case (28).

The pinnae may be normal. However, they may be large, may be deficient in cartilage, and may protrude laterally (10). Occasionally, they are hypoplastic, but most instances of severe hypoplasia probably do not represent true examples of the Moebius syndrome. Likewise, the hearing deficits that are reported occasionally with these hypoplastic ears are very infrequent findings in the Moebius syndrome.

Bilateral, unilateral, or asymmetric hypoplasia or aplasia of the pectoralis major muscle or complete Poland anomaly (33) occurs in 15%. Polythelia or athelia may be present (15). Spinal curvatures are occasionally noted but, as a rule, only in those few instances associated with arthrogryposis (13).

Limb defects occur in approximately 50%. Thirty percent constitute talipes deformities (15). The remaining 20% include primarily hypoplasia of digits, syndactyly, or more severe reduction deformities of the limbs. Clinodactyly, polydactyly, joint contractures, and congenital hip dislocation occur less frequently (15,27).

Other findings rarely may include congenital heart defects, urinary tract abnormalities, hypogenitalism, and hypogonadism (13,24,33) and premature thelarche (17). The authors have seen two examples with congenital heart defects.

Ten percent to 15% are mentally retarded (9,15). The degree of mental retardation is usually mild (15). Estimates of early psychomotor development tend to be erroneously low (5,10). The severe physical deformities often cause a relative delay in apparent psychomotor development that tends to disappear as the child grows older.

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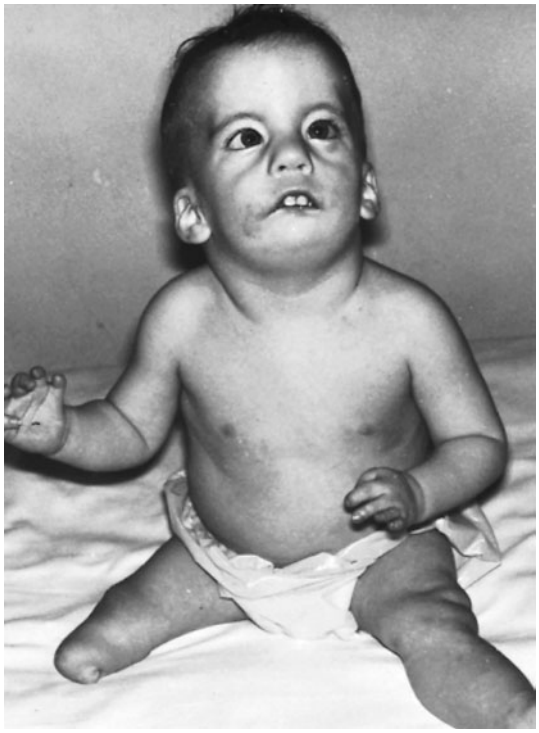

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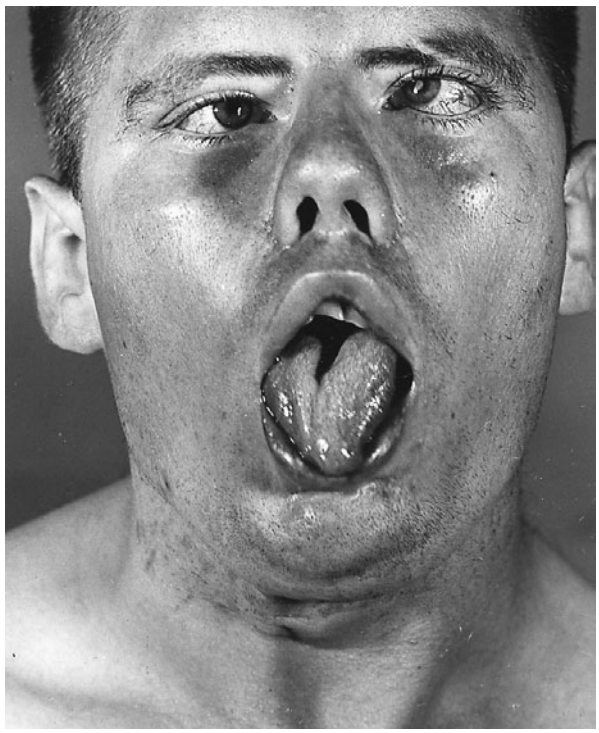

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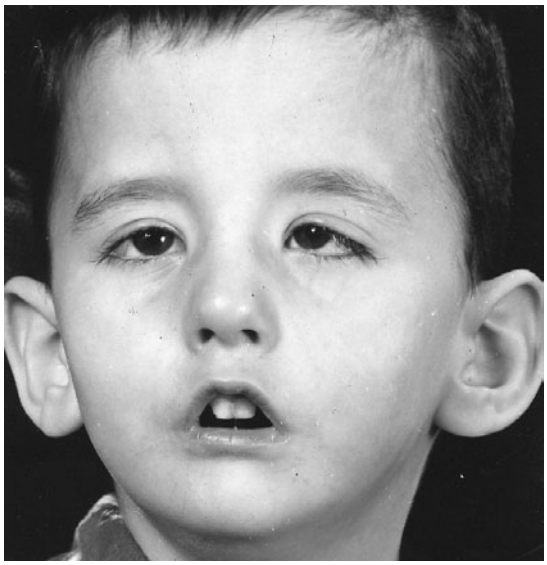

B

Fig. 19–24. *Moebius syndrome*. (A) Variable degrees of limb hypogenesis. Strabismus, micrognathia, mask-like facies. Child had small tongue. (B) Patient had clubfoot, inability to execute horizontal eye movements, and expressionless face. (C) Similar anomalies in a 23-year-old male with defective ocular rotation, bilateral facial paralysis, and atrophy of tongue evident from birth. (A from SM Harwin and LC Lorinsky, New Britain, Connecticut. B from R Sogg, Arch Ophthalmol 65:16, 1961. C from MW Van Allen, Figure 64, Grinker's Neurology, Charles C. Thomas, Springfield, Illinois, 1960.)

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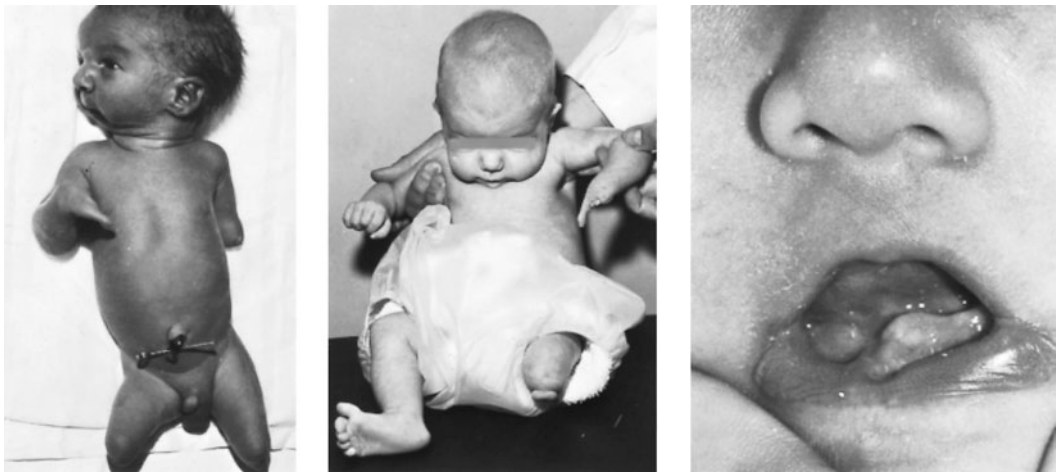

A B C

Fig. 19–25. *Hypoglossia-hypodactylia syndrome*. (A,B) Small mandible and variable limb deformities. (C) Attachment of anterior oral floor to lower lip. Small tongue was located in posterior part of mouth. (A from NC Nevin et al, Oral Surg 29:443, 1970. B courtesy of N Freire-Maia, Curitiba, Brazil, and JM Opitz, Helena, Montana. C from WH Boon and CT Seng, J Singapore Paediatr Soc 8:75, 1966.)

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Hypoglossia-hypodactylia syndrome. In a critical review of the literature in 1971, Hall (17) was able to confirm only nine cases of the hypoglossia-hypodactylia syndrome (Fig. 19–25) including one of his own (6,11,13,17,20,21,26,30,32). Since then, many other cases have been recorded (1–4,7–9,12,14–16,18,19,22,24,25,31,33). Of six patients reported by Johnson and Robinow (19), four had hypoglossia-hypodactylia and two had Moebius syndrome. The cases reported by Temtamy and McKusick (31) had either hypoglossia-hypodactylia syndrome or glossopalatine ankylosis syndrome. The case described by Schuhl (28) is an example of Moebius syndrome. To date, approximately 30 cases have been recorded, although a few of these, as already mentioned (31), had glossopalatine ankylosis. The condition is frequently called aglossia-adactylia, a misleading term, in our opinion, because the tongue is never completely absent, and adactylia does not convey the variation in limb defects of affected individuals.

All cases of the hypoglossia-hypodactylia syndrome have been sporadic to date. Etiologic, pathogenetic, and nosologic considerations have been addressed in an earlier section.

The mandible is small and the chin recedes. Hypoglossia is variable in degree, being extreme in the cases of Rosenthal (26), Fulford et al (11), and Thornton (32), but the tongue was reduced only 25% in Hall's case (17). Mandibular incisors have been noted to be absent, with concomitant hypoplasia of the associated alveolar ridge (17,26). Marked enlargement of the sublingual muscular ridges and hypertrophy of the sublingual and submandibular glands have been described (11,26). A mild defect of the lower lip was noted by Rosenthal (26). Fusion of the anterior alveolar processes and cleft palate have been noted in several cases (4,18,25). In some patients, the size of the oral opening is markedly reduced (Fig. 19–25).

Limb anomalies are extremely variable. Any limb may be affected, and variability may be observed in the same patient as well as in different patients. For example, hemimelia of all four limbs was noted by Temtamy and McKusick (31). Involvement of both left limbs with normal right limbs was reported by Nevin et al (22). Oligodactyly and syndactyly of both hands and complete adactyly of one foot with absence of the hallux on the other foot were observed by Kelln et al (20).

Speech is surprisingly good, and patients have been of normal intelligence. Other findings have included fused labia majora (20), unilateral renal agenesis [19 (case 5)], and congenital occlusion of the superior mesenteric artery [19 (case 2)]. Because of associated abducens and oculomotor palsies, the patient reported by Ernst and Meinhold (10) represents a nosologic bridge. The patient reported by Cohen et al (5) had Moebius facies with sixth and seventh nerve palsies, limb anomalies, and severe microglossia.

Isolated hypoglossia was first reported by de Jussieu (8) in 1718. Other such cases have been described by several authors (27,33,35,36). Shah (29) tabulated 30 cases of hypoglossia and found cleft palate in 11 of these and other malformations in 24. Watkin (34) reported hypoglossia in association with transposed viscera and dextrocardia. Oulis and Thornton (23) observed a patient with severe hypoglossia, micrognathia, oligodontia, enamel hypoplasia, situs inversus, dextrocardia, and asplenia.

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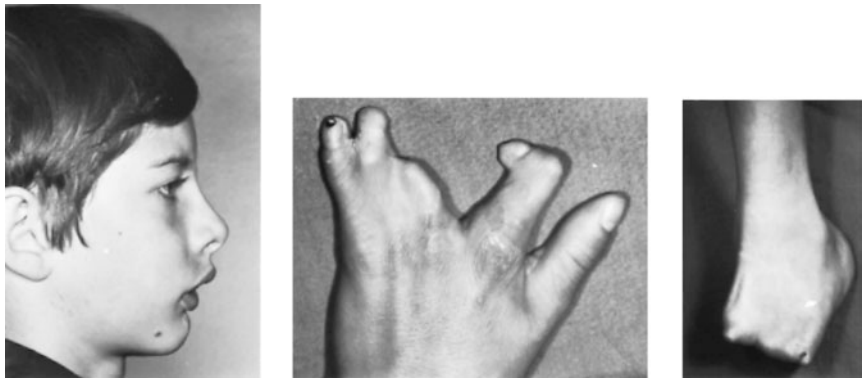

A B C

Fig. 19–26. *Hanhart syndrome*. (A) Micrognathia. (B,C) Oligodactyly of hands and feet.

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Hanhart syndrome. Hanhart syndrome as originally defined consisted of micrognathia and peromelia (Fig. 19–26). Using this definition, approximately 12 cases have been described (1,2,5–8,10–14). The patient reported by Bökesoy et al (3) had microglossia and glossopalatine ankylosis. The two patients reported by Dellagrammaticas et al (4) had severe microglossia and fit the original definition of the hypoglossia-hypodactylia syndrome. Using a broader definition of Hanhart syndrome that encompasses several conditions with oromandibular-limb hypogenesis, Herrmann et al (8) tabulated 31 cases from the literature and presented four of their own. To date, all cases have been sporadic. Nosologic, etiologic, and pathogenetic considerations have been addressed previously. American clinicians should carefully note that in the European literature, although four conditions are called Hanhart syndrome (9), they are nosologically unrelated and are as distinct as von Recklinghausen's neurofibromatosis and von Recklinghausen's disease of bone. None of the other three conditions named after Hanhart has oligodactyly or partial syndactyly, despite a report to the contrary [5 (case 1)].

Micrognathia has been a feature in all cases. In Case 2 of Garner and Bixler (5), a fibrous band was noted connecting the maxilla and mandible on both sides but not anteriorly. The tongue was noted to be relatively normal in size in their patient. Most authors have not commented upon tongue size except Herrmann et al (8) who specifically mentioned microglossia. In one case, the tongue was fused to the lower lip, alveolus, and the floor of the mouth. Because of the degree of micrognathia expressed in some cases of Hanhart syndrome, we feel that hypoglossia should certainly be looked for in any suspected case. Hypodontia has been reported (7,8,13). Assemany et al (1) reported Robin sequence in their case. Absence of major salivary glands has been noted (2).

Limb anomalies range from stunted digits and oligodactyly to more severe peromelia. Any limb may be affected, and variability of involvement in the same patient and in different patients is well illustrated by Hanhart (7). Coxa valga was noted in one instance (7). Imperforate anus has also been recorded (2).

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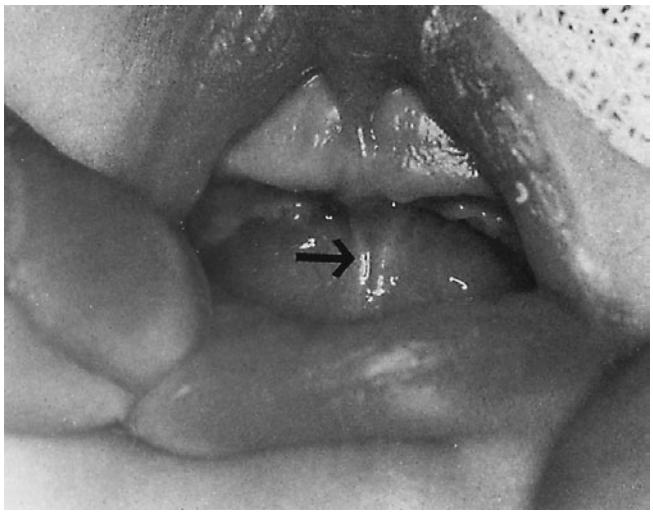
Glossopalatine ankylosis syndrome. This syndrome, first described in 1887 by Illera (7) and early in the twentieth century by Kettner (9) and Kramer (10), is rare. Approximately 15 cases have been reported (1–19). To date, all cases have been sporadic. Nosologic, etiologic, and pathogenetic considerations have been previously discussed. Shah (15) published a summary of cases of intraoral attachments. In 14 cases with glossopalatine ankylosis, cleft palate was present in six and other types of malformations (e.g., limb anomalies) in four.

The tongue is usually attached to the hard palate (Fig. 19–27) (1,5), but may also be adherent to the maxillary alveolar ridge (5). Highly arched palate has been documented in some instances (3). Cleft palate has also been observed (8,18) and, in these cases, the tongue may be attached to the lower edge of the nasal septum. In glossopalatine ankylosis, palatal attachment usually occurs to the anterior portion of the tongue. The tongue tip has been noted to be mildly cleft (1). Its mobility is reduced, and its extension beyond the teeth is limited (1,3). The mandible may be hypoplastic, and the central portion of the upper lip has also been described as hypoplastic (1,3). Hypodontia principally affects the incisor teeth (1,3). Ankylosis of the temporomandibular joint has also been recorded (1). Facial paralysis has been noted in several instances (1,10,16). Limb anomalies are extremely variable and may affect both hands and feet. Oligodactyly, syndactyly, polydactyly, and more severe peromelia have been observed (1–3,8,14,16,18,19).

Fig. 19–27. *Glossopalatine ankylosis syndrome*. At arrow, see attachment between ventral tongue tip and hard palate. (From Minami K et al, J Oral Maxillofac Surg 53:588, 1995.)



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Charlie M. syndrome. In 1969, Gorlin (1) observed that the Moebius syndrome category had been overworked as a repository for several different disorders and cited the Charlie M. syndrome as an example (Fig. 19–28). The condition is characterized by hypertelorism, facial paralysis in some instance, absent or conically crowned incisors, cleft palate, and variable degrees of hypodactyly of the hands and feet. We have observed several cases and, in each instance, the affected individual has represented a sporadic occurrence. Another patient was reported by Kaplan et al (2).

References (Charlie M. syndrome)

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Limb deficiency-splenogonadal fusion syndrome. Splenogonadal fusion was first mentioned by Bostroem (5) in 1883 and described in detail by Pommer (17) in 1889. By 1985, 84 cases were on record (9), and by 1999, 150 cases were known (4). However, only 25 of these cases had associated limb defects (1–4,7,8,10–19,22) and approximately 70% of these had mandibular hypoplasia (4).

Although there is a strong male bias in ascertaining splenogonadal fusion (4,9,24), the sex ratio is misleading because of the rarity of ovarian complications in females during their lifetimes or by difficulty in examining ovaries compared to testes. Putschar and Manion (18) divided splenogonadal fusion into two types: a continuous type in which a fibrous cord-like structure connects splenic tissue between the spleen and the gonad (Fig. 19–29) and a discontinuous type in which no connection exists between the main spleen and the ectopic spleens. When splenogonadal fusion is associated with limb reduction defects, 83% of the cases are continuous (4). In all cases of splenogonadal/limb deficiency cases

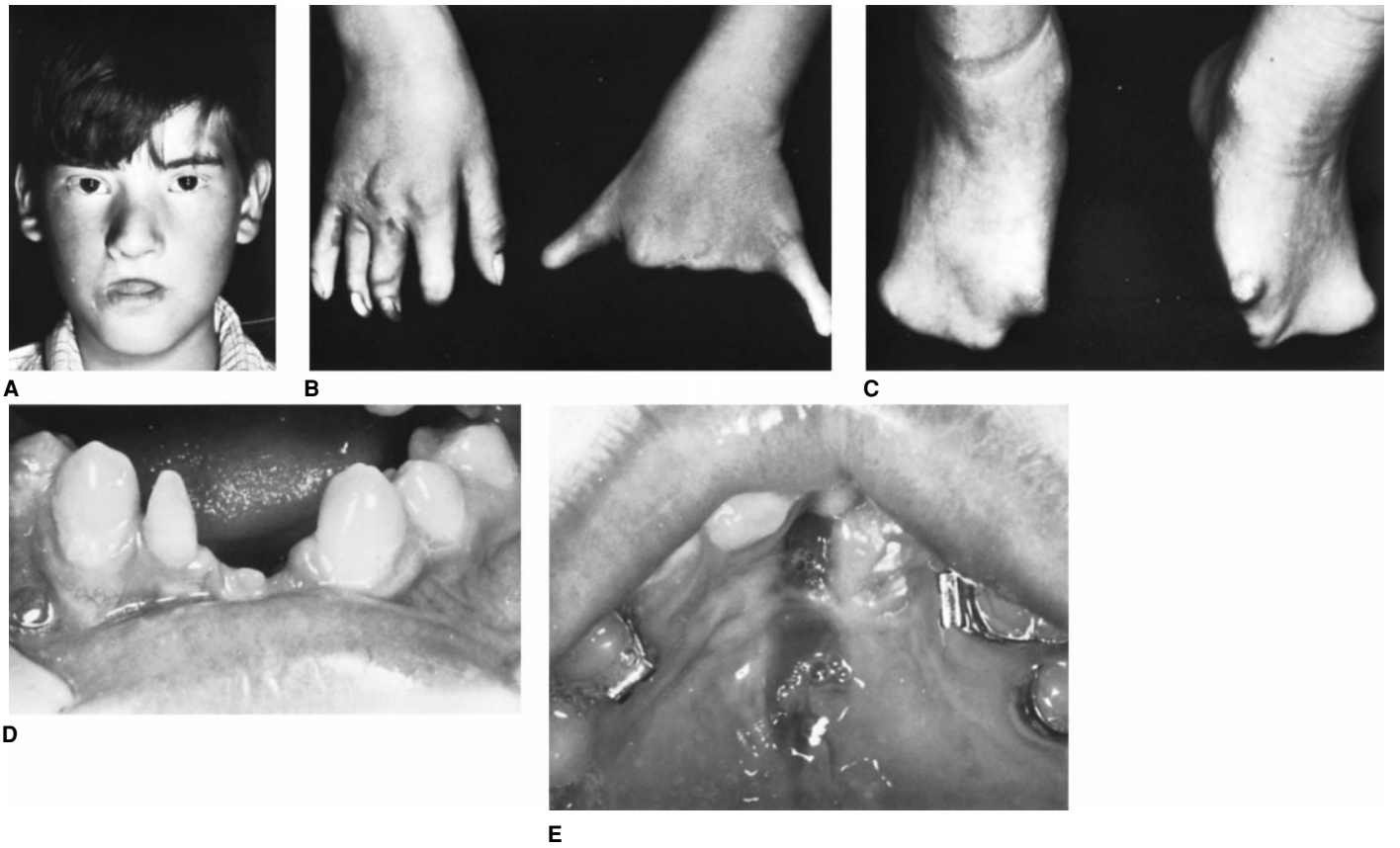

Fig. 19–28. *Charlie M. syndrome*. (A) Upslanting palpebral fissures, ocular hypertelorism, lower facial palsy. (B,C) Bizarre digital agenesis and malformations. (D) Absence of three lower incisors, conical crown form of remaining incisor. (E) Repaired cleft of anterior palate. [From RJ Gorlin, Birth Defects 5(2):65, 1969.]

analyzed by Bonneau et al (4), 70% had severe limb reduction defect (4). More complex defects involving the upper limbs, femora, and fibulae were found in 23% (4). Mandibular hypoplasia was found in 70% (4).

To date, all cases have been sporadic (1–19,22). Excellent reviews are those of Pauli and Greenlaw (15) and Bonneau et al (4). Gouw et al (9) provided an analysis of splenogonadal fusion and its associated anomalies. Nosologic (3,4,14,15,20,22,23), etiologic (18), and pathogenetic (9) concepts have been dealt with in the general section on oromandibular limb hypogenesis.

Craniofacial anomalies have been reported in some patients, but less frequently than micrognathia. Findings have included plagiocephaly (15), malformed and/or low-set ears (4,18), deviated nose (16), cleft palate or bifid uvula (4), V-shaped palate (15), microglossia (4), and unerupted teeth (15). Splenogonadal fusion has also been associated with oral anomalies in patients with normal limbs. Tsingoglou and Wilkinson (23) reported micrognathia and Watson (24) described micrognathia, microstomia, and cleft soft palate. Sieber (21) noted a patient with splenogonadal fusion and Moebius syndrome.

Limb reduction defects have great variability. Involvement appears to be more severe more frequently than in other syndromes of oromandibular-limb hypogenesis.

In males, splenogonadal fusion almost always involves the left gonad; in females, the left ovary or adnexal structure is usually involved (9). Male infertility has been noted (1). In the patients reported by Barr (3), four accessory spleens were found along the descending colon and a fifth accessory spleen was fused to the left ovary.

In males, correct preoperative diagnosis is rarely made, differential diagnosis usually including supernumerary testis, epididymitis, testicular tumor, hydrocele, and angioma or cyst of the lower spermatic cord (6,10). Splenogonadal fusion should be suspected in any patient with limb reduction defects and either a scrotal mass or left cryptorchidism. A bloody tap from a punctured scrotal mass should arouse suspicion of an aberrant spleen even more. Paratesticular spleen occasionally may produce clinical symptoms such as pain and swelling of the scrotum (18,22). In rare instances, a continuous splenic-gonadal band may cross ventral to the intestinal loops, resulting in bowel obstruction (12). In Sommer's case (22), a unique alternate drainage of considerable magnitude shunted blood directly into the inferior vena cava via the spermatic and left renal vein, bypassing the liver.

Various other anomalies have also been reported. Significantly, imperforate anus and other anorectal abnormalities have been noted (14,16,17), a finding also reported in one instance of Hanhart syndrome. Low-frequency findings have included hypoplastic lungs (4,16), abnormal lung fissures (15), agenesis of left diaphragm (4,16), congenital heart defects (3,4,16), spina bifida (22), and coccygeal defect (17). Central nervous system abnormalities have been variable and nonspecific (1,2,7,13,15,22). Polymicrogyria was described by Fritzsche (7). Pauli and Greenlaw (15) reported mild mental deficiency.

References (Limb deficiency-splenogonadal fusion syndrome)

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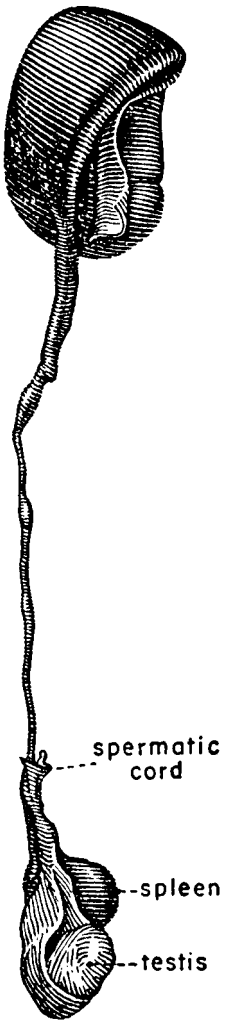

Fig. 19–29. *Limb deficiency-splenogonadal fusion syndrome* (*continuous type*). (From WA Sheath, J Anat Physiol 47:340, 1912–13. Redrawn by WGJ Putschar and WC Manion, Am J Pathol 32:15, 1956.)

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Oral-facial-digital syndromes

It is becoming increasingly apparent that striking heterogeneity exists among the oral-facial-digital (OFD) syndromes. In common to all are minor facial anomalies, oral findings (e.g., cleft or lobulated tongue, oral frenula, and/or cleft palate), and digital anomalies, including brachydactyly, syndactyly, clinodactyly, and polydactyly. Other anomalies are often present, which make it difficult to ascertain whether cases with unusual anomalies indicate variable expressivity of an OFD or represent other conditions, thus indicating heterogeneity. Often these examples are sporadic in otherwise normal families; in the few instances in which affected sibs are reported, information is often incomplete on all but the propositus. Classification of many of the new OFD syndromes is therefore tentative, and is usually based on the consistent occurrence of an unusual anomaly in all affected cases (1–4). Only in OFD I has the gene been mapped. We await further molecular mapping for true classification.

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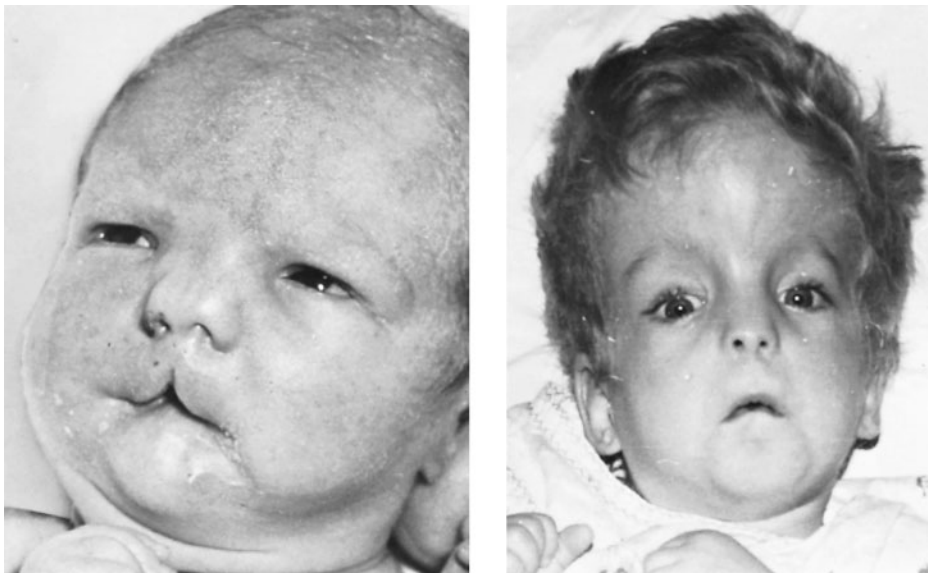
OFD type I (Papillon-Léage/Psaume syndrome). In 1954, Papillon-Léage and Psaume (25) defined a syndrome of hyperplastic frenula, multilobulated tongue, hypoplasia of nasal alar cartilages, median pseudocleft of upper lip, asymmetric cleft palate, various malformations of digits, and mild mental retardation.

Similar cases had been reported under a variety of names as early as 1860. To date, more than 250 cases have appeared in the literature. There are several comprehensive reviews (2,9,10,13,14,20,21,30). Wahrman et al (35) suggested that the frequency of the syndrome is probably approximately 1/50,000 live births.

OFD I syndrome has dominant X-linked inheritance although 75% of the cases are sporadic. It is limited to females and is lethal in male heterozygotes (6,10,14,19). It has been described in a male with XXY Klinefelter syndrome (35) and in karyotypically normal males who died soon after birth (11,12). One of the most perplexing pedigrees is that of Vaillaud et al (33) and Vissian and Vaillaud (34). In this family the disorder appears to have been transmitted through unaffected males. Several other reported "affected" males probably had Mohr syndrome (OFD II syndrome). The gene, *OFD1*, maps to Xp22.2–Xp22.3 (8,9a,10a). Discordant monozygotic twins have been noted (28), possibly because of postzygotic mutations. The gene escapes X inactivation (9a).

Facies. The facies is remarkably distinctive. Frontal bossing has been documented in 30%. Usually there is euryopia, but in approximately 35% dystopia canthorum (lateral displacement of the inner canthi) is evident (19). Some aquiline thinning of the nose, due, at least in part, to hypoplasia of alar cartilages, and a pseudocleft in the midline of the upper lip are present in approximately 45% (Fig. 19–30). The upper lip is usually short, and the nasal root is broad. One nostril may be smaller than the other, and there may be flattening of the nasal tip. Because of zygomatic hypoplasia, the midfacial region is flattened in approximately 25% (21).



A B

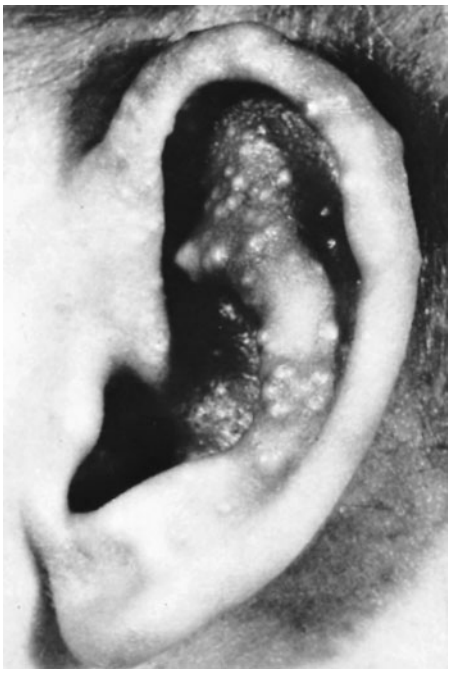
Fig. 19–30. *Oral-facial-digital syndrome, type I.* (A) Pseudocleft in midline of upper lip, lack of nasal alar flare. (B) Note frontal bossing, widely spaced eyes, hypoplastic alar cartilages, and downturned mouth. (A from H Reinwein et al, Humangenetik 2:165, 1966.)

Skin and skin appendages. Commonly there are evanescent milia of the face and ears (Fig. 19–31). These usually disappear before the third year of life (15). Approximately 65% have dryness, brittleness, and/or alopecia of the scalp hair (26), especially over skull prominences and following Blaschko lines (5a,16). There is marked decrease in sebaceous glands.

Dermatoglyphics have been studied (5,6,26). A preponderance of whorls has been noted.

Skeletal manifestations. Malformations of fingers, seen in 50%–70% include clinodactyly, syndactyly, and brachydactyly of digits 2–5 (Fig. 19–32A,B). Toe malformations, noted in 25%, include unilateral hallucal polysyndactyly, syndactyly, and brachydactyly (Fig. 19–32C). Bilateral polydactyly of halluces has been documented on one occasion (31). The hallux is often bent in a fibular direction, with brachydactyly and hypoplasia of the second to fifth toes. Occasionally, there is a postminimus finger or toe (6,19,26,28,30). A patient was reported with unilateral pseudoarthrosis of the tibia (23).

Fig. 19–31. *Oral-facial-digital syndrome, type I.* Milia of pinna, which ordinarily disappear by the third year of life. (From F Majewski et al, Z Kinderheilkd 112:89, 1972.)



The nasion-sella-basion (cranial base) angle is increased, being about 144(and exceeding the normal value of 131° (SD = 4.5°) by almost 3 SD (1,14,30) in approximately one-half of the patients.

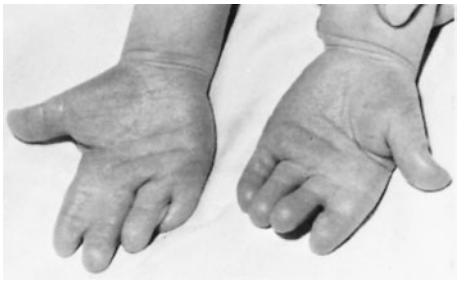
Radiographic examination shows the short tubular bones of the hands and feet to be irregularly short and thick. Irregular reticular pattern of radiolucency and/or spicule-like formation are observed in metacarpals and, especially, phalanges (36). Some patients have cone-shaped epiphyses in the fingers. Irregularities of the long bones were also reported by Stapleton et al (31).

Central nervous system. Mild mental retardation is seen in approximately 40% (19,21,27,32). The intelligence quotient usually ranges from 70 to 90. Various central nervous system alterations have been described: hydrocephaly, hydranencephaly, microcephaly, porencephaly, and agenesis of corpus callosum (Fig. 19–33) (4,5,13,14,18,19,22,26–28,36). Precocious puberty has been noted in association with hypothalamic hamartoma (29). Pachygyria, heterotopic gray matter, bilateral arachnoid cysts, and Dandy-Walker cyst have been noted (18,32). These and other anomalies have been reviewed by Wood et al (36) and Baraton (3). Decreased hearing has also been noted (6).

Urinary system. Adult onset bilateral polycystic kidneys and medullary cystic renal disease, usually asymptomatic, have been reported in approximately 50% (4,5,7,19,22,27,35). In the case reported by Stapleton et al (31), the kidneys were normal at 1 year; reevaluation at 11 years demonstrated bilateral polycystic kidneys. Others have found progressive renal insufficiency (5,22). Even fetal polycystic disease has been described (21a).

Oral manifestations. The most striking oral manifestations are the clefts associated with hyperplasia of frenula (Fig. 19–34). There is often (in approximately 45% of whites) a small midline cleft in the upper lip extending through the vermilion border. Blacks apparently rarely have upper lip midline clefts (27). Upon retraction of the short upper lip, a wide, thickened, or hyperplastic reduplicated frenum is seen to be associated with the pseudocleft. This, in part, eradicates the mucobuccal fold in the area. Because of these bands, complete retraction of the lip is often not possible. Thick frenula are seen in virtually all patients (10,13,19).

The palate is cleft laterally, deep bilateral grooves extending medially from the maxillary buccal frenula, dividing the palate into an anterior segment (containing the incisors and canines) and two lateral palatal



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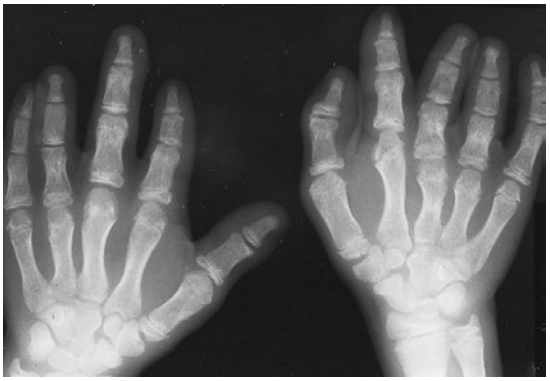

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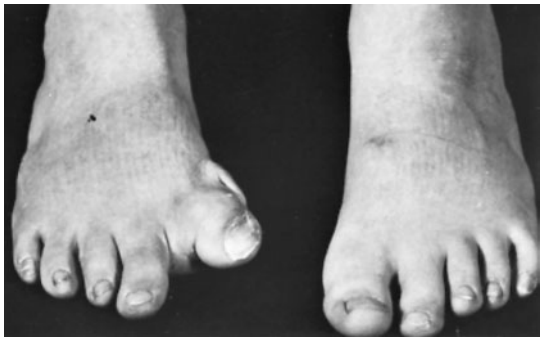

C

Fig. 19–32. *Oral-facial-digital syndrome, type I.* (A) Asymmetric soft-tissue syndactyly, abbreviation of fingers. (B) Shortened metacarpals, malformed, abbreviated phalanges. (C) Unilateral preaxial polysyndactyly of hallux. (A from H Reinwein et al, Humangenetik 2:165, 1966. B from JA Dodge and DC Kernohan, Arch Dis Child 42:214, 1967. C from JW Curtin, Plast Reconstr Surg 34:579, 1964.)

processes. The soft palate is completely and asymmetrically cleft in at least 80% in whites and in 25% of blacks (10,21,27). In some persons, a large bony ridge extends from the alveolar crest medially to the midline in the canine–premolar area, somewhat resembling a misplaced torus.

Numerous thick fibrous bands are evident in the lower mucobuccal fold in 75%. Cleft tongue with two lobes is seen in 30%, with three or more lobes in 45%. On the ventral surface of the tongue, between the tongue halves or lobules, a small whitish to yellowish hamartomatous mass is seen in approximately 70% (19,21). This consists of fibrous connective tissue, salivary gland tissue, fat, a few striated or smooth muscle fibers, and, rarely, cartilage (21). Ankyloglossia or tongue-tie of a diffuse nature is present in at least 30% (19,21).

Malposition of the maxillary canine teeth, supernumerary maxillary deciduous canines and premolars, and infraocclusion are common. Supernumerary canines, often separated by the clefts, are noted in approximately 20%. The canine crown form is often T-shaped. Aplasia of mandibular lateral incisors occurs in approximately 50% and appears to be predicated on the effect of the fibrous bands on developing tooth germs. The mandible is small or hypoplastic with a short ramus (17).

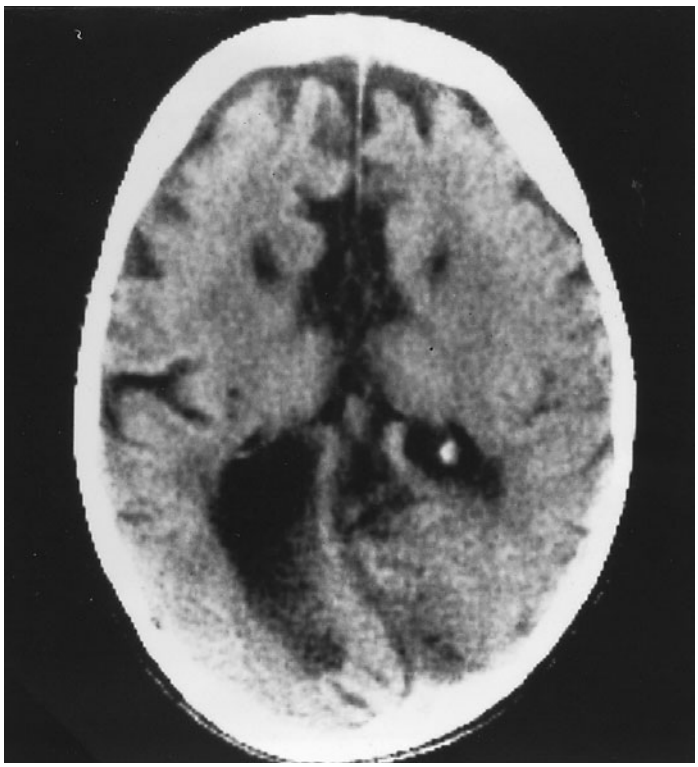

Fig. 19–33. *Oral-facial-digital syndrome, type I.* Agenesis of corpus callosum and cerebral atrophy. (From AA Connacher et al, J Med Genet 24:116, 1987.)

Differential diagnosis. Several of these components may be seen in other syndromes. For example, in *Ellis-van Creveld syndrome*, the upper or, occasionally, the lower lip may be attached to the gingiva, there being no mucobuccal fold anteriorly. Associated with this may be a mild mid-upper lip defect. Alar cartilage hypoplasia and dystopia canthorum occur in *Waardenburg syndrome*, but to a greater degree. Postaxial polydactyly of the hands and feet, unusual facial appearance (metopic prominence, upward-slanting palpebral fissures, epicanthal folds, anteverted nostrils), labiogingival frenula, highly arched palate, short stature, skin laxity, and failure to thrive occur in the *Opitz trigonocephaly (C) syndrome*. Hamartomata of the tongue may be an isolated finding (24).

Most closely related to this syndrome is *OFD II syndrome*. It has autosomal recessive inheritance. These patients also have midline cleft of the upper lip, lobate tongue with small excrescences, bilateral manual hexadactyly, and bilateral polysyndactyly of the halluces. In contrast to patients with OFD I syndrome, these patients may be male. They do not have hyperplastic frenula, the lower central incisors may be absent, and occasionally there is a hearing defect. Other oral-facial-digital syndromes can also usually be distinguished on clinical grounds. Hallucal polydactyly can be found in many syndromes: *cephalopolysyndactyly, Greig syndrome, acrocallosal syndrome, Apert syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome, Saethre-Chotzen syndrome, craniofrontonasal dysplasia, Rubinstein-Taybi syndrome, femoral hypoplasia-unusual facies syndrome, del(4p) syndrome*, and *del(7p) syndrome*.

Laboratory aids. A CAT scan and/or and an MRI can be employed for brain and kidney abnormalities, pre- and postnatally (27a).

References [OFD type I (Papillon-Léage/Psaume syndrome)]

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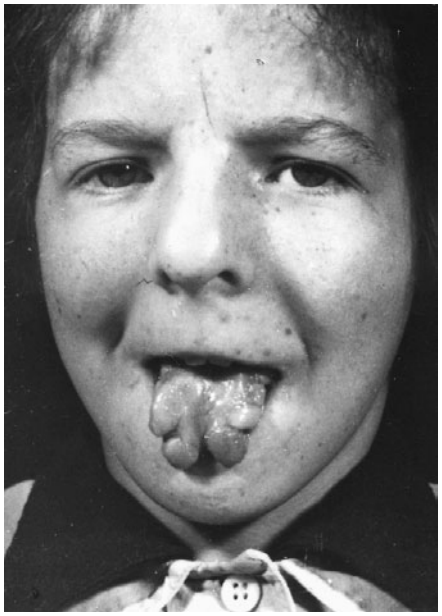

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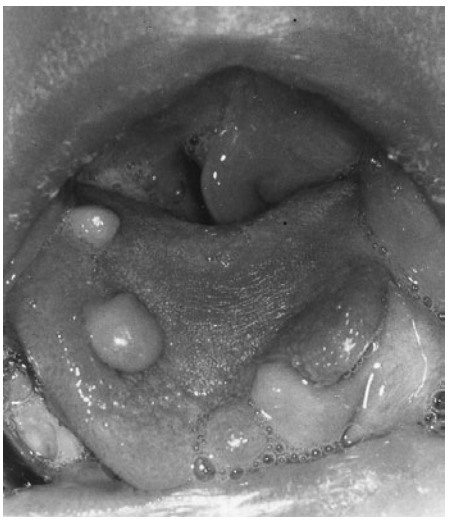

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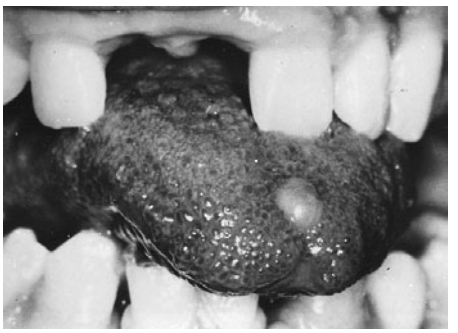

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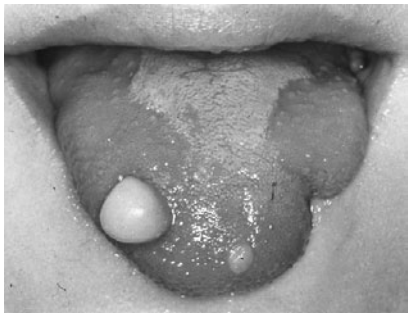

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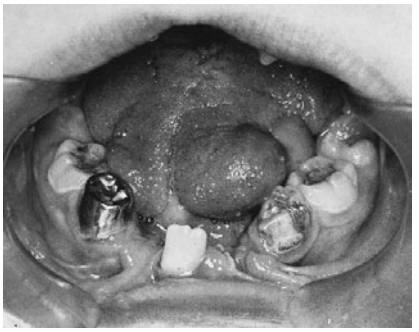

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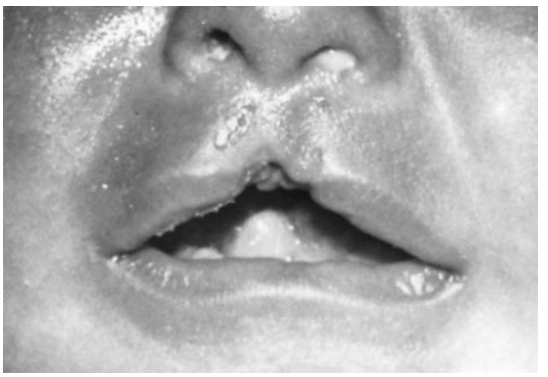

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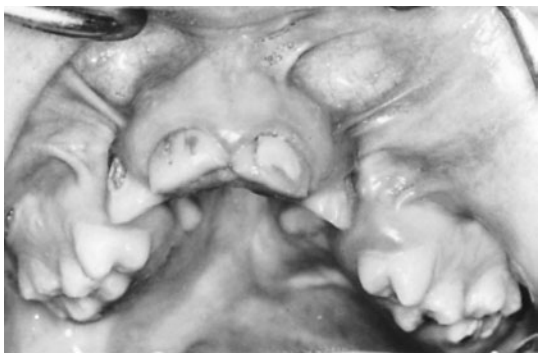

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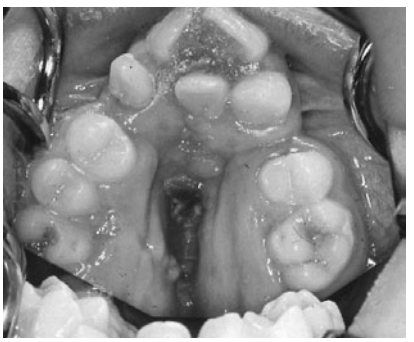

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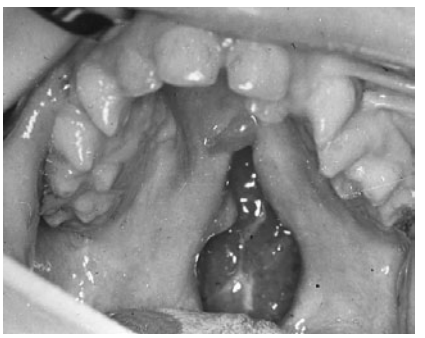

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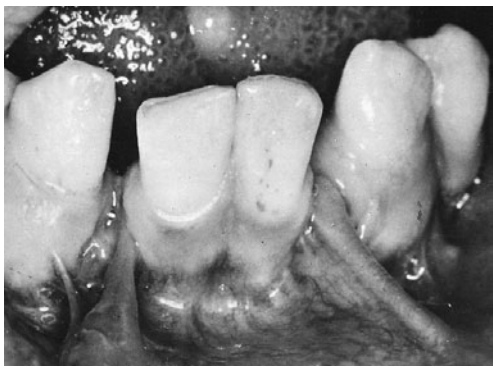

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Fig. 19–34. *Oral-facial-digital syndrome, type I.* (A) Tongue may be cleft into 2, 3, or 4 lobes. Note tetrafid tongue. (B–D) Note hamartoma formation and irregular lobulation of tongue. (E) Lobulated tongue. Note hyperplastic fibrous bands traversing mucolabial fold. (F) Midline defect in upper lip. (G) Maxilla is divided into an anterior segment, which includes the canine teeth, and two posterior segments. (H) Note bizarre clefting and division of maxilla into anterior and posterior segments. (I) Irregular cleft palate. (J) Absence of lower lateral incisors, large hyperplastic fibrous bands traversing the mucobuccal fold. (B,D,H,I from S Lähnert, Dtsch Zahnarztl Z 24:993, 1969. F,G from W Fuhrmann et al, Humangenetik 2:133, 1966.)

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OFD type II (Mohr syndrome). In 1941, Mohr (20) described a family later expanded upon by Claussen (8). Several sibs and a cousin exhibited lobed tongue, manual polydactyly, and bilateral polysyndactyly of the halluces (Fig. 19–35). Earlier cases may have been described by Otto (21) in 1841 and Dreibholz (11) in 1873. Subsequently, a number of well-defined examples have been published (2,5,10,12–15,18). Less certain are several other cases (3,4). Although some examples previously described as Mohr syndrome have been subsequently recognized as being distinct conditions (vide infra), further heterogeneity within this group is very likely.

The syndrome clearly has autosomal recessive inheritance. Parental consanguinity has been demonstrated (8) and there have been several examples in sibs (8,21). Its frequency may be approximately 1/300,000 live births (1).

Facies. Frequently there is a midline cleft of the upper lip. Hypertelorism and micrognathia are also common (1,7,16). The ears may be lowset and/or posteriorly angulated (1). Facial milia are not present (Fig. 19–35A).

Skeletal alterations. Bony changes appear to be limited to hands and feet. Bilateral manual hexadactyly and bilateral polysyndactyly of the halluces are characteristic (1,5,10,15,18) (Fig. 19–35). The hallucal polysyndactyly in the patients described by Beaudry (4) and Mayer and Schnidder (19) was, however, unilateral. Christophorou and Nicolaidou (7) and Cordero and Holmes (9) reported duplicated thumbs in their patient. Patients described by several authors (4,8,9,18) also had one or more postminimus digits of hands and/or feet.

Bimanual hexadactyly apparently is not requisite for the diagnosis of the syndrome, since in some cases there have been five fingers with ulnar deviation of the fifth finger, 3–4 syndactyly with extra bones in the web, or hexadactyly of only one hand (8,16).

Central nervous system. Mental retardation has been reported in several cases (15,21). Various other neurologic anomalies have been described, including microcephaly (15), porencephaly (15), hydrocephalus (10,23), subarachnoid cyst and hypoplastic vermis (2,23), conductive hearing loss (16), choroid coloboma (10,19), and muscular hypotonia with poor coordination (8,15,18).

Other findings. There appears to be increased susceptibility to respiratory infection, which in several patients has resulted in death during infancy (3,8,10). Tachypnea has also been reported (8). Cryptorchidism (4,8) and inguinal hernia (15) have been noted. Complex heart malformations have been reported occasionally (9,14).

Oral manifestations. Cleft tongue is probably a constant feature of the syndrome, and several authors have spoken of general ankyloglossia (3,4) (Fig. 19–35G). In a few cases, cleft or highly arched palate (1,3,16,18) has been mentioned. However, in most patients, the palate has been intact (15,18). A small median cleft of the upper lip is a relatively common feature, but was missing in the case described by Mohr (20) and Claussen (8) (Fig. 19–35A). Multiple frenula are occasionally present (1,15,18), but far less frequent than in OFD I syndrome. Fatty hamartomas on the dorsum of the tongue have been found in several cases (3,4,8,18,19,21).

Differential diagnosis. Median cleft of the upper lip is also seen in other OFD syndromes (vide infra). There are a number of cases in which there is overlap between OFD II and OFD IV (13,24) (see OFD IV for discussion). There are also examples of overlap between OFD II and

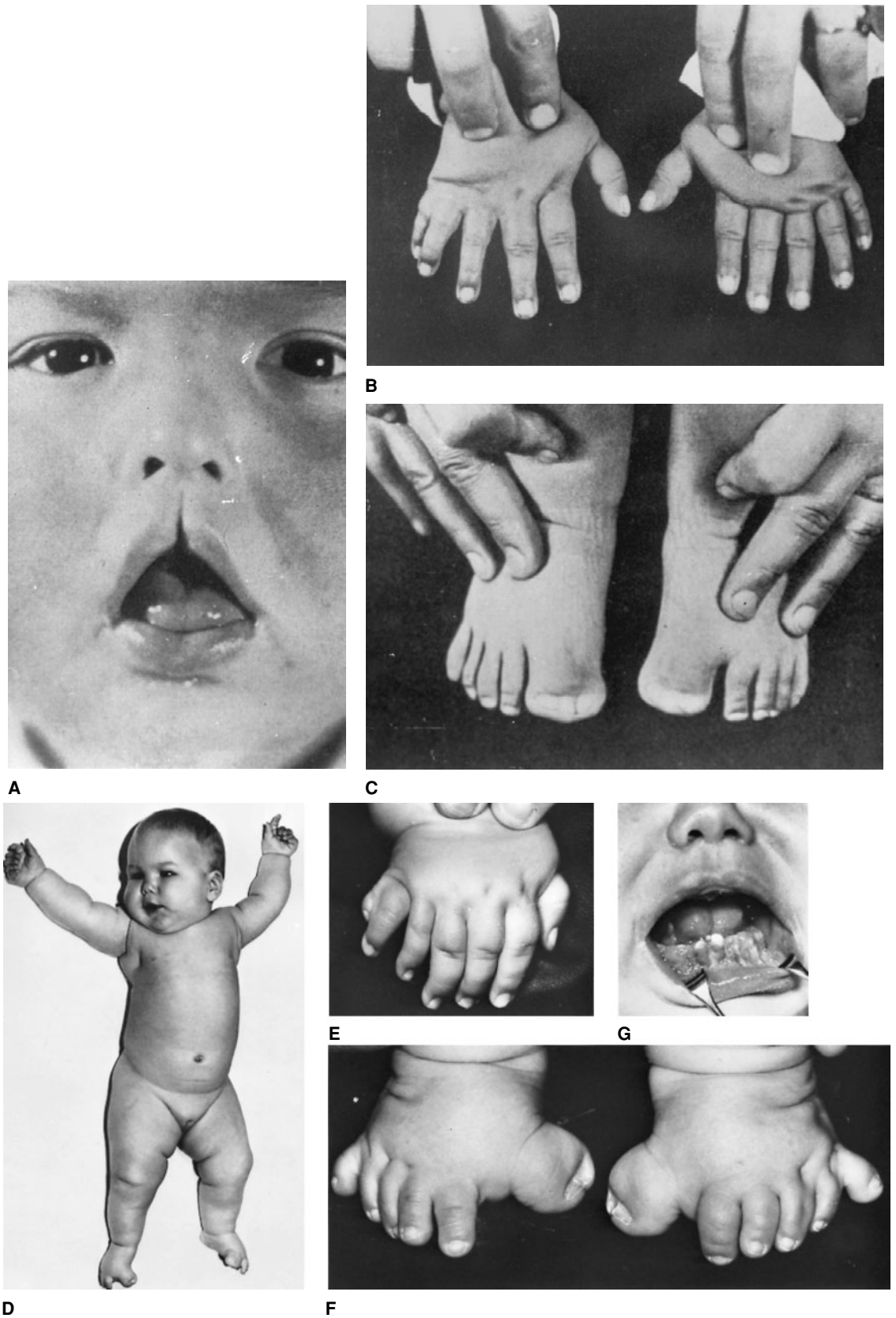

Fig. 19–35. *Oral-facial-digital syndrome, type II*. (A–C) Note median cleft of upper lip and bimanual hexadactyly. Child also had bilateral polysyndactyly of halluces. (D–G) Compare with patient in A–C. Note bilateral manual hexadactyly, polysyndactyly of halluces, defect in middle of upper lip, hamartoma of tongue. (A–C courtesy of F Burian, Prague, Czechoslovakia. B from RA Pfeiffer et al, Klin Padiatr 185:224, 1973.)

OFD VI (6). We suspect that the children reported by Lyons (17) have *Carpenter syndrome*.

Laboratory aids. Prenatal diagnosis has been accomplished (2a).

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OFD type III [see-saw winking with oral-facial-digital anomalies and postaxial polydactyly of the hands and feet (Sugarman syndrome)]. Sugarman et al (2) reported female sibs with a syndrome similar to, but distinct from OFD I and II syndromes. Both sisters had lobulated, hamartomatous tongue, dental anomalies, including malocclusion and extra teeth, bifid uvula and normal palate, postaxial hexadactyly of hands and feet, pectus excavatum, short sternum, kyphosis, and profound mental retardation. In addition, the younger sister had frontal bossing, hypertelorism, down-slanting palpebral fissures, esotropia, apparently low-set ears, brachydactyly with hyperconvex nails, and continuous alternating winking of the eyelids that the authors termed *see-saw winking* (Fig. 19–36). The older sister did not exhibit this phenomenon, but did have blepharospasm. McKusick (personal communication, 1986) has seen a similar case. Smith and Gardner-Medwin (1), in 1993, reported male and female sibs with lingual hamartomas, postaxial polydactyly, mental retardation, see-saw eye movements and hypoglossia of cerebellar vermis. We cannot exclude *OFD VI* or Joubert syndrome (see *Differential diagnosis*).

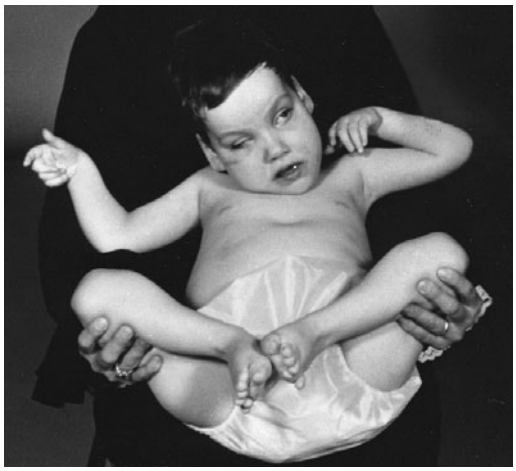

Fig. 19–36. *Oral-facial-digital syndrome, type III*. See-saw winking, strabismus, pectus excavatum, short sternum, polydactyly, profound mental deficiency. (Courtesy of GI Sugarman, Los Angeles.)

Inheritance is likely autosomal recessive.

References [OFD type III (see-saw winking with oral-facial-digital anomalies and postaxial polydactyly of the hands and feet [Sugarman syndrome])]

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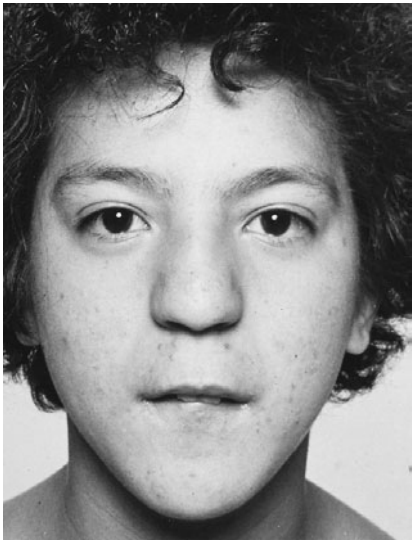
OFD type IV (oral-facial-digital syndrome with tibial dysplasia, Baraitser-Burn type). There have been 25 reported cases (1–9,11–20) of patients with oral, facial, and digital anomalies who have also had tibial dysplasia and/or mesomelia (Fig. 19–37). Sensenbrenner and Jorgenson (15) reported a case they described as having Mohr syndrome and skeletal dysplasia; Temtamy and McKusick (18) later described the same case and suggested this entity represented an overlap of Majewski and Mohr syndromes. Baraitser et al (1) also reported a case with features of both Mohr and Majewski syndromes; Burn et al (3) later described an affected sib of the proband in Baraitser's report and suggested this entity be named OFD IV.

Inheritance is probably autosomal recessive. Three reports have involved affected sibs (3,8,14); the remaining reports have been sporadic cases. Consanguinity has been noted (2,19).

Facial anomalies have included broad nasal root (2,11,14,16,18), broad nasal tip (6,8,14,15,17), hypertelorism or telecanthus (2,3,11,14,16,18), micrognathia (3,14,15,17,18), hypoplastic mandible (2,3,14), and low-set ears (3,8). Numerous oral anomalies are present, including cleft lip (6,8,11,14,18), cleft or highly arched palate (3,6,8,11,12,14,15,17), bifid uvula (17), cleft or hypoplastic maxillary and/or mandibular alveolar ridge (3,8,14,17,18), oral frenulae (7,10), and lingual hamartoma (2,3,6,12,15,17,18). Dental anomalies are also common, and generally include absent and supernumerary teeth (6,8,14–18). Goldstein and Medina (8) further described the teeth as being small, and exhibiting abnormal crown and root morphology (hypertaurodontism and talonism). Absent or hypoplastic epiglottis has been found (12,18).



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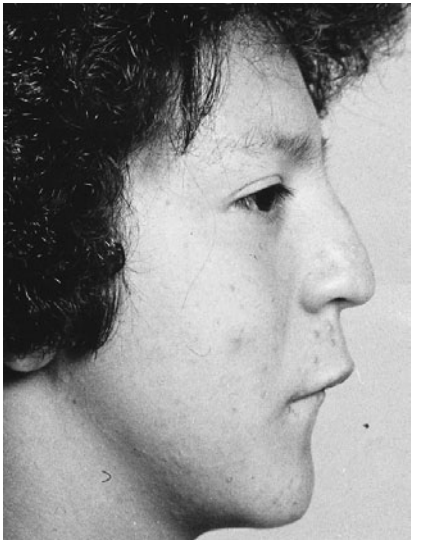

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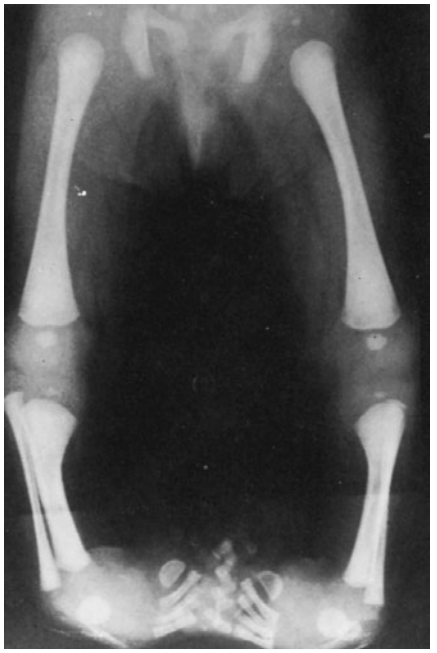

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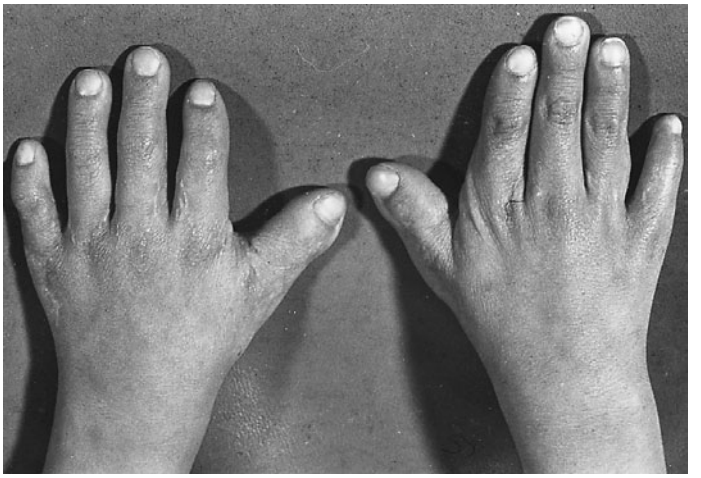

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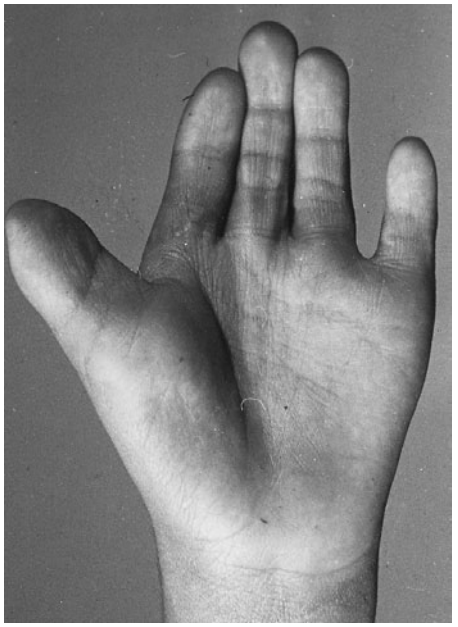

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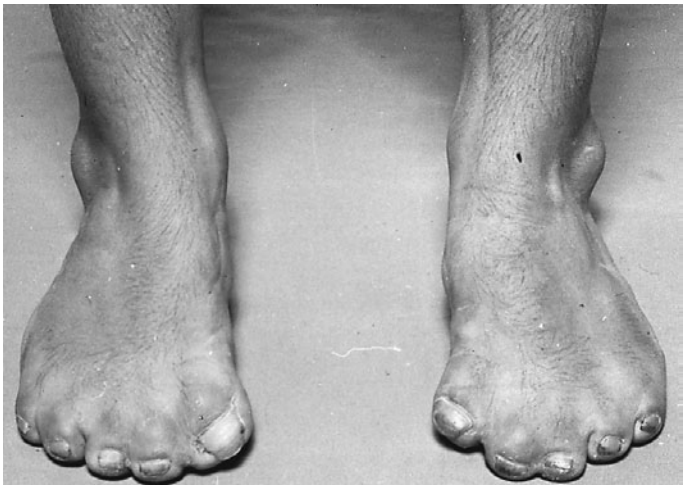

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Fig. 19–37. *Oral-facial-digital syndrome, type IV*. (A,B) Broad nasal root, broad nasal tip, micrognathia. (C) Short stature with short tibiae. (D) Note short tibiae with midshaft bowing, talipes equinovarus. (E,F) Brachydactyly. Extra postaxial digit surgically removed from each hand. (G) Syndactyly. Excision of postaxial digit from each foot. (A–C, E–G from GI Sugarman, J Clin Dysmorphol 1:16, 1983. D from J Burn et al, J Med Genet 21:189, 1984.)

Digital anomalies were varied, but generally present. Both pre- and postaxial polydactyly of the hands have been described (7–14); syndactyly (6,7,17), clinodactyly (2,7,8,14,16,18), and brachydactyly (7,14,16–18) can also occur. Preaxial polydactyly of the feet was described in three cases (2,14,18) and both pre- and postaxial polydactyly in five cases (2,10). One patient had six toes on each foot, but whether they were pre- or postaxial was not specified (7). Neither of the sibs reported by Goldstein and Medina (8) had polydactyly of either hands or feet, so this finding is apparently not consistent.

Talipes equinovarus has also been described (3,12,17). Mesomelia of varying degrees is present in most cases, and often the tibia is described as dysplastic. Several authors (3,7,17) described the tibia as being short with midshaft bowing. Büttner and Eysholdt (4) and Fenton and Watt-Smith (6) reported the tibia as pseudoarthrotic. Other tibial anomalies include proximal metaphyseal or epiphyseal flattening (3,8,14,17) and/or metaphyseal flaring (2,8,14). Forearms can also be short (15,16) and stature, when noted, is below the third centile (8,14,15–17).

Conductive hearing loss occurs in some patients (3,8,12,14,17). Although intellect has been reported as normal in several cases (14–16), most have been mentally retarded (2,3,6). We have also seen a child with OFD IV with retardation secondary to porencephaly.

The chest is sometimes small (17–20) and pectus carinatum or excavatum has also been reported (14,15).

Two additional cases of OFD IV may be the sibs reported by Michels et al (10). These sibs had oral, facial, and digital anomalies, and were thought to have OFD II; however, one or both sibs also had clubfeet, pectus excavatum, and short stature, which is more consistent with OFD IV. Because it was not noted whether X-rays of the long bones were made, classification of these cases as examples of OFD IV is tentative.

In conclusion, all cases of OFD IV have tibial defects in common, ranging from metaphyseal and epiphyseal abnormalities detected by X-ray (2,14) to dysplasia severe enough to necessitate amputation (16). Tibial defects may be unilateral (6) or bilateral. The presence of postaxial polydactyly and pectus excavatum in some cases also helps distinguish this condition from OFD II. However, it is likely that this group is very heterogeneous, and resolution of this question awaits description of further cases of affected siblings, and delineation of degree of intrafamilial variability (19).

References [OFD type IV (oral-facial-digital syndrome with tibial dysplasia, Baraitser-Burn type)]

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OFD type V [median cleft of upper lip and postaxial polydactyly of hands and feet (Thurston syndrome)]. Thurston (7), in 1909, appears to be the first to describe a syndrome of median cleft of the vermilion of the upper lip and postaxial polydactyly of the hands and feet (Fig. 19–38). All reported patients have been from India (1–7). Inheritance is autosomal recessive.

Thurston's patients were brothers. In one brother, the extra digit was of normal morphology, but of somewhat smaller size. The extra toe was of normal size and appearance. The other brother had seven fingers on each hand. There were six toes on one side and five on the other. No other anomalies were present.

Chowdhury (2) described nine cases in one family. Two sets of second cousins sibs were affected. Consanguinity was noted. Another large kindred was reported by Chaurasia and Goswami (1). Two sibs had heptadactyly.

Khoo and Saad (4) and Sidhu and Grewal (5) reported isolated cases in Indian males. Another Indian male was noted by Gopalakrishna and Thatte (3). There was hexadactyly of one hand and heptadactyly of the other. Both feet exhibited hexadactyly. A sister had similar hand abnormalities. The upper median frenum was duplicated.

References [OFD type V (median cleft of upper lip and postaxial polydactyly of hands and feet [Thurston syndrome])]

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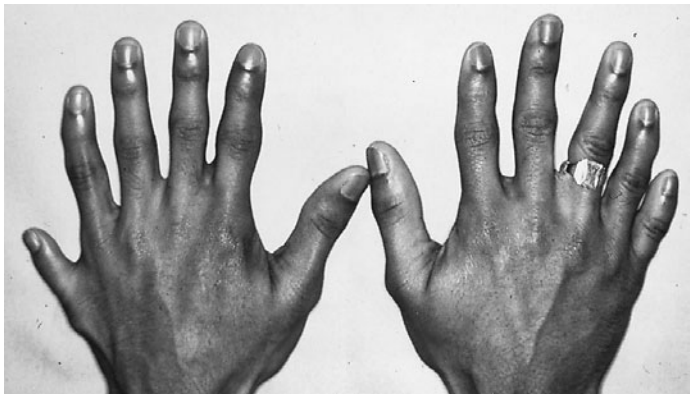
OFD type VI [polydactyly, cleft lip/palate, lingual lump, and cerebellar anomalies (Váradi syndrome)]. In 1980, Váradi et al (23) reported a syndrome of polydactyly, cleft lip/palate, and mental retardation in an inbred Gypsy family. Mattei and Aymé (14) reported a similar case, and suggested this condition should be distinguished from other OFD syndromes. There are numerous other cases in the literature (1,7–9, 11,15), some of which were reported as examples of OFD II syndrome or Joubert-Boltshauser syndrome with polydactyly. Other possible examples were reviewed by Muenke et al (15). We agree with Toriello (22) and Neri et al (18) that until there has been some molecular breakthrough that classification of this group will be unsatisfactory.

The presence of consanguinity in one family (23) and affected sibs in other families (7,8,11,14) suggest autosomal recessive inheritance.

Facial features are often described as consisting of hypertelorism (1,8,9,11,15), epicanthal folds (1,9,15), broad nasal tip (8,11,23), and cleft lip (Fig. 19–39A) (1,14,15,23). In some cases there is also a mild midline cleft of the upper lip. Microphthalmia has also been noted (8). Rotary nystagmus, oculomotor apraxia, and esotropia are common (9,15,23). Posteriorly angulated and/or apparently low-set ears were reported in several examples (8,11,13,14,23).



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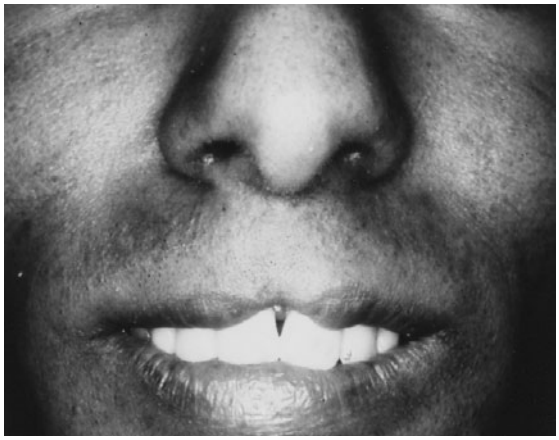

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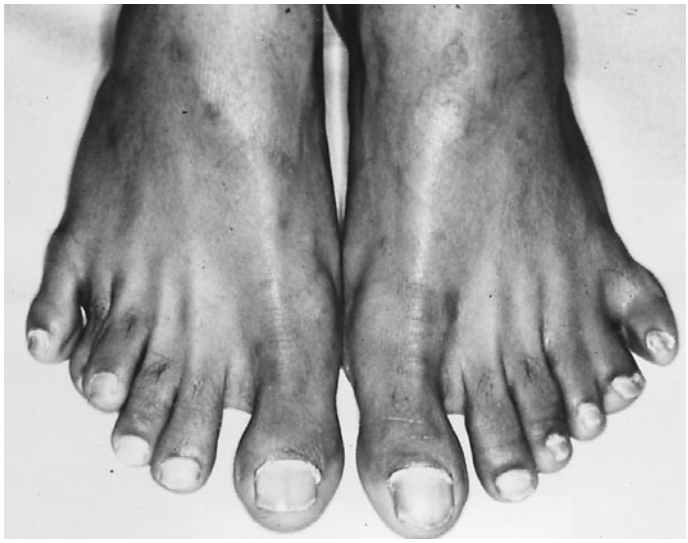

B

Fig. 19–38. *Oral-facial-digital syndrome, type V*. (A,B) Postaxial polydactyly of hands and feet. (C) Typical midline cleft of upper lip. (From CT Khoo and MN Saad, Plast Reconstr Surg 33:407, 1980.)

Both intraoral frenulae (8,11,15) and lingual or sublingual lumps (8,9,14,15,23) have been noted. The palate can be highly arched or cleft (1,8,9,11,23). Dental anomalies are generally not present, although one patient had enamel hypoplasia (23).

Postaxial polydactyly of the hands is common (Fig. 19–38B,C) (1,7–9, 11,14,15,23). Preaxial polydactyly of the hands (15) has been described. Clinodactyly and syndactyly can also occur (8,9,11,14,15,23). Most striking, however, and present in nearly all cases thus far examined, is the presence of a central Y-shaped or forked metacarpal noted on X-ray (Fig. 19–39B,C).

The feet usually have bilateral preaxial polydactyly (Fig. 19–39D) (1,8,9,11,14,15,20,23), although four patients had an accessory fifth toe as well (7,9,15). Cutaneous syndactyly has also been reported (9).

Nearly all affected children have severe mental retardation with rare exception (15); postnatal growth retardation (9,14,15,23), hypotonia and/or gait disturbance (9,15,23), and deafness (9,14,15) can also occur.

Several internal anomalies have also been described. Cardiac defects included aortic stenosis in one case (23) and common atrioventricular canal and coarctation of the aorta in the other (9). Unilateral renal agenesis was reported in one affected sib by Mattei and Aymé (14). Hypogonadism with micropenis has been reported (15,23).

A distinguishing feature of this condition seems to be various degrees of cerebellar defects ranging from absent or hypoplastic cerebellar vermis (Fig. 19–39E) to include all variants of the Dandy-Walker malformation (7,11), or evidence of cerebellar defects such as motor incoordination and delayed or absent speech (1,8,9). Recurrent episodes of tachypnea and hyperpnea are common (15). Hyperthermia has been reported (23). Hypothalamic hamartoma has also been found (vide infra).

The twins described by Hingorani et al (12) and the fetus reported by Muenke et al (16) have features that overlap those of OFD VI, hydrolethalus syndrome, and Pallister-Hall syndrome, thus raising the question of whether they are three separate entities. Hypothalamic hamartoma, supernumerary maxillary central incisor and precocious puberty was reported moreover by Stephan et al (21). Doss et al (6) describe a glial defect. Other examples of overlap cases are those of Hart et al (10), Anyane-Yeboa et al (2), Shashi et al (19), Bankier and Rose (3), and Hsieh and Hou (13a). One child reported by Váradi et al (23) also had arhinencephaly. Although Baraitser (4) considers some of these cases (7,9,11) to be examples of Joubert-Boltshauser syndrome with polydactyly, it seems more appropriate to classify these cases as examples of Váradi syndrome because of the overall phenotype (22).

Another possible example of Váradi syndrome may be the sibs reported by Hooft and Jongbloet (13). One or both had oral frenulae, ocular coloboma, microphthalmia, palatal malformations, and postaxial polydactyly. One sib had a tumor at the base of the brain, although no additional data are given regarding the nature of the tumor. We cannot classify the patients of Cleper et al (5).

Dandy-Walker malformation (hydrocephalus, incomplete cerebellar vermis, and posterior fossa cyst) may occur as an isolated finding or in association with myriad conditions, including Joubert-Boltshauser syndrome, *Coffin-Siris syndrome, Meckel syndrome, Ellis-van Creveld syndrome, cryptophthalmos syndrome* (17), and *Jones craniosynostosis/ Dandy-Walker syndrome*.

Fetal ultrasonography may possibly be used to detect the anomalies of the extremities, cleft lip and palate, and partial agenesis of the cerebellar vermis.

References [OFD type VI (polydactyly, cleft lip/palate, lingual lump, and cerebellar anomalies [Váradi syndrome])]

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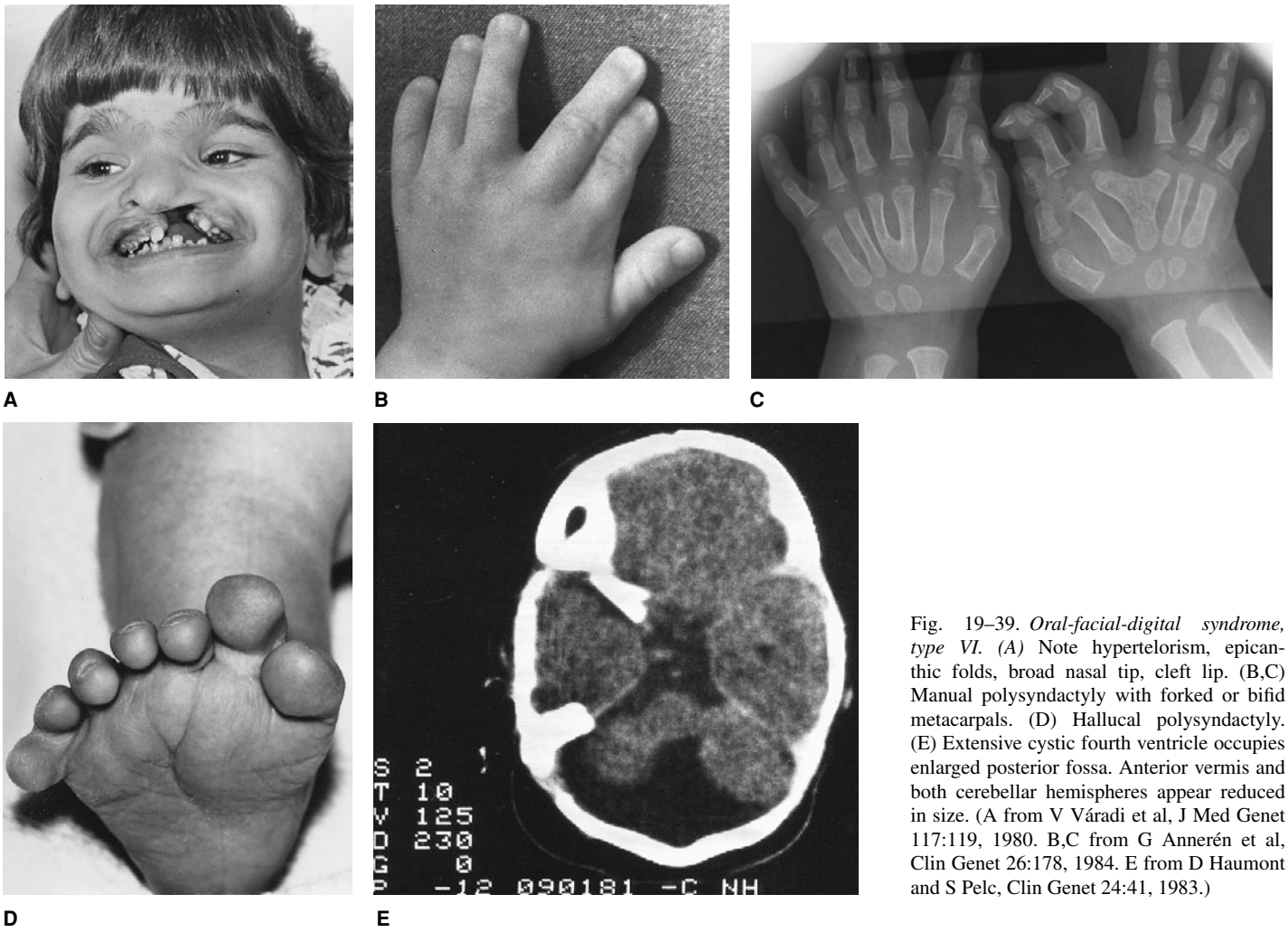

Fig. 19–39. *Oral-facial-digital syndrome, type VI. (A)* Note hypertelorism, epicanthic folds, broad nasal tip, cleft lip. (B,C) Manual polysyndactyly with forked or bifid metacarpals. (D) Hallucal polysyndactyly. (E) Extensive cystic fourth ventricle occupies enlarged posterior fossa. Anterior vermis and both cerebellar hemispheres appear reduced in size. (A from V Váradi et al, J Med Genet 117:119, 1980. B,C from G Annerén et al, Clin Genet 26:178, 1984. E from D Haumont and S Pelc, Clin Genet 24:41, 1983.)

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OFD type VII [facial asymmetry, pseudo cleft lip, lobulated tongue, and hydronephrosis (Whelan syndrome)]. Whelan et al (1) reported a mother and daughter with similar findings, which the authors suggested represented OFD I syndrome. However, some of the findings are inconsistent with that diagnosis, and this likely represents a distinct entity.

Both mother and daughter had apparent hypertelorism, with pseudocleft of the upper lip, highly arched palate, bifid tongue, and facial asymmetry. The daughter also had a low-set, posteriorly angulated ear, preauricular tags, and mucosal frenulae. Polydactyly was not present; the only digital anomaly was clinodactyly in both mother and daughter. In addition, both had bilateral hydronephrosis. The daughter was developmentally delayed, whereas the mother had low-normal intelligence. Inheritance is either X-linked or autosomal dominant.

Reference [OFD type VII (facial asymmetry, pseudo cleft lip, lobulated tongue, and hydronephrosis [Whelan syndrome])]

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OFD type VIII (OFD and retinal abnormalities). Edwards et al (1), in 1988, described a family with what was thought to be an X-linked form of oral-facial-digital syndrome with tongue lobulations and hamartomas, median cleft upper lip, dystopia canthorum, broad or bifid nasal tip, bilateral preaxial and postaxial polydactyly of the hands and feet, duplication of the halluces, shortened tibiae and/or radii, short stature, recurrent aspiration pneumonia, and developmental delay. There was forking of metatarsals 6–7 in one boy.

There were four affected males in three generations. Female heterozygotes had mild expression (tongue hamartoma, ankyloglossia, mild tongue clefting). Death occurred in three of the affected males during infancy, probably from aspiration pneumonia.

Gurrieri et al (2) reported brothers affected also with retinochoroideal lacunae of colobomatous type, similar to those seen in Aicardi syndrome. Sigaudy et al (5) and Stevens and Marsh (6) reported females with areas of chorioretinal atrophy. Jameison and Collins (3) described a similarly affected male. Nagai et al (4) added Dandy-Walker malformations

We cannot say that type III is not the same as type VIII.

References [OFD type VIII (OFD and retinal abnormalities)]

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Miscellaneous or unclassifiable syndromes

There are a plethora of syndromes that defy categorization.

Tucker et al (16) reported a patient with oral, facial, and digital anomalies. In addition to hypertelorism, micrognathia, oral frenulae, bifid tongue, and an extra finger, the deceased newborn female had posterior encephalocele, omphalocele, and talipes valgus. Autopsy revealed cerebral microgyria, partial hypoplasia of parietal lobes, and polycystic liver and kidneys. Moran-Barroso et al (11) described a male infant with myelomeningocoele, stenosis of the aqueduct of Sylvius and congenital heart anomalies.

Iaccarino et al (10) described three cases of an oral-facial-digital syndrome with cardiac, but not brain, abnormalities. The first case, in addition to midline cleft upper lip, had lobulated tongue, pseudocleft palate, and pre- and postaxial polydactyly of hands and feet, a complex cardiac defect, including common atrium, single atrioventricular valve, single ventricle, and truncus arteriosus, small epiglottis, anteriorly placed anus, and absent lobation of the left lung. Iaccarino et al (10) further reported sibs each having cardiac, oral, facial, and digital anomalies. The first sib had cleft lip, polydactyly of hands and feet, VSD, and mitral valve atresia; the second sib had preaxial polysyndactyly of the hands and feet, and complete atrioventricular canal. Whether oral, facial, and digital anomalies with cardiac defects represent yet another type of OFD syndrome remains to be seen; however, the presence of cardiac defects in both sibs reported by Iaccarino et al (10) suggests that this is a distinct possibility. A similar condition has been noted by Bonneau et al (3).

Örstavik et al (12) noted a brother and sister with hamartomas of tongue, polysyndactyly, and congenital heart defects (coarctation of aorta, subaortic stenosis, atrioventricular canal).

Toriello et al (15) reported an infant with features of frontonasal malformation, as well as polydactyly of the hands and feet, agenesis of corpus callosum, Dandy-Walker malformation, persistent fetal circulation, short limbs, and cryptorchidism. X-ray examination demonstrated narrow ribcage, elongated trunk, and long bones that were shorter than average (65%–90% for age). The tibiae were most severely affected. This case has features of both OFD IV and Váradi syndrome, and may be a unique condition.

Berberich et al (2) reported a patient with centrally notched upper lip, frenulae extending from the alveolar ridge to the buccal mucosa, lobulated tongue, partial cleft palate, thoracic dystrophy, preaxial polysyndactyly involving one thumb and both halluces, mild shortening of humeri, bowed tibiae, short penis, and imperforate anus. The condition was compatible with survival during the first year of life.

Figueroa et al (7) noted a female with cleft palate, vestibular frenulae, oligodactyly, preaxial polydactyly, radial shortening, fibular agenesis and coalescence of tarsal bones. This has been called OFD type X.

Adès et al (1) reported a fetus with occipitoschisis, polydactyly, campomelia, cleft palate, laryngeal dysplasia, ocular colobomata, hepatic fibrosis, ambiguous genitalia, cystic kidneys and brain malformations. The parents were first cousins.

Gabrielli et al (9) described a male with hypertelorism, down-slanting palpebral fissures, tongue clefts, multiple frenulae, cleft palate, bulbous nose, postaxial polydactyly of hands and feet and fusion of C_2 and C_3. There was a striking resemblance to those with terminal deletion 3p.

Richmond and Mene (13) reported female sibs with microcephaly, extra digits, natal teeth, mental retardation and hamartomata of tongue.

Chitayat et al (5) described male and female sibs with postaxial polydactyly of hands and feet, syndactyly and brachydactyly, pectus excavatum, mesomelic shortness of upper and lower limbs, see-saw winking, and a host of anomalies that spanned types II, III, IV and VI.

Fujiwara et al (8) noted a girl with tongue hamartomata, multiple frenulae, hypoplasia of ulnae, fibulae, tibiae, polysyndactyly of hands and feet, hydronephrosis, hypothalamic hamartoma, seizures and central precocious puberty. This child was found to have a GLI3 mutation.

Lukusa and Fryns (10a) described a boy with oral, facial, and digital anomalies associated with dup(7q21.2), macrocephaly, hypertelorism, small down-slanting palpebral fissures, lobulated tongue, multiple frenula, oligodontia, cutaneous syndactyly of fingers 2–3 and 3–4, fetal finger pads, and broad thumbs and halluces.

Differential diagnosis. There are a significant number of disorders that have midline defect of the upper lip ranging from isolated midline cleft to encephalocele to Ellis-van Creveld syndrome to short rib-polydactyly syndrome, Majewski type. None of these disorders should present problems in differential diagnosis of the OFD syndrome for the clinician.

Of all the disorders reported in this text, the oral-facial-digital syndromes have afforded us the least satisfaction in addressing them. Each new report describes a patient that differs in some respect from the types already described. One can easily distinguish OFD types I and V, but then one runs into problems. Types II, III, IV, and VI are not clear cut and there are some patients that seem to bridge two or more types. Type III, for example, is presumably distinguished by "see-saw" eye movements, but this has been noted in other types. Type IV has short tibiae as a hallmark but so do some miscellaneous forms of OFD. This also applies to type VI with the forked midmetacarpal. Some of the rarer types have been grouped by their association with eye findings similar to those seen in *Aicardi syndrome*. *Pallister-Hall syndrome* has overlaps. To further confound the problem, Joubert syndrome (not otherwise discussed because of lack of facial dysmorphism), an autosomal recessive syndrome, is characterized by mental retardation, cerebellar vermis agenesis or hypoplasia, episodic panting tachypnea, abnormal eye movements, hypotonia, retinal dysplasia (25%), and a host of overlapping features (occipital meningocele/encephalocele, seizures, and various digital anomalies) (4). At least one gene for Joubert syndrome maps to 9q34.3 (14).

Until we obtain help from the molecular geneticists, we are lost in this morass.

References (Miscellaneous or unclassifiable syndromes)

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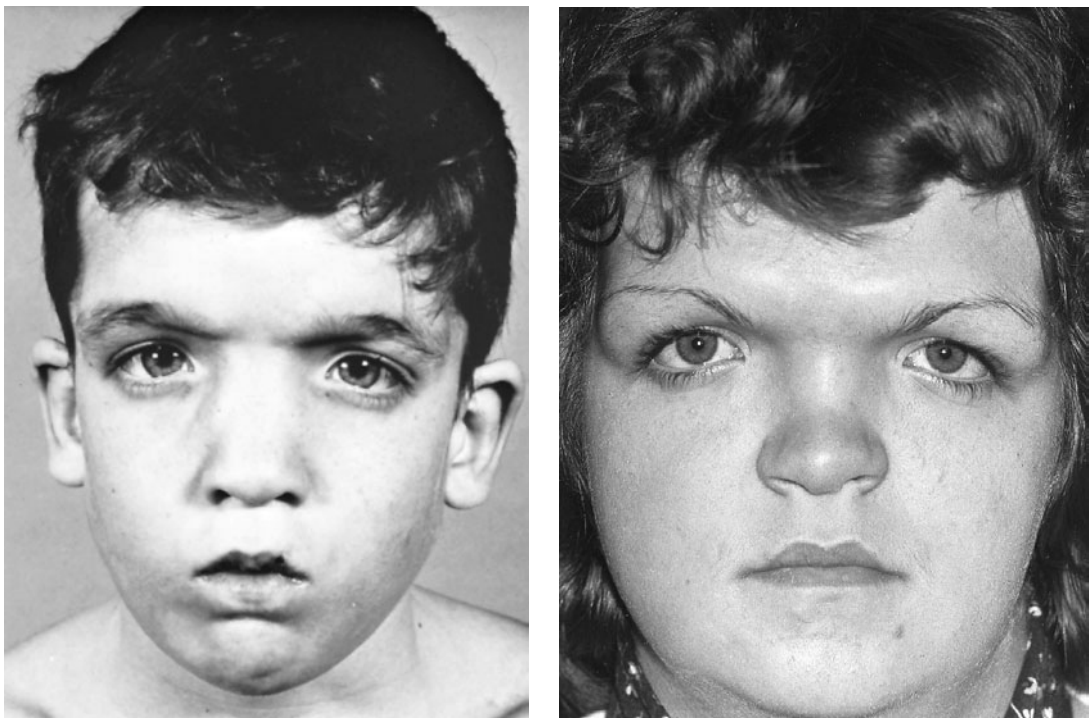
Otopalatodigital syndrome, type I

Otopalatodigital syndrome, type I (OPD I), first reported by Taybi (29) in 1962 and by Dudding et al (4) in 1967, is characterized by short stature, pugilistic facial appearance, conductive hearing loss, cleft palate, and generalized bone dysplasia. Inheritance is X-linked with variable heterozygote expression (8,9,13,16,18,24). The gene has been mapped to Xq28 (2,10,11). Verloes et al (30) has opined that OPDI and II, *frontometaphyseal dysplasia* and *Melnick-Needles syndrome* are but variants of a single disorder. This has been echoed by Superti-Furga (24a).

Craniofacial and orofacial findings. The facies in males is characteristic (4,18,19) (Fig. 19–40). An overhanging brow, prominent supraorbital ridges, and down-slanting palpebral fissures are noted. Hypertelorism and broad nasal root give the patient a pugilistic appearance. Slight notching may be noted at the junction between the medial third and lateral two-thirds of the upper eyelid margin in some affected males (6). The corners of the mouth are often down turned. Facial features in affected females are more variable and usually more mild than in affected The most constant features in affected females are overhanging brow, hyperteloric appearance, prominent lateral supraorbital ridges, depressed nasal bridge, and flat midface (6). Cleft palate has been seen in all affected males except one (20); it has not been found in affected females.

Auditory system. Mental retardation and slow speech development may be related to the conductive hearing loss that, in the few patients tested, ranged from 30 to 90 dB. However, not all patients have hearing loss (18). Abnormally shaped middle ear ossicles and small external auditory canals have been found (1–4,9,13,17,20,29).

Fig. 19–40. *Otopalatodigital syndrome, type I.* (A) Overhanging brow with prominent supraorbital ridge and wide nasal bridge resulting in pugilistic appearance. (B) An affected female. (A from BA Dudding et al, Am J Dis Child 113:214, 1967. B courtesy of HD Rott, Nürnberg, Germany.)



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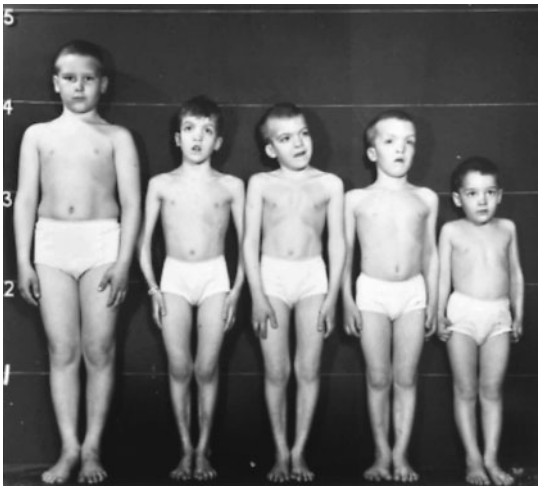
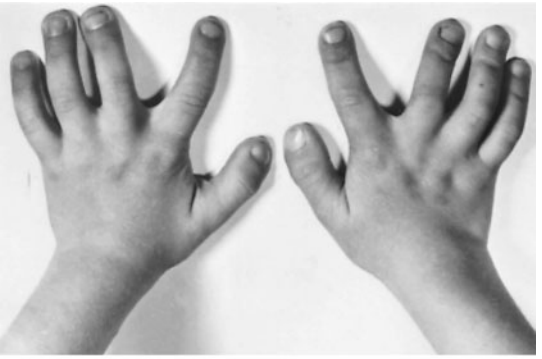


Fig. 19–41. *Otopalatodigital syndrome, type I.* Skeletal growth is retarded. Three affected sibs, ages 8, 7, and 6 years, are flanked by their two normal brothers, ages 10 and 4 years. Note subluxation of elbows of affected. (From BA Dudding et al, Am J Dis Child 113:214, 1967.)

Central nervous system. Most male patients have mild mental slowness, intelligence quotients ranging between 75 and 90. Speech development is slow. Hypoplasia of the transverse sinus and hyperplasia of the occipital sinuses have been noted (27).

Musculoskeletal system. Skeletal growth is retarded; all male patients are below the 10th centile and may be below the 3rd centile for height (6) (Fig. 19–41). The trunk is small, and there is pectus excavatum(4,25). Limited elbow extension and wrist supination have been noted in several patients, some of whom have subluxation of radial heads (4,15,24,29). Hands and feet are striking (4). Thumbs and halluces are spatulate and especially abbreviated (Fig. 19–42). Clefting between the hallux and the other toes is exaggerated. The toes and fingers are irregular in form and direction of curvature. The second and third fingers may deviate to the ulnar side, whereas the fifth finger often bends to the radial side. Affected females are not unusually short; although only mild abnormalities may be observed in the hands, the feet usually have more obvious abnormalities (6).



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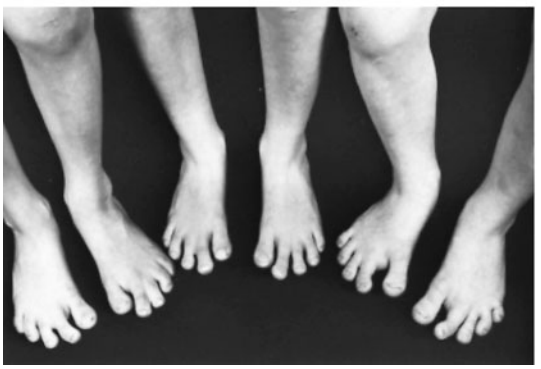

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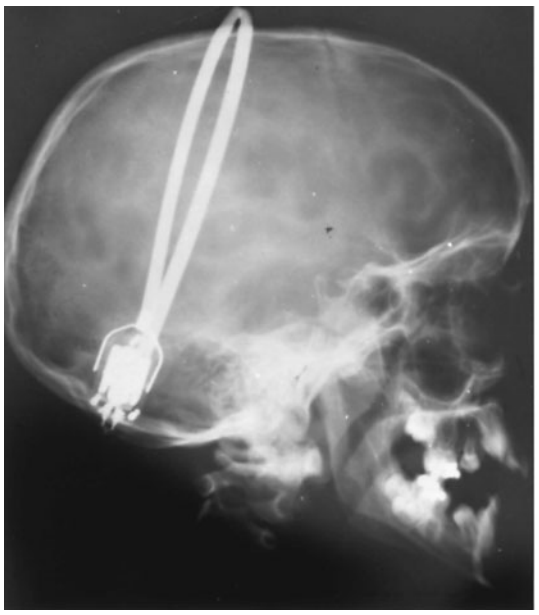
Fig. 19–42. *Otopalatodigital syndrome, type I.* (A) Mild syndactyly and clinodactyly of digits. Note abbreviated and flattened terminal phalanges. (B) Short big toes, variable soft-tissue syndactyly and clinodactyly, gap between hallux and second toes. (A from A Prader, Zürich, Switzerland. B from BA Dudding et al, Am J Dis Child 113:214, 1967.)

Radiographic alterations are marked. Frontal and occipital bossing and thickening give the skull a mushroom-like appearance. The skull base is



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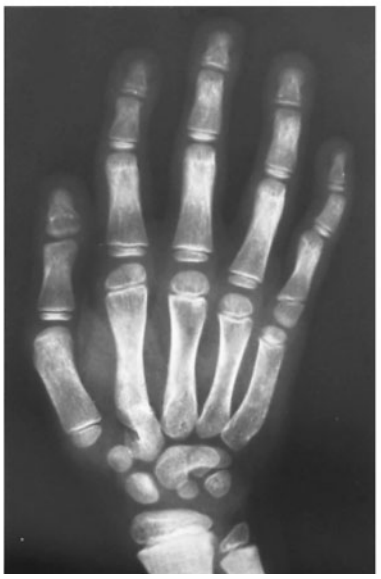

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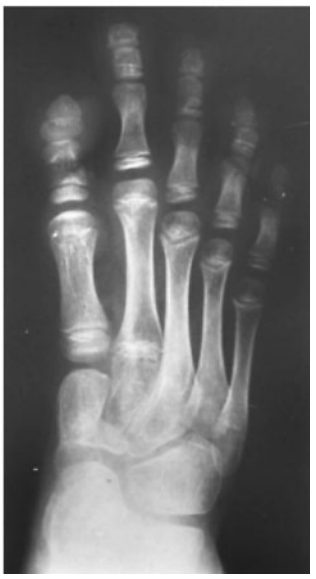

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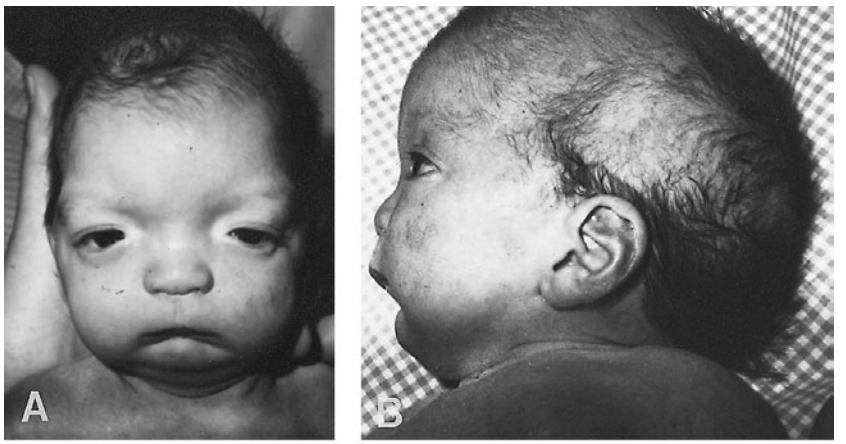
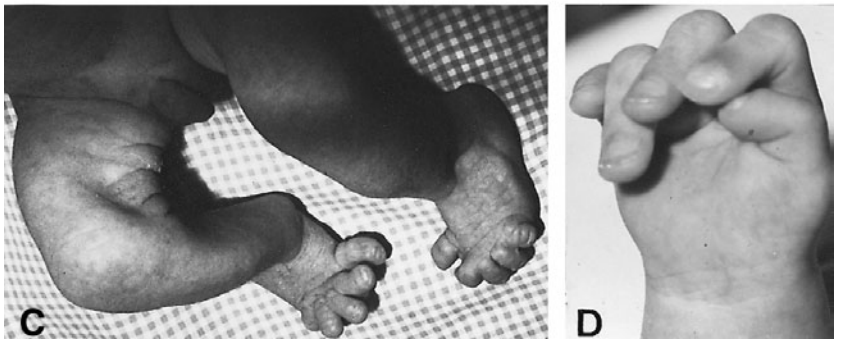
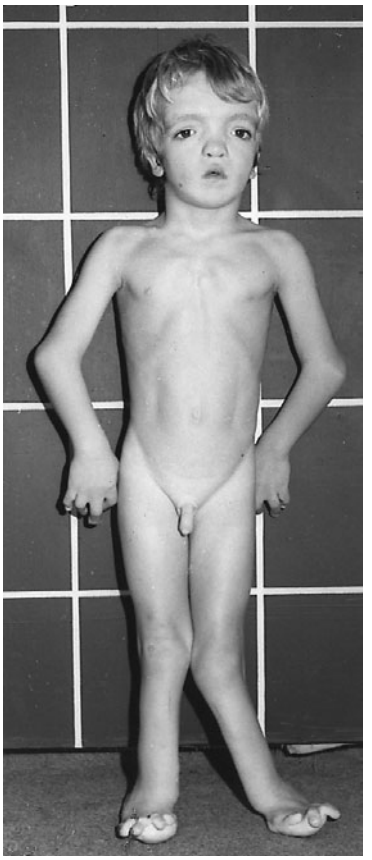
Fig. 19–43. *Otopalatodigital syndrome, type I.* Radiographs. (A) Vertical basisphenoid. (B) Abnormal middle phalanx of fifth finger, shortened terminal phalanges, capitate–hamate complex, accessory ossification center of second metacarpal. (C) Short hallux, fusion between middle and lateral cuneiforms and corresponding metatarsals, forming paddle-shaped structures. (B,C from BA Dudding et al, Am J Dis Child 113:214, 1967.)







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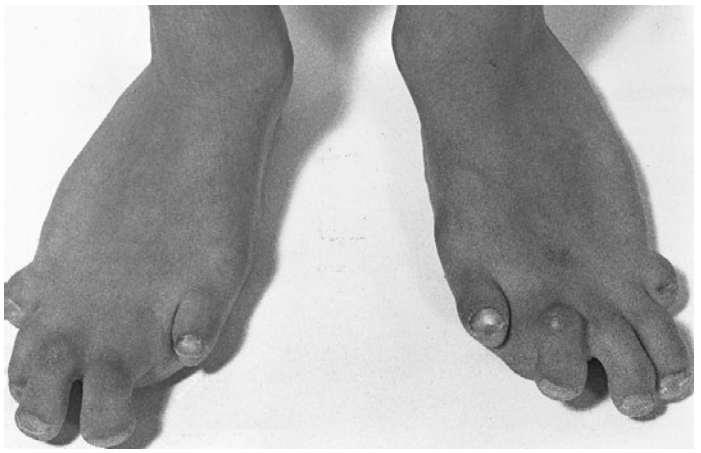

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Fig. 19–44. *Otopalatodigital syndrome, type II.* (A) Hypertelorism, downslanting palpebral fissures, small mouth. (B) Posteriorly angulated ears, micrognathia. (C) Curvature of lower limbs, fanned-out toes. (D) Abnormal position of fingers. (E) Flattened face, dislocated elbows and hips, fingers held in flexed overlapping position. (F) Severely abbreviated halluces and fifth toes, and camptodactyly. (A–D from M André et al, J Pediatr 98:747, 1981. E,F from K Kozlowski, Pediatr Radiol 6:97, 1977.)

thick, the facial bones are hypoplastic, and the paranasal sinuses and mastoids are poorly pneumatized. The nasion-sella-basion angle is approximately 116 degrees (normal mean = 132 degrees), and the mandibular plane angle is increased. The mandible is small and the mandibular angle more obtuse than normal (6,15,15a,23). The clivus, or basisphenoid, lies further posteriorly than normal in relation to the cervical spine. These changes are essentially limited to affected males (Fig. 19–43A).

Iliac bones are small, with decreased flare. Coxa valga is a common finding. The lower tibia is laterally bowed. Failure of fusion of several vertebral arches is common.

Distinctive changes in hands of males include shortening of radial side of middle phalanx of fifth finger, clinodactyly, short distal phalanx of thumb (which during development has a cone-shaped epiphysis), accessory ossification center in second metacarpal, tear-drop-shaped trapezium, transverse capitate, and trapezium-scaphoid fusion (6,15, 22,26,28) (Fig. 19–43B). Females may have greater multangular-scaphoid fusion.

In affected males, radiologic abnormalities in the feet include short phalanges and metatarsals of great toes. The second and third metatarsals are long and abnormally shaped because of their fusion with the cuneiform bones (Fig. 19–43C). The fifth metatarsal may be prominent, with an extra ossification center. Tarsal fusions are common, and males usually have two ossification centers in the navicular bone.

Diagnosis. *Larsen syndrome* shares a number of features, such as cleft palate and joint dislocations, with the OPD I syndrome. However, patients with Larsen syndrome have a different facies, multiple carpal bones, a juxtacalcaneal bone, and false flexion creases of the fingers. Larsen syndrome is far more severe in its skeletal manifestations. *Acro-cranio-facial dysostosis syndrome* is also more marked in its expression. The patients reported by Salinas et al (22) have a different disorder than OPD I or OPD II. The patients described as having X-linked cleft palate in one paper (30) are examples of OPD, type I. It is difficult to classify the patients described by Jäger and Refior (14) and García-Cruz et al (7).

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Otopalatodigital syndrome, type II

Otopalatodigital syndrome, type II (OPD II), first described by Fitch et al (7) in 1976, is characterized by short stature, unusual facies, cleft palate, and multiple skeletal anomalies. Skeletal manifestations are far more severe in this syndrome than they are in OPD syndrome, type I. Approximately 30 cases have been reported to date. We cannot accept the case of Holder and Winter (10) as a valid example. The patients of Stoll and Alembik (21) and Alembik et al (1) fit better Larsen syndrome. We cannot diagnose the cases of Eccles et al (5) and Preis et al (16). The cases of Gendall and Kozlowski (9) are male Melnick-Needles examples.

Death has occurred, usually because of respiratory infection, within the first 5 months of life in at least 12 cases (2,6,7,19,24); another died of similar causes at age 2 1/2 years (11). Those who survive have short stature.

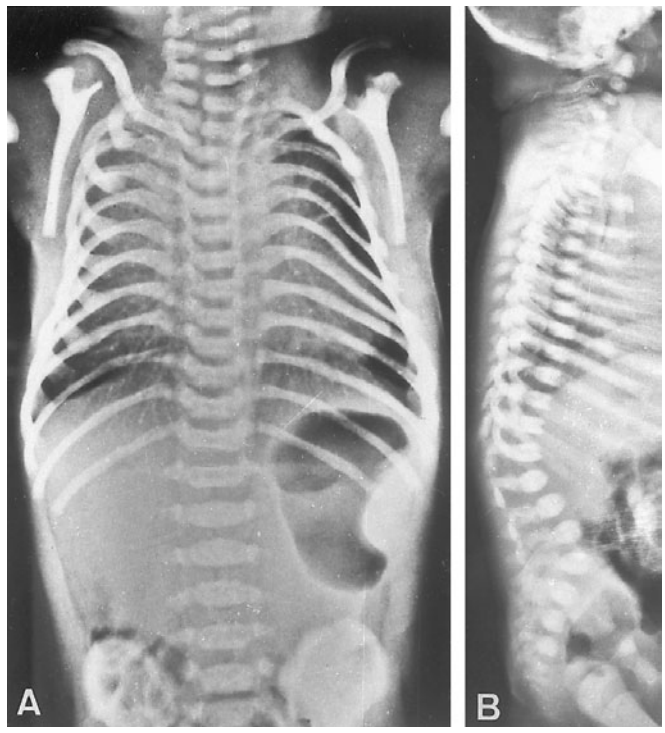
Heredity is X-linked recessive. Presumably OPD type I and II are allelic. However, Melnick-Needles syndrome should be studied for allelism (3,4a,10,18).

Craniofacial findings. Hypertelorism, frontal bossing, lateral fullness of supraorbital ridges, broad nasal bridge, stubby nose, downslanting palpebral fissures, midface hypoplasia, low-set ears, microstomia with down-turned bow of upper lip, and marked mandibular micrognathia are noted (2,4,16,19) (Fig. 19–44). Carrier females may have midfacial abnormalities (2,4,16,19,24) but many appear quite normal (14,18a). Cleft palate is found in 85% of affected males, and bifid uvula in a carrier female has been noted (7). In some instances, frank Robin sequence may be present (2).

Central nervous system. Psychomotor development and intelligence appear normal in some patients (8), whereas others are mentally retarded (11). Hydrocephalus has been noted (8,22,24). Hearing loss has been reported (2,8,12,16,19,22).

Musculoskeletal system. The anterior fontanel may be large (7). The base of the skull is sclerotic (7). Midface hypoplasia is evident. Clavicles are thin and wavy. The thorax is narrow, and there may be

Fig. 19–45. *Otopalatodigital syndrome, type II*. (A) Steeply sloping sinuous clavicles, sinuous ribs. (B) Dorsolumbar kyphosis, increased lumbar lordosis. (From M André et al, J Pediatr 98:747, 1981.)



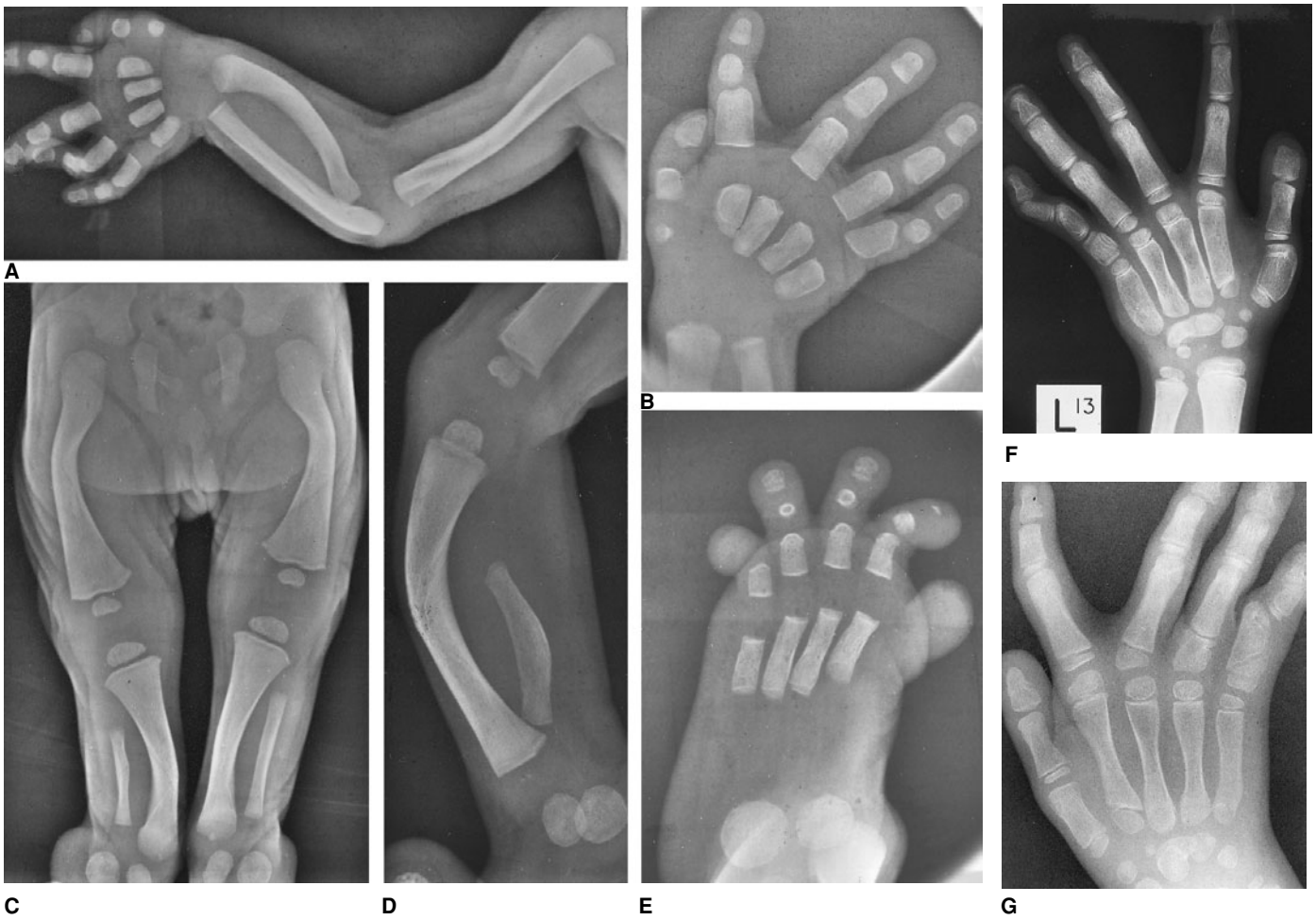


Fig. 19–46. *Otopalatodigital syndrome, type II*. Radiographs. (A) Curvature of humerus and radius, anomalies of metacarpals and phalanges. (B) Small first metacarpal, large proximal phalanges. (C) Hip dislocation, curvature of femora, hypoplastic fibulae. Advanced bone age. (D) Curvature of tibia. (E) Absence of ossification of first metatarsals and its phalanges, short fifth metatarsal. (F) Anomalies of metacarpals and phalanges. Note extra bone between proximal phalanx and metacarpal on fifth finger, enlarged epiphyses, capitate-hamate complex. (G) Compare this patient with patient in B and patient in F. Note unusual proximal phalangeal epiphyses, transverse capitate, extra bone in carpal complex. (A–E from M André et al, J Pediatr 98:747, 1981. F from K Kozlowski et al, Pediatr Radiol 6:97, 1977. G from N Fitch et al, Am J Med Genet 15:655, 1983.)

pectus excavatum. Ribs are wide posteriorly and anteriorly, but narrow in their middle portions. Vertebrae are flattened (Fig. 19–45). There may be scoliosis. The humeri, radii, femora, and tibiae are bowed; curving of long bones may disappear early in life (8). Radial heads may be dislocated. Fibulae are small or absent in 70%. Ilia are hypoplastic. Thumbs are broad and short, as are the great toes (Fig. 19–46). Fingers are held in a flexed, overlapping position. Syndactyly of the fingers and toes is variable. Tubular bones of hands and feet are deformed and bones of the wrists and ankles are hypoplastic and malformed and some may fail to ossify (Fig. 19–46). Rocker-bottom or equinovarus feet may be present (2,4,12). Carrier females may have abnormalities of the hands and feet (7,19). Ogata et al (14) found defective ossification.

Other findings. Omphalocele (17,20,24), hydronephrosis, hydroureter, and chordee (6,8,24) have been noted.

Auditory system. Hearing loss has been described (8,11,12); one patient (8) had aseptic meningitis twice during the first year of life. Bilateral conductive hearing loss was described in a carrier female (2); malformed ossicles were noted at surgery. The 2 1/2-year-old male reported by Shi (19) likely had OPD II (H Schucknecht, personal communication, 1985). Histologic studies of his temporal bone revealed malformed ossicles and abnormalities of the bony labyrinth.

Laboratory aids. Prenatal diagnosis has been done by ultrasound (17,23). Both membranous bone formation and bone remodeling are defective (18a).

Diagnosis. There is much overlap among oto-palato-digital syndrome I and II, *Larsen syndrome, atelosteogenesis I and II, boomerang dysplasia*, and the lethal male *Melnick-Needles syndrome* (3,13,18). This syndrome should be distinguished *from otopalatodigital syndrome, type I, campomelic dysplasia*, and *trisomy 18*. There is similarity to acrocoxo-melic dysplasia, an autosomal recessive disorder described by Plauchu et al (15).

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Chapter 20
Orofacial Clefting Syndromes: General Aspects

Facial clefts and associated anomalies

Introduction. The first evidence of clefting is in an Egyptian mummy dating from 2400 to 1300 BC (12). A 2000-year-old ceramic statue of a king with a cleft has been reported from Colombia (22), and an African mask showing cleft lip and palate has been described (5). It is curious that in spite of the frequent occurrence of facial clefts, Greek and Roman physicians made no mention of them. A Ming dynasty painting depicts cleft lip (8) as does a twentieth century Russian work by Vrubel (7). Treatment of cleft lip was apparently first carried out by a Chinese physician in 390 AD (2).

Before cleft lip and cleft palate syndromes are considered, the embryologic, epidemiologic, and genetic aspects of isolated cleft lip and cleft palate are reviewed. Readers wishing to examine the subject in greater detail should consult Fraser (10), Millard (21), Melnick et al (20), Dronemaraju (6), and Bear (1).

Clefts of the primary and/or secondary palates are included among the more common congenital anomalies. Clinically there is great variability in degree of cleft formation. Minimal involvement includes bifid uvula, linear lip indentations with or without nostril deformity (intrauterine-healed clefts), lateral upper lip fistula, and submucous palatal cleft (3,4,9,11,13–18,23,26–29). Martin et al (19) suggested that they could detect the carriers among first degree relatives by ultrasound of the orbicularis oris.

A cleft may involve only the upper lip or may extend to involve the nostril and the hard and soft palates. An isolated palatal cleft may be limited to the uvula (bifid uvula) or may be more extensive, cleaving the soft palate or both the hard and soft palates. A combination of cleft lip and cleft palate is most common. Breakdown according to type has differed somewhat in several large surveys. Roughly, however, cleft lip with cleft palate comprises approximately 45%, isolated cleft palate approximately 30%, and cleft lip approximately 25%. The rare instance of separate clefts of the lip and palate represents a variant of cleft lip-palate (24).

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Embryology. Neural crest cells play an integral part in facial morphogenesis (5,10,23,27). Just prior to the time when the neural folds fuse to form the neural tube, ectodermal cells adjacent to the neural plate migrate into the underlying regions where they act as mesenchyme (ectomesenchyme). Crest cells in the head and face form essentially all the skeletal and connective tissues of the face: bone, cartilage, fibrous connective tissue, and all dental tissues except enamel.

During the fourth week (day 25), the anterior neuropore has closed. The face, if one can call it that at this time, consists of a large frontal prominence that constitutes the upper boundary of the stomodeum (primitive mouth) and results from ectodermal proliferation ventral to the developing brain (17). The primary mouth is separated from the foregut by the buccopharyngeal membrane that undergoes selective cell death and ruptures at this time in development (18). On each side of the lower aspect of the frontonasal prominence, the nasal placodes are forming. These bilateral structures located just above the primary mouth are represented by local thickenings of the surface ectoderm. Rapid proliferation of ectomesenchyme results in nasal swellings both lateral to and medial to the nasal placodes. By means of selective cell death and proliferation of tissues, the nasal or olfactory pits are formed and extend into the primitive mouth. These are primitive nostrils (Fig. 20–1). Sulik and

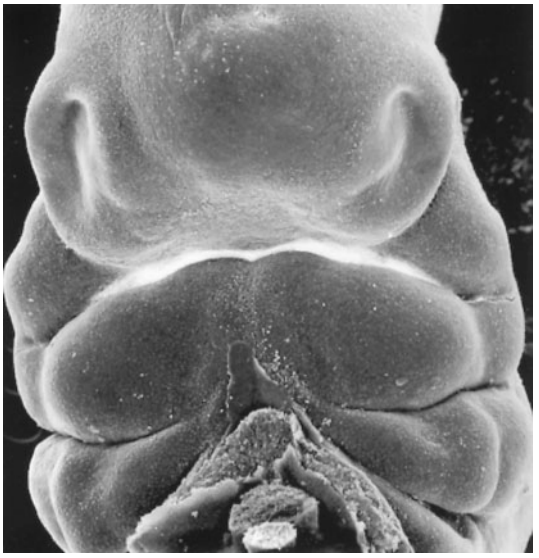


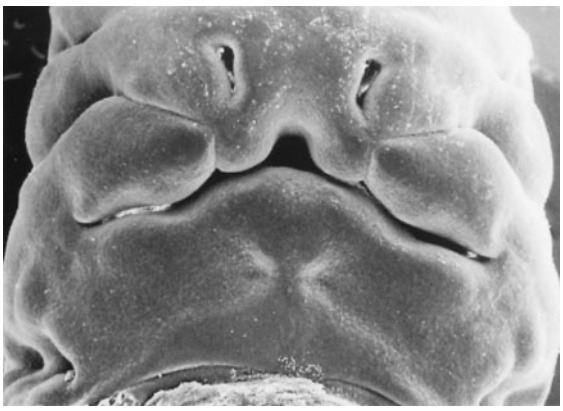
Fig. 20–1. *Facial clefts and associated anomalies*. Scanning electron microscopy of face of 5-week-old embryo. Note olfactory pits developing on lateral portions of fronto-nasal prominence. (Courtesy of K Sulik, Chapel Hill, North Carolina.)

Schoenwolf (23) have elegantly illustrated these changes by scanning electron microscopy.

Extremely active growth occurs during the fifth and sixth weeks. The maxillary swellings, which represent the upper anterior portion of the first pharyngeal arch, enlarge considerably, again through ectomesenchymal proliferations. During the sixth and seventh weeks, the medial nasal prominences merge with each other and with the bilateral maxillary processes (17). Thus, the upper lip is formed laterally by the maxillary prominences and medially by the fused medial nasal prominences (Fig. 20–2). It should be emphasized that the lateral nasal prominences play no role in formation of the upper lip but form the alae or wings of the nose. The philtral ridges have nothing to do with facial prominences. They do not appear until the third to fourth embryonal month (16).

The primary palate consists of the two merged medial nasal prominences that form the intermaxillary segment. This, in turn, consists of two portions: (*1*) a labial component that forms the philtrum of the upper lip, that is, the indented area flanked by roughly parallel ridges that run from the columella of the nose to the middle of the upper lip, and (*2*) the triangular palatal component of alveolar bone that includes the four maxillary incisor teeth. The primary palate extends posteriorly to the incisive foramen or, clinically, to the incisive papilla (22). The rare paramedian pit or fistula of the upper lip occurs at the line of fusion of the median nasal prominence and the maxillary process (2,3,8,14,15,24). The etiology of the midline sinus of the upper lip is not known (1), but likely involves entrapment of epithelium.

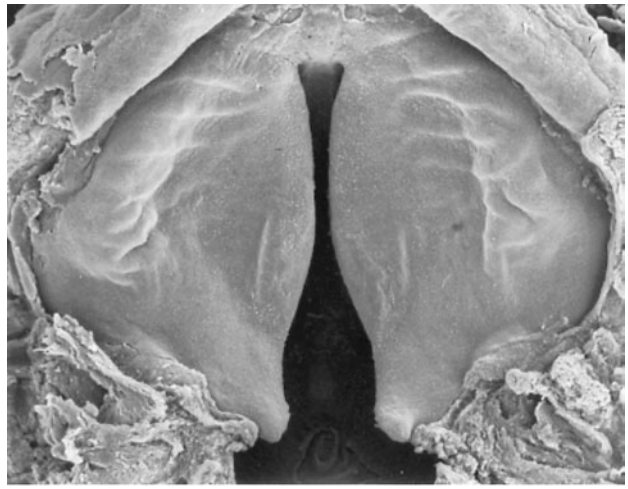
Fig. 20–2. *Facial clefts and associated anomalies*. Scanning electron microscopy of 6-week-old embryo. Upper lip formed from fusion between notched median nasal prominence has not yet fused with maxillary processes. (Courtesy of K Sulik, Chapel Hill, North Carolina.)



The so-called secondary palate comprises at least 90% of the hard and soft palates, that is, all except the anterior portion that holds the incisor teeth. Its development is more complicated than originally thought. The palatal shelves originate as swellings or shelf-like burgeonings of the medial surfaces of the maxillary prominences. They appear in the sixth week and grow downward, lateral to the tongue. Elevation of the palatal processes to a horizontal plane is more vigorous anteriorly, that is, in the part nearer the primary palate. Elevation begins in the seventh week (7). Final closure, by fusion, occurs somewhat later in females than in males (20) (Fig. 20–3). The soft palate and uvula are formed by merging, not fusion, of two growth centers at the caudal end of the hard palate. Good reviews of secondary palate formation are those of Greene and Pratt (6) and Ferguson (4).

What promotes the elevation has been called *intrinsic shelf force* and has a complex biochemical and physiochemical basis. The tongue appears to play little role in shelf elevation. Elevation of the shelves is associated with widening and forward growth of the mandible. Once the shelves are elevated to the horizontal plane, there is programmed cell death of the medial edge. When the shelf edges touch, the epithelium has thinned and

Fig. 20–3. *Facial clefts and associated anomalies*. (A) Scanning electron microscopy of secondary palate in 53-day-old embryo. Fusion with primary palate has occurred. (B) At 59 days, complete fusion of secondary palate has occurred. (Courtesy of L Russell, Chapel Hill, North Carolina.)



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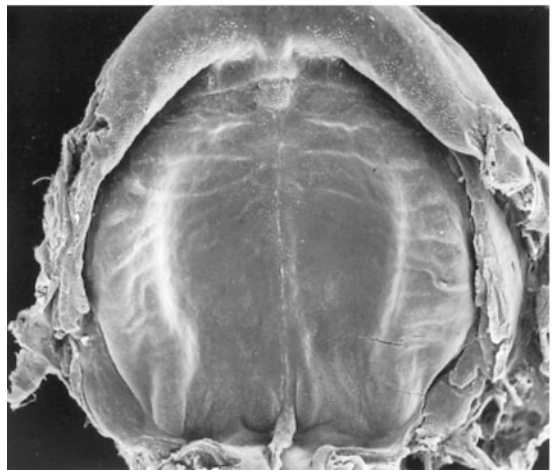

B

has undergone advanced stages of degeneration allowing mesenchyme from each side to join in the midline (13). Complete fusion of the palatal shelves is effected by the tenth week (20). The soft palate and uvula are formed from secondary growth centers by successive merging. In some infants, there is cystic degeneration of the epithelial remnants that produces evanescent midline palatal microcysts (Epstein's pearls).

Knowledge concerning mechanisms involved in regulation of embryonic growth is, at best, sparse. The blueprints for the rate at which facial prominences burgeon and for the direction in which they grow are in part determined by the genetic template, the DNA code located in the cell nucleus. But hereditary factors do not act alone. Growth patterns can also be influenced by environmental factors. For example, there are several mouse models for cleft lip and for cleft palate. There are both susceptible and nonsusceptible strains and a large list of teratogenic substances that produce clefting in mice. However, there is little evidence that these agents play a significant role in cleft production in humans (11), the exceptions being phenytoin, folic acid antagonists, and retinoic acid (see Chapter 2).

Various genetic and/or environmental factors may inhibit the flow of or decrease the number of neural crest cells or may affect their mass so that contact between prominences is impossible or inadequate (9,11). The epithelium covering the mesenchyme may not undergo programmed cell death so that fusion cannot take place. Exact timing and positioning play critical roles. For example, Johnston and Sulik (9) showed that if the bilaterally formed nasal placodes contact one another, there is severe to complete suppression of development of medial nasal prominences.

Altered positioning of the nasal placodes or abnormal directional growth of the facial prominences may be reasonable for cleft of the primary palate (cleft lip). This has been supported not only by animal models but by the clinical observation that parents of children with cleft lip exhibit some degree of reduction in overall midface size.

There may be many mechanisms by which a cleft of the secondary palate (cleft palate) occurs. Failure of growth of the mandible (micrognathia) may inhibit elevation of the shelves. For example, the Robin sequence is associated with U-shaped cleft palate.

Clefts of the primary and secondary palates occur together in about one-half the cases. A common mechanism of production has been sought. It has been suggested that the tongue tip becomes wedged in the labial cleft, produced by failure of fusion of the medial nasal and maxillary prominences. This, it has been argued, would not allow the tongue to drop and, consequently, would interfere with midline contact and inhibit fusion. This explanation appears to be simplistic. It would seem that reduction in size of both the labial maxillary prominences and the palatine process of the maxillary prominences is a more reasonable explanation.

Clefts of the secondary palate likely result from either hypoplasia of the shelves or delay in timing of shelf elevation. Experiments carried out on susceptible strains of mice have suggested that both mechanisms are operative, but at different times in gestation. For example, large doses of vitamin A given early in gestation inhibit palatal shelf growth whereas cortisone given later in gestation inhibits palatal shelf elevation (19).

Recent evidence for reduction of neural tube defects (anencephaly, spina bifida) by administration of dietary supplements of folic acid has caused several teams of investigators to study whether a similar reduction in cleft lip and/or cleft palate might be effected. There seems to be a 25%–50% reduction in the rate of clefting (21,25,26), but a multicenter randomized double-blind study is needed.

Cigarette smoking during pregnancy seems to be correlated with clefting (12).

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Epidemiology. Cleft lip with or without cleft palate. Cleft lip with or without cleft palate [CL(P)] occurs in approximately 1/1000 white births (range 0.7–1.3), although data differ somewhat from study to study in various parts of Europe and the United States, depending on source of information (birth records, birth certificates, pregnancy follow-up data, surgical records, hospital records, multiple sources), whether the data were obtained retrospectively or prospectively, and whether stillbirths or syndromal disorders were included (1,4–6, 13,16,18,22,25,41,42,45,50,58,70,72,75,78,80,83). A good summary of these data is that of Derijcke et al (20). The problems of data gathering have been elegantly discussed by Vanderas (80) and Sayetta et al (65). Greene et al (27) has shown that birth certificate data are extremely inaccurate. Data gathered from parents may also be suspect (59).

There is marked racial predilection. The frequency of CL(P) in Native Americans appears to be the highest of any group in the world (over 3.6/1000 live births) (17,22,35,42,57). It is also high in Japanese (approximately 2.1/1000 births (13,17,22,37,42,52–54,) and Chinese (approximately 1.4/1000 births) (16a,21,31,42) and, in contrast, it is lower among blacks (approximately 0.3/1000 births) (2,15,17,19,33,

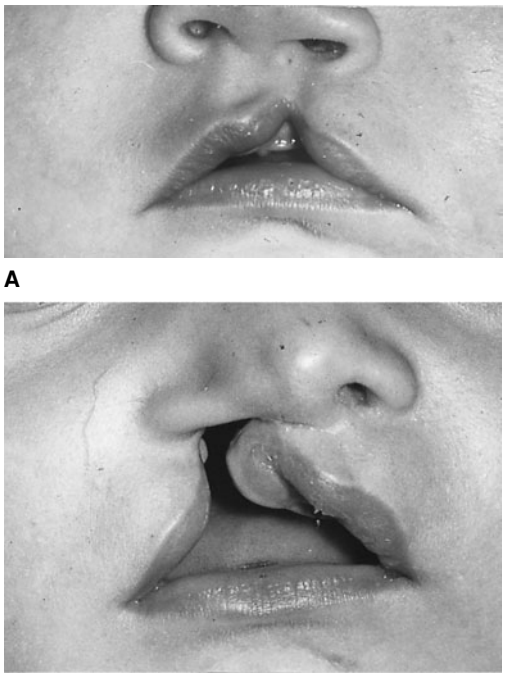


Fig. 20–4. *Facial clefts and associated anomalies*. (A,B) Unilateral cleft upper lip showing various degrees of completeness. [From W Hoppe, Arch Kinderheilkd 171(Suppl 52):1, 1965.]

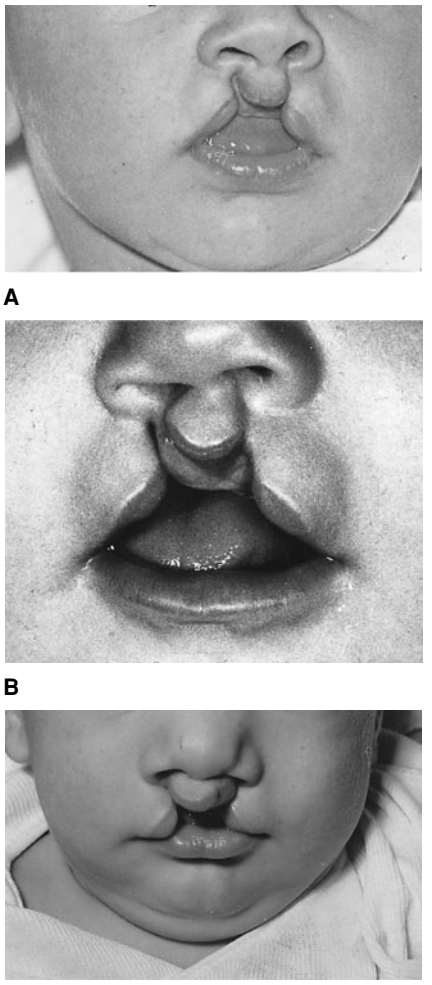


Fig. 20–5. *Facial clefts and associated anomalies*. (A–C). Bilateral cleft lip showing varying degrees of completeness. (From T Skoog, Plast Reconstr Surg 35:34, 1965.)

76,80) and Maori (12). Data from African blacks are cited by Cervenka (10). In the Philippines, the birth prevalence was 1.94 for cleft lip with or without cleft palate (51). Data from Turkey is also summarized (7).

In general, the more severe the defect, the greater the proportion of males affected [i.e., CL(P) (2M:1F) is greater than CL (1.5M:1F) and bilateral CL is greater than unilateral CL (26,58)]. However, not all races have similar sex predilections; for example, most Japanese studies have shown that females with CL outnumbered males with CL. However, males with CL(P) outnumbered females, as in whites.

Isolated CL may be unilateral (80%) or bilateral (20%) (83) (Figs. 20–4 to 20–6). However, when only cleft lip is involved, bilateral cases amount to approximately 10%; when cleft lip is combined with cleft palate, approximately 25% are bilateral (10a,18,44,45,78). When unilateral, the cleft is more common on the left side (approximately 70%), although no more extensive. Approximately 85% of cases of bilateral CL and 70% of unilateral CL are associated with cleft palate. Cleft lip is not always complete (i.e., extending into the nostril). In approximately 10%–30%, the cleft is associated with skin bridges (Simonart's bands) (67,73). Minimal involvement is manifested by linear lip indentation(s) (9,29,39) or, very rarely, lateral fistulas of the upper lip (8,30,63,77) (Fig. 20–7). Both are located at the position of fusion of the median nasal and maxillary prominences. Bilateral sinuses have been documented (61).

Isolated cleft palate. Cleft palate (CP) appears to be an entity separate from CL(P) (Fig. 20–8). Sibs of patients with CL(P) have an increased frequency of the same anomaly but not of isolated CP and vice versa (26).

The frequency of CP among whites and blacks would appear to be approximately 0.4/1000 births and is more common in females (64). Cleft palate among the Maori of New Zealand is approximately 1.9/1000 births (12). When cases of CP are broken down according to extent, a 2:1 female predilection for complete clefts of the hard and soft palate is clearly indicated, but the ratio approaches 1:1 for clefts of the soft palate only (47,55). This is consistent with the observation that the soft palate forms by merging, after closure of the hard palate.

The incidence of cleft uvula (1/80 white individuals) is much higher than that for cleft palate (1/2500 births) (16,46,69,79). Clefting of the uvula varies in degree but some clefting is present in 2%–4% (71). Total cleft of the uvula is approximately 1 in 300 (84). Like cleft of the soft palate, cleft uvula approaches a 1:1 sex ratio (14,41,47). The frequency of cleft uvula among various American Indian and Inuit groups is high, ranging from 1/9 to 1/14 individuals (11,28,34,41,68) and in Asians in 1/10 to 1/25 (41). In blacks, it is comparatively rare (1/250) (41,62,66,68).

Submucous palatal cleft refers to the condition in which there is imperfect muscle union across the velum but an intact mucosal surface (60) (Fig. 20–9A). An incidence of approximately 1/1200 to 1/2000 births has been reported (3,74,82). Over 50% occur in males, an unusual finding

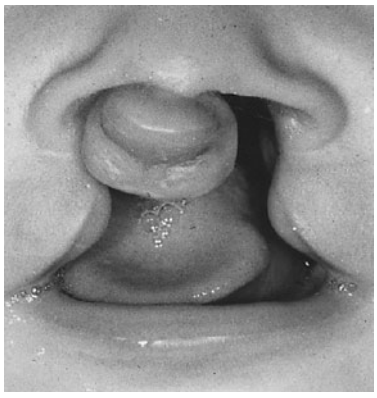
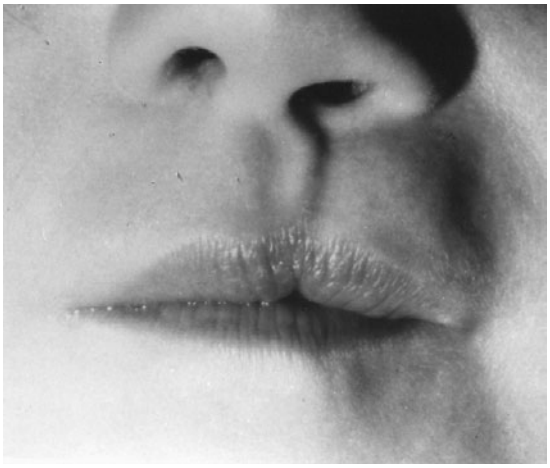
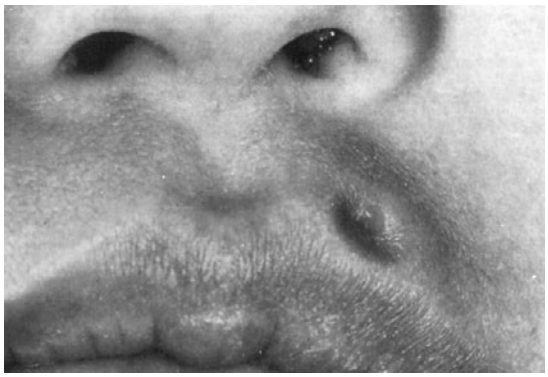


Fig. 20–6. *Facial clefts and associated anomalies*. Bilateral cleft with "floating" primary palate. (Courtesy of W Hoppe, Lübeck, Germany.)



A

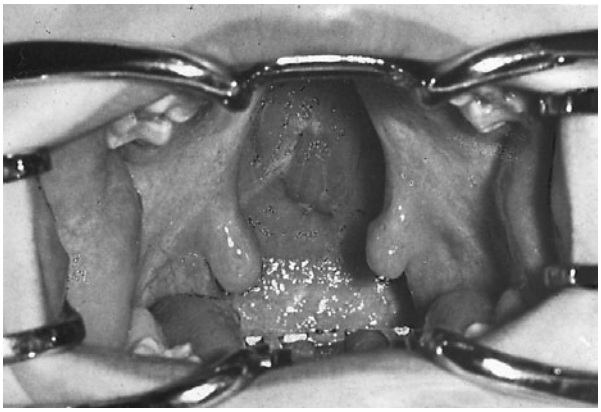


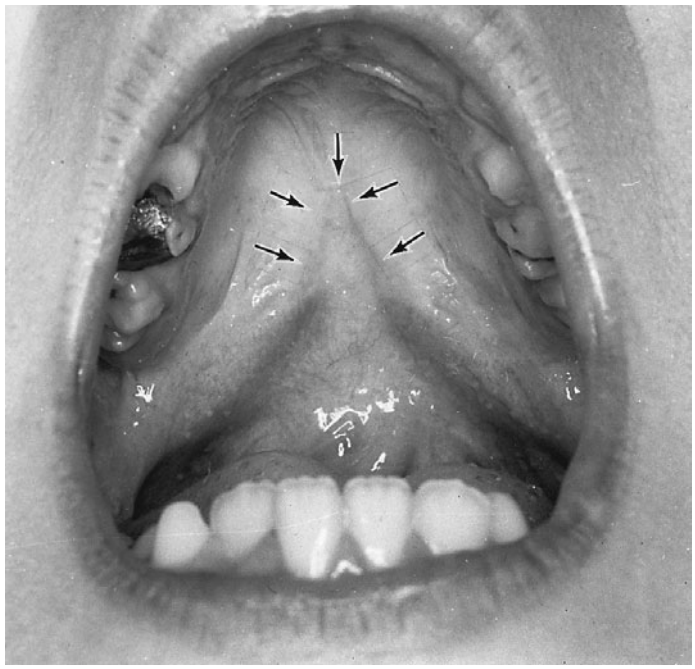
B

Fig. 20–7. *Facial clefts and associated anomalies*. (A) Minimal cleft lip showing groove extending from vermilion to nostrils representing defect in orbicularis oris. (B) Lateral fistula of upper lip. (A from FR Heckler et al, Cleft Palate J 16:240, 1979.)

since cleft palate has a distinct female predilection. The palate is short in approximately 60% with poor mobility demonstrated in 20%. This makes velopharyngeal closure incompetent, resulting in hypernasal speech. There is frequently a notch in the bone at the posterior edge of the hard palate and bifid uvula is found in most but not all patients (40). Conversely, bifid uvula is usually accompanied by submucous cleft palate (71) and the former has been considered a marker for that condition. Rarely, the hard palate is entirely perforated (24,38,49) (Fig. 20–9B). Kono et al (38) estimated that approximately 13% of patients with clefts of the primary palate have submucous cleft palate. Rarely, the soft palate is asymmetrically

Fig. 20–8. *Facial clefts and associated anomalies*. Complete isolated cleft palate. [From W Hoppe, Arch Kinderheilkd 171(Suppl 52):1, 1965.]





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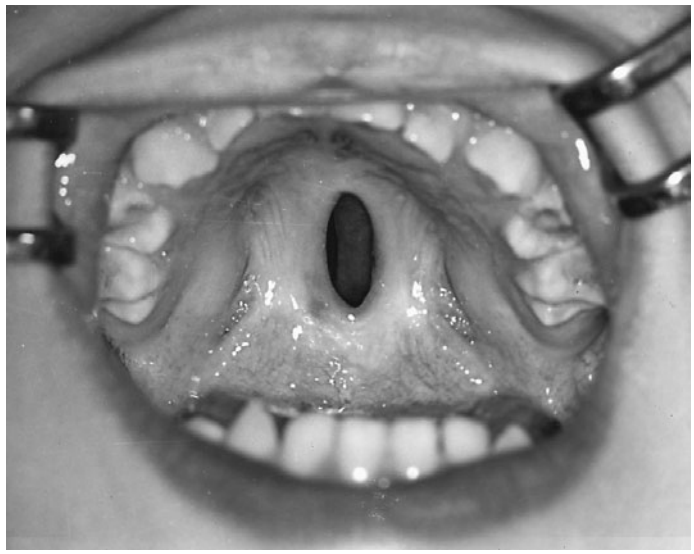

B

Fig. 20–9. *Facial clefts and associated anomalies*. (A) Submucous palatal cleft with arrows showing V-shaped groove at posterior edge of hard palate. (B) Perforated soft palate representing extreme form of submucous cleft palate. (A courtesy of HW Smith, New Haven, Connecticut. B from M Fára, Plast Reconstr Surg 48:44, 1971.)

cleft (23,32,43,48,81). Some may represent oral manifestations of oblique clefts. The soft palate may be absent in *Nager syndrome*.

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Genetics. During the early decades of the twentieth century, it became evident that recurrence risks for clefting did not correspond to any simple mendelian pattern of inheritance. Between 50% and 75% of cases are sporadic (48). This was bolstered by twin studies that indicated the relative roles of genetic and nongenetic influences in cleft production. We have tabulated twin studies in 1996 (Table 20–1). In twins with CL(P), concordance is far greater for monozygotic twins (40%) than for dizygotic twins (4.2%). In twins with isolated CP, the difference in concordance is not quite as great between the groups (MZ—35%; DZ—7.8%), suggesting a stronger genetic basis for CL(P) than for isolated CP. Heritability has been estimated at approximately 0.74 (82). Twin studies are, at best, of limited value; the concordance of 3.8% for dizygotic twins (greater than that for sibs) implies that maternal factors are operative. Microforms such as submucous palatal cleft could alter these data markedly. An unusual report is that of clefts in three of quintuplets (84). Mirror image clefts have been reported in monozygotic twins (36,38). Conjoined twins also have exhibited this phenomenon, but this example is the exception, all others having been discordant (46).

In the 1970s–1980s, enthusiasm waxed regarding multifactorial inheritance of CL(P) and CP. This view was supported by Woolf et al (81), Carter (10), Mendell et al (50), and Tolarová (75,76,78). Fraser (23–28), however, although generally supporting the multifactorial-threshold inheritance of CL(P), expressed skepticism that CP obeyed the rules and suggested that environmental factors played a major role. Bixler and coworkers (5), in a reexamination of the Danish data of Fogh-Andersen, noted that there was little support for the sex-modified threshold polygenic model for CL(P), but also found little evidence for major gene effects. They agreed that CP did not fit the polygenic threshold concept and suggested genetic heterogeneity (68). For CP, they proposed three categories: syndromal, autosomal dominant, and environmental etiologies. Czeizel (16), in his analysis of Hungarian patients, found CL(P) in agreement with polygenic multifactorial inheritance but did not find similar support for CP. Melnick et al (48), Shields et al (67), and Marazita et al (43), reassessing the Danish data, indicated that CL(P) and isolated CP data were not compatible with the multifactorial threshold model, and posed an alternate hypothesis that CL(P) and CP result from the effects of a single major gene (most likely recessive) with reduced penetrance. The same was true for studies of CL(P) families in England (44), Shanghai, China (45,49), and Madras, India (56). Chung et al (14), employing complex segregation analysis, could not distinguish between major gene versus multifactorial inheritance on Hawaiian data, but later Chung et al (15) suggested that a major gene with low penetrance fits the Danish material but that a multifactorial model best fit the Japanese data. Cephalometric evidence has been used to support the major gene hypothesis (80). Extremely well-balanced discussions of the problems are those of Melnick (47), Wyszynski et al (82), and Mitchell and Risch (52).

Table 20–1. Concordance in facial clefts—twin studies (1922–1996)

	Monozygotic twins		Dizygotic twins	
	CL(P), $n = 105$	CP, $n = 40$	CL(P), $n = 236$	CP, $n = 89$
Concordance (n)	42.0	14.0	10.0	7.0
Percent	40.0	35.0	4.2	7.8

Based on Gorlin et al (29) together with cases of Blake and Wreakes (7), Christensen and Fogh-Andersen (12), Czeizel (16), Davies and Thompson (18), Keusch et al (37), Nordström et al (57), Schweckendiek (64), Shields et al (67), Tolarová (personal communication, 1988), and other authors.

Allelic association studies (*TGFα, BCL3, RARA, TGFβ*3, and *MSX1*) abound (63a). Ardinger et al (3) and others (11,21,32,33,62,66) found association with transforming growth factor-alpha (*TGFα*), but linkage has not been found (40,63a,78a,79). *TGFα* maps to 2p13. It is a potent epithelial mitogen and plays a role in palatal development, modifying severity of the cleft (22,58). However, other studies have failed to demonstrate the association (40,65,73). A possible association has been described for a joint effect of maternal smoking and carrying the *TGFα Tag IC2* allele and the risk for cleft palate (33,65). Other candidate genes have been investigated such as retinoic acid receptor alpha and *MSX1* (11,78a,79). Epithelial growth factor receptor has been shown to be intimately involved in palate closure (51). Beiraghi et al (3a) noted a possible major gene on 4q.

Linkage studies date from the work of Eiberg et al (19) who found susceptibility to CL(P) and blood clotting factor XIIIa on chromosome 6. The same chromosome was suggested earlier (70) and later (55) as the site of a major gene. Carinci et al (9) and Scapoli et al (63) also found linkage at a 6p23 marker (D6S89). Davies et al (17) studied deletions in three unrelated patients and concluded that a major gene was located at 6p24.3. Stein et al (72) found significant linkage to the proto-oncogene, *BCL3*, at 19q13. This was supported by Amos et al (1). However, linkage was not found by Wyszynski et al (82,83), but association was noted. An MSX1 mutation has been found in a family with various combinations of cleft lip, cleft palate, and tooth agenesis (4).

Romitti et al (60) found that mothers who smoke *and* who have allelic variants of *TGFβ3* or *MSX1* have increased risk for having children with cleft palate. Mothers who drink *and* have allelic variants of *MSX1* have elevated risks for infants with cleft lip/palate. At this writing, *TGFβ3* and *MSX1* appear to be the most consistent and important (40).

Kurnit et al (39) revolutionized our thinking about the role that chance may play in the occurrence of malformations. Their model may be applicable to malformations that are presently thought to have "low risk multifactorial recurrence." They suggested that variability may be inherent in the role that chance itself plays in the process of development. Based on computer simulations, a stochastic single gene model generated a continuous liability curve resembling that obtained from a multifactorial threshold model. Outcomes were quite variable despite using identical genotypes and environments. Thus, segregation of a given malformation may be explained by a single defective gene that predisposes to, but does not necessarily result in, the malformation. Their model was successfully applied to VSD. Whether the model can be used for other malformations, such as clefting, remains to be determined.

Cleft lip and/or palate is seen in families with autosomal dominant holoprosencephaly, but a relationship with *Sonic Hedgehog* has been denied (57c).

It certainly appears that clefting is heterogeneous, the variation in liability probably being determined by a number of major genes, minor genes, environmental insults, and a developmental threshold (28). Within recent years, recurrence risk calculations have purposely excluded syndromal clefting, and lethal disorders such as trisomy 13, from the data. Recurrence risk is thereby related to both the genome and environmental exposure. We would agree that both CL(P) and CP do not fit the original multifactorial model very well. Further, CP is probably more heterogeneous than CL(P) (13).

Since one cannot at this time distinguish clearly among the mixed model, a major gene with reduced penetrance, and an admixture of sporadic cases in most instances, it seems foolish to argue heatedly about one or the other (26). Until more evidence has been presented, we can see little error being made using empiric risk data or, in fact, even mathematical model data such as that of Spence et al (69) or Bonaiti-Pellié, (8). Whereas one may fault the models, the figures derived are very close to the empiric risks found (20).

It should be pointed out that a few families appear to have X-linked inheritance of isolated cleft palate with or without ankyloglossia (4,6,30,31,41,53,59,61). Female heterozygotes have variable expression. However, there is clearly genetic heterogeneity. The German and Icelandic families map to Xq21.3–q22 (34,42) whereas a native British Columbian kindred maps to a gene at Xq13–q21.31 (30,71). One family apparently had autosomal dominant inheritance of cleft palate (35,59) and a few cleft lip-palate (74). Autosomal dominant inheritance of velopharyngeal incompetence has been observed in a large kindred by Andres et al (2), but we wonder whether that family had velocardiofacial syndrome.

Moosey et al (54) suggested that by finding the molecular aberrations at the parental TGFα genotype and factoring in parental craniofacial measurements, they were able to predict CP in 76% and CL(P) in 94% of the cases.

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Recurrence risks. Data regarding recurrence risks of CL(P) and CP for an affected parent or in case of normal parents who have an affected child have been ascertained in numerous studies. In general, the data do not differ drastically from the Falconer estimation, that is, the recurrence risk being the square root of the frequency of the disorder in the population. In the case of CL(P), $\sqrt{1/900} = 1/30 = 3.3\%$ and for isolated CP $\sqrt{1/2500} = 1/50 = 2\%$. Of course, many factors can modify the data: similarly affected sib(s) or parent, racial group, sex of proband, severity of cleft, etc. These have been dealt with by an inordinate number of investigators (1–3,5–13,16–18,20,21,23–25). Tenconi et al (22) have also devised a theoretical recurrence risk.

Table 20–2. Comparative empiric risks for cleft lip–palate and cleft palate

	CL ± P		CP	
	Proband (%)		Proband (%)	
Relative	Male	Female	Male	Female
Brother	6.7	6.8	1.8	2.8
Sister	2.8	4.4	3.7	1.7
Son	6.7	2.4	11.5	6.0
Daughter	4.0	8.7	5.6	17.2

Modified from M Melnick et al, Clinical Dysmorphology of Oral-Facial Structures, John Wright, Boston, 1982.

For CL(P) and CP, if the proband has no other affected first or second degree relatives, the empiric risk is 3%–5%. However, for CL(P) if the proband has other affected first degree relatives, the risk to sibs or offspring is 10%–20% (23,25, Melnick, unpublished data, 1987). In the rare case of both parents being affected, empiric risk data range from 25% to 50% (23). For these and other situations, see Tolarová (unpublished data, 1987), Melnick et al (15), and Woolf (25) (Tables 20–2 and 20–3). Regarding sex and severity, Tolarová (24) calculated the following risk figures (%) for sibs of those with CL±P: unilateral male—2.9 ± 0.5; unilateral female—4.6 ± 0.9; bilateral male—6.0 ± 1.7; bilateral female—6.8 ± 2.4. Similar data may be found in Woolf (25). Naturally, the usual caveat applies; one must exclude cleft syndromes. The number of cleft syndromes has grown from about 75 in our second edition to over 350 in this fourth edition of our text. They have been reviewed by a number of authors (4,12,14,19).

References (Recurrence risks)

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Table 20–3. Recurrence risk for clefts in sibs of propositi

Affected parent	CL(P) %	CP %
Mother affected		
Affected sibs		
0	2.7	2.3
1	9.9	11.2
2	18.3	21.1
Father affected		
Affected sibs		
0	2.3	5.0
1	9.3	14.4
2	17.6	23.9
Both parents affected		
Affected sibs		
0	24.0	45.0
1	31.7	51.6
2	37.6	54.5

Source: M Tolarová, Ph.D. Thesis, Charles University, Prague, Czechoslovakia, 1984.

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Associated anomalies. Many investigators have tabulated the frequency and types of anomalies that accompany facial clefts (3,5,10a,11,13,14,21). For a thorough critical review of the earlier data, see Shprintzen et al (21). Data secured at birth differ from those on patients who have undergone surgery, since those with more serious defects often succumb prior to surgery. Recent studies have suggested that as high as 44%–64% of cleft patients have associated anomalies (18,21). Over 350 cleft syndromes have been reported by 2000 (4). When the data are broken down according to subtype, there is general agreement that isolated CP (13%–50%) is far more often associated with other congenital defects than either isolated CL (7%–13%) or CL(P) (2%–11%) (8,9). However, Milerad et al (15) found that patients with CL(P) (28%) had more associated anomalies than those with CP (22%). Growth retardation is more marked in those with cleft lip/palate than in controls (10,10a).

More malformations have been found in infants with bilateral CL(P) than with unilateral CL (15). The more malformations a child has, the lighter the birth weight. Clefts are more frequently found in spontaneously aborted and in stillborn infants, reflecting, in part, chromosomal aneuploidy (13). Associated anomalies are more frequently noted in patients without a family history of clefts than in patients with affected relatives. Conversely, the recurrence risk is lower in sibs of patients with, rather than without, associated malformations. Congenital velopharyngeal incompetence has been noted to be frequently associated with cervical spine anomalies (9). Congenital heart defects have been found in 3%–7% of cleft cases (21,25,26). Milerad et al (15) noted heart anomalies in 24% of their series. Tetralogy of Fallot is especially frequent. Some of these patients surely have velocardiofacial syndrome (26).

Strunz et al (23) noted an increased rate of urinary tract anomalies, especially in association with CP. Biewald et al (3) found approximately 40% of patients with facial clefts to have minor anomalies of the urinary tract. Azmy et al (1), examining 114 patients with esophageal atresia, found 5% with CL(P). Sandham (20) and Osborne et al (16), studying cervical vertebral anomalies in cleft lip/palate patients, found 15%–20% to have either posterior arch deficiency or fusion anomalies versus 7% in the normal population. Those with cleft palate had an even higher frequency of cervical anomalies (45%). Richman et al (17) described olfaction defects in approximately 50% of males with cleft palate. Mean IQ scores tend to be lower in those with clefts (22).

Dronemaraju and Bixler (6,7) noted a greater fetal mortality in sibs of probands with CL(P) than in those with isolated CL, but this has been denied by Bear (2) and Tolarová (24).

Rudman et al (19) found that children with isolated cleft lip-palate have short stature four times and growth hormone deficiency 40 times more often than those without cleft lip-palate. Short stature was also found by Shprintzen et al (21).

References (Associated anomalies)

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Skull, facial bones, and dentition. Postnatal studies of patients with facial clefts have shown that growth of the face proceeds in harmony with the deviation initially induced by the cleft. However, overall head size is slightly smaller and the length of the cranial base slightly shorter than normal in individuals with CP. Facial growth and development in those with clefts has been extensively reviewed (5,13,15).

The anomalous growth associated with CL(P) is generally considered to be limited to the middle part of the face. Bony interorbital distance is slightly increased. Approximately one-third of those with CP exhibit an anteroposterior deficiency of the middle third of the face, and over 50% with bilateral clefts manifest this alteration (1–3,8).

Nasopharyngeal widths are greater than normal in patients with clefts. The mandible is shorter in length with a shorter ramus, thus reducing posterior facial height. The mandibular plane angle is increased and the gonial angle more obtuse.

The teeth in the cleft area, most commonly the maxillary lateral incisors, are commonly missing or supernumerary and may be natal or neonatal. In general, the more severe the cleft, the more teeth are missing or eruption delayed. In patients with clefts of the lip and alveolus, a median fissural tooth is found in almost 50% in the primary dentition and in approximately 25% in the secondary dentition (6,11). Corresponding figures for a distal fissural tooth are 75% and 45%, in the primary and secondary dentitions, respectively. Agenesis of teeth in the cleft area is found in 15% in the primary and 45% in the secondary dentition, and both fissural teeth are present in approximately 35% in the primary and 15% in the secondary dentition. Hypodontia is not uncommon outside the area of clefting in children with CL(P) (10). Over 40% have missing teeth, more often in the upper jaw. Even in isolated CP, which does not involve a tooth-bearing area, hypodontia is present in approximately 35%. The teeth most commonly missing are premolars and maxillary lateral incisors. The size of the permanent teeth tends to be smaller and there is often metric asymmetry (7,11,12,17). Wisdom teeth tend to be missing (14). Natal and neonatal teeth are found in 10% of those with bilateral cleft lip/palate and in 2% of those with unilateral cleft lip/palate (4). Taurodontism may be increased (9).

An inordinate number of cephalometric studies have been carried out on the parents of children with clefts with no conclusive results. These have been reviewed by Ward et al (16). Within an affected family, Ward et al (16) described how, with discriminant function analysis, they were able to find some correlation with increased midfacial and nasal cavity widths, reduced facial height and flat facial profile.

References (Skull, facial bones, and dentition)

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Prenatal diagnosis. Ultrasonography has been used to detect clefting prenatally (1–8). The more severe the cleft, the more likely diagnosis will be made. With improvement of real-time ultrasound equipment on adequate examination of facial structures may be done as early as 16 weeks when formation of the palate and development of soft tissues of the face are complete. Doppler ultrasonography allows observation of fluid flow of amniotic fluid through the mouth to reveal cleft palate. Most people would not elect to have prenatal counseling for cleft lip and palate.

References (Prenatal diagnosis)

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Robin sequence

The well-recognized combination of micrognathia, cleft palate, and glossoptosis, known as Robin sequence, was named after Pierre Robin (44) whose first report appeared in 1923. However, the condition was described earlier by St. Hilaire in 1822, Fairbairn (19) in 1846, and Shukowsky (56) in 1911. Historic development is thoroughly discussed by Grimm et al (23) and Randall et al (39).

Birth prevalence estimates have varied from 1/2000 (37) to 1/30,000; Bush and Williams (8) suggested 1/8500. Definitions of Robin sequence are variable. Our own definition is based on the triad of micrognathia, cleft palate, and glossoptosis. However, others have been advocated. For example, one definition permits the presence of submucous cleft palate (43). Another consists of micrognathia ± cleft palate ± glossoptosis. Such a view allows cleft palate or isolated micrognathia to qualify as Robin sequence as well as the binary combination of cleft palate and micrognathia. Williams et al (64) have cautioned against describing every infant with cleft palate and micrognathia as an example of Robin sequence, indicating that respiratory difficulty is an essential component of the condition. It is obvious that differences in definition result in differences in estimated birth prevalence and differences in the list of syndromes said to be associated with Robin sequence. Extensive discussions of this problem are those of Shprintzen (55) and Cohen (16).

An animal model based on intrauterine mandibular constraint resulting in failure of the tongue to descend and resultant cleft plate has been described by a number of investigators (12,37). Explaining Robin sequence on a deformational basis has been supported by several authors (13,30,37). Others have considered absent or delayed lowering of the embryonic tongue as the primary pathogenetic event. Still others have suggested that growth disturbance affecting both the maxilla and mandible can result directly in cleft palate and micrognathia. Cohen, in 1979 (14) and in 1999 (16), indicated that a unitary etiologic and pathogenetic hypothesis was unlikely, noting that clinical evidence was most consistent with etiologic and pathogenetic heterogeneity and phenotypic variability. These include malformational and deformational causes and connective tissue dysplasia.

Table 20–4 lists some representative syndromes in which Robin sequence may be a feature with variable frequency. In Stickler syndrome (50,62), Robin sequence may occur in some patients. Since abnormalities of bones and joints are characteristic, the major pleiotropic effect appears to be on connective tissue. Thus, in this condition, Robin sequence may result from intrinsic mandibular hypoplasia and failure of connective tissue penetration across the palate.

Another condition that may have Robin sequence is dup(11q) syndrome. With the hypoplastic growth that accompanies most chromosomal syndromes, there may not be significant mandibular catch-up growth in infants with dup(11q) syndrome who survive. Therefore, to include such patients in a mandibular growth study of Robin sequence would be to study "fruit" since "oranges" are being confused with "apples."

Some instances of Robin sequence have been associated with oligohydramnios. It is thought that reduced amnionic fluid results in compression of the chin against the sternum, restricting mandibular growth and impacting the tongue between the palatal shelves. Because micrognathia is based on intrauterine molding, mandibular catch-up growth is expected after birth when intrauterine deforming forces are no longer acting. However, Vegter et al (62) denied catch-up growth. Poswillo (37) produced a phenocopy of Robin sequence in rats by puncturing the amniotic sac prior to palatal closure. Some experimental animals also had anomalies of the limbs, ranging from clubfoot to ring constrictions and intrauterine amputations. Such limb abnormalities have also been observed with Robin sequence in humans.

The association of amputations and/or limb reduction defects in some human cases suggests that Robin sequence may occur on a disruptive basis. For example, an amnionic tear may cause oligohydramnios that can result in severe compressive disruption, causing limb reduction defects, and bands, causing amputations. Such primary disruption with oligohydramnios can also cause secondary deformation such as mandibular constraint, leading to Robin sequence (30a).

Finally, Robin sequence has been associated with congenital hypotonia (51). If neurogenic hypotonia occurred prior to complete closure of the palate, it is conceivable that Robin sequence might result from lack of mandibular exercise. Different etiologic and pathogenetic possibilities are summarized diagramatically in Figure 20–10. Further evidence for etiologic and pathogenetic heterogeneity was provided by Carey et al (10).

Hanson and Smith (24) found Robin sequence in specific syndromes in 25% of their patients. Another 35% had multiple anomalies, but no specific syndrome was recognized. The remaining 40% were instances of isolated Robin sequence. In the study of Williams et al (64), only 26% of children with Robin sequence had other anomalies including both recognized and unrecognized syndromes. Caouette-Laberge et al (9) found 57 of 125 patients to have an additional finding. Among 64 patients analyzed by Sheffield et al (52), 16 died and 12 of these were thought to have a syndrome. Of those that lived, 26% had an underlying syndrome, one-half of these having Stickler syndrome. There was no recurrence in sibs of those with nonsyndromal Robin sequence. Conditions associated with Robin sequence listed in Table 20–4 are derived primarily from Cohen (13–15), Hanson and Smith (24), Carey et al (10), and Shprintzen (54). The reader is referred to several articles on some of these conditions (3,22,26,35,45,53,59,60). With hindsight, it is fascinating to note that of the six patients with Robin sequence and multiple anomalies reported by Holthusen (27) in 1972, two had spondyloepiphyseal dysplasia congenita, two had Catel-Manzke syndrome, and one had unusual facies/femoral dysgenesis syndromes, and one had Robin/amelia association. It should be recognized that the list of conditions associated with Robin sequence found in Table 20–4, although representative, is not complete. Robin sequence may be found with other conditions. Since there is further ill-defined heterogeneity, the reader may expect to find Robin sequence with various other anomalies, especially involving the eye, ear, heart, and limbs.

Table 20–4. Some representative conditions associated with Robin sequence

Condition	References
Monogenic	
Abruzzo-Erickson syndrome	1
Beckwith-Wiedemann syndrome	13,14,15
Campomelic syndrome	13,14,15
Carey neuromuscular syndrome	10
Carey-Fineman-Ziter	49
Catel-Manzke syndrome	27,60
Cerebrocostomandibular syndrome	13,14,15
Chitayat syndrome	11
Congenital myotonic dystrophy	13,14,15
Diastrophic dysplasia	13,14,15
Distal arthrogryposis-Robin sequence	50
Donlan syndrome	10
Froster contracture-torticollis syndrome	20
Larsen syndrome	55
Mandibulofacial dysostosis	55
Miller-Dieker syndrome	55
Nager acrofacial dysostosis	10
Otopalatodigital syndrome II	3
PARC syndrome	63
Persistent left superior vena cava syndrome	22
Popliteal pterygium syndrome	55
Postaxial acrofacial dysostosis	10
Radiohumeral synostosis syndrome	24
Richieri-Costa syndrome	42
Robin-oligodactyly syndrome	46
Sanderson-Fraser syndrome	47
Spondyloepiphyseal dysplasia congenita	13,14,15,55
Stickler syndrome	55,61
Stoll syndrome	59
Toriello-Carey syndrome	61
Velocardiofacial syndrome	53–55
Chromosomal	
del(4q) syndrome	10,32
del(6q) syndrome	55
dup(11q) syndrome	13,14,15
Teratogenetically induced	
Fetal alcohol syndrome	24,55
Fetal hydantoin syndrome	24
Fetal trimethadione syndrome	24
Disruption	
Amniotic band disruption	26,55
Unknown genesis	
Bruce-Winship syndrome	7
CHARGE association	35
Femoral dysgenesis-unusual facies syndrome	13,14,15,55
Martsolf syndrome	15
Median cleft of lower lip, cleft palate, hypodontia	40
Moebius sequence	10
Robin/amelia association	13,14,15,27
Sickle-shaped scapulae and club feet	6

From MM Cohen Jr, The Child with Multiple Birth Defects, Oxford University Press, New York, 1997.

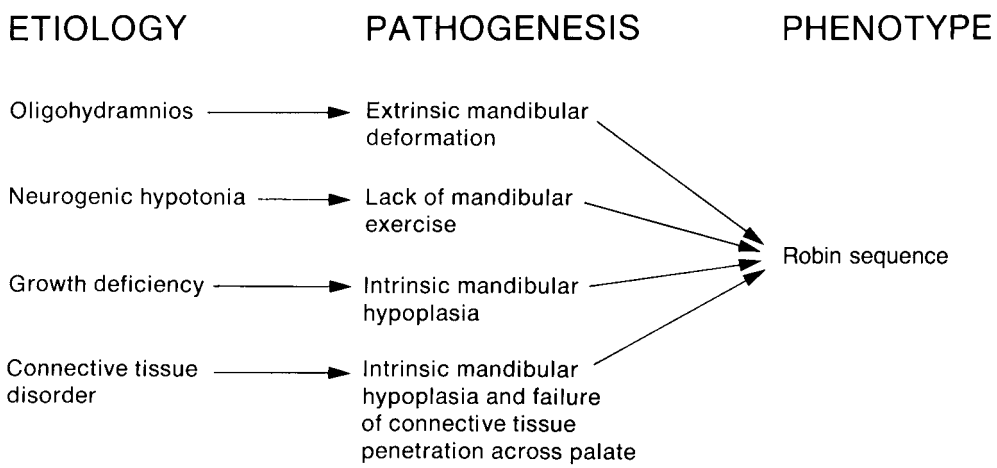


Fig. 20–10. *Robin sequence*. Etiologic heterogeneity suggests pathogenetic heterogeneity in Robin sequence. The following pathogenetic possibilities should be considered. (I) Oligohydramnios results in decreased amnionic fluid, compressing the chin against the sternum and thus restricting mandibular growth. (II) If hypotonia restricts mouth opening during early fetal life prior to complete palatal closure, Robin sequence might result from lack of mandibular exercise. (III) Growth deficiency, as observed in chromosomal syndromes such as dup(11q) syndrome, may produce Robin sequence by intrinsic mandibular hypoplasia. (IV) In a connective tissue disorder such as Stickler syndrome, Robin sequence may result from intrinsic hypoplasia and failure of connective tissue penetration across the palate. (From MM Cohen Jr, The Child with Multiple Birth Defects, Raven Press, New York, 1982.)

Genetic factors are clearly implicated in many examples of Robin sequence (11,22,33,45). The most common genetic syndrome associated with Robin sequence is *Stickler syndrome* (18a). A personal account of just such an example is highly recommended reading (36). Active detection of myopia should be sought because blindness, resulting from retinal detachment, can probably be prevented in this syndrome. The second most common is *velocardiofacial syndrome*.

Clinical manifestations. The facies is striking at birth. The mandible is small and symmetrically receded (Figs. 20–11 and 20–12). Commonly the base of the nose is flattened. The palatal cleft may be U-shaped (Fig. 20–13) (24). Rintala et al (43) and Amaratunga (2) indicated that both U- and V-shaped clefts (Fig. 20–14) were found in Robin sequence and in isolated cleft palate with equal frequency. However, on the average, the width of the cleft was greater in Robin sequence than in isolated cleft palate. We have not been impressed by the so-called U-shaped cleft being a constant feature.

Difficulty in the inspiratory phase of respiration is apparent, with periodic cyanotic attacks, labored breathing, and recession of the sternum and ribs. This becomes especially apparent when the child is in the supine position. Respiratory difficulty is usually evident at birth, although it may not be severe for the first week. Only rarely is its initiation delayed until the first month (46).

Although there is no complete agreement concerning the exact mechanism by which respiratory and feeding difficulties are produced, the classic explanation suggests that the micrognathia makes for little support of the tongue musculature (51). This allows the tongue to fall downward and backward (glossoptosis) into the lower postpharyngeal space, obstructing the epiglottis. In this position, the tongue permits egress of air but prevents inhalation, acting much as a ball valve, causing period cyanosis and sternal retraction. Feeding problems are thought to be because of inadequate control of the tongue. Nursing, even when performed in a favorable position, is an ordeal (17).

Routledge (46), however, suggested that the respiratory difficulty might be due, in large part, to impaction of the tongue tip in the palatal

Fig. 20–11. *Robin sequence*. Characteristic facial features. (From M Gewitz et al, J Med Genet 15:162, 1978.)

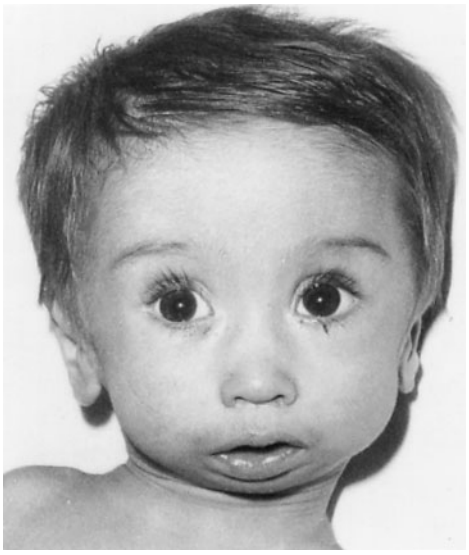
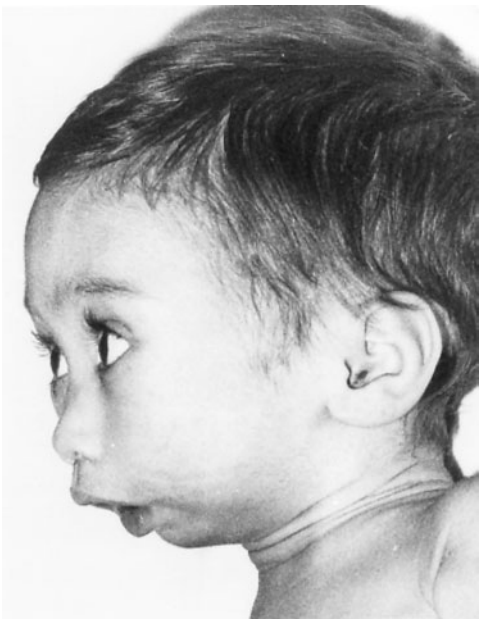


Fig. 20–12. *Robin sequence*. Severe micrognathia. (From M Gewitz et al, J Med Genet 15:162, 1978.)



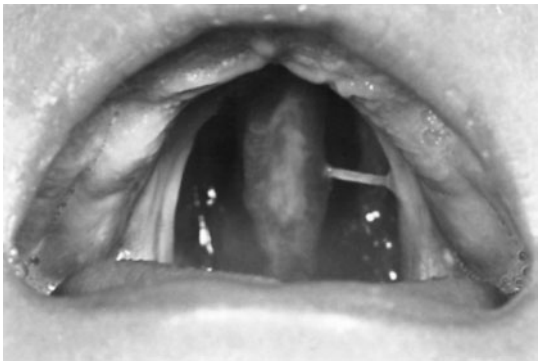


Fig. 20–13. *Robin sequence*. U-shaped cleft palate.

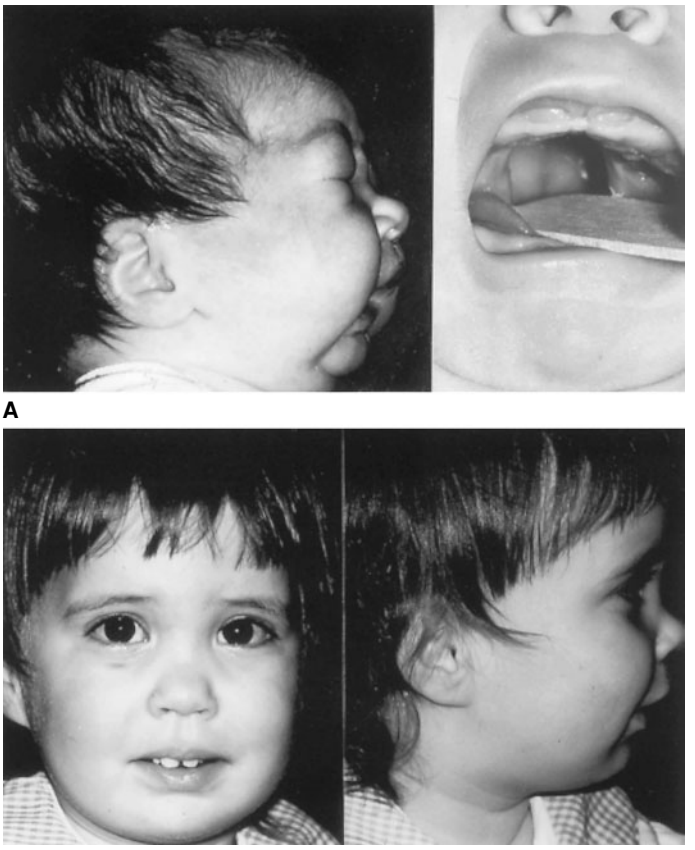


Fig. 20–15. *Robin sequence*. (A) Patient with Robin sequence showing micrognathia and U-shaped cleft palate. (B) Same patient showing mandibular catch-up growth. (From MM Cohen Jr, The Child with Multiple Birth Defects, Raven Press, New York, 1982.)

cleft, from which it is not easily disengaged. Violent muscular contractions resulting from efforts to free it cause the tongue to bulge into the nasopharynx resulting in asphyxia. Routledge realized that his theory did not explain those cases in which surgical repair of the palate failed to correct the respiratory difficulty or those cases associated with ankyloglossia, which does not permit upward movement of the tongue tip.

It has also been shown, most notably by Pruzansky and his co-workers (5,38,39) and Stellmach and Schettler (58), that mandibular catch-up growth often results in a normal profile by 4–6 years of age (Figs. 20–15 and 20–16). This was not substantiated by Laitinen and Ranta (29). Pruzansky (38) described the mandible as having a foreshortened body with a characteristic ratio of the ramus to mandibular body length.

The tongue has been stated by some investigators to be small, by others, normal, and by still others, large. Depending on particular syndromic diagnoses, all may be correct. For example, the tongue may be small in Moebius sequence but large in Beckwith-Wiedemann syndrome. It has also been suggested that there may be disproportionate growth of the tongue (46). Pruzansky and Richmond (38) concluded from cephalometric studies that micrognathia, *sui generis*, is not sufficient to produce respiratory embarrassment unless the tongue is normal in size or enlarged. Ankyloglossia is a commonly associated complication. For additional discussion of cephalometric findings, see Ranta et al (41).

Growth deficiency, which sometimes accompanies Robin sequence, may be related to severity of airflow obstruction or to the overall syndromic condition if it is caused by a chromosomal abnormality or teratogenic agent. Heaf et al (25) found that failure to thrive was significantly correlated with severity of airflow obstruction. Failure to thrive was reversed in infants managed with a nasopharyngeal airway. In a large series of patients reported by Williams et al (64), 26% died within the first 3 months. Of those who survived, 13% showed delayed language development. Other authors have indicated that as many as 25% exhibit major mental deficiency and various anomalies may be associated such as microcephaly and hydrocephaly (9).

Congenital murmurs and/or heart defects have been observed in 15%–25% of patients who die in early infancy (52). Necropsy has revealed PDA, patent foramen ovale, ASD, VSD, ventricular hypertrophy, cor triloculare, coarctation of the aorta, biventricular aorta, and dextrocardia (17,46,57). Congestive cardiac failure with signs of cor pulmonale

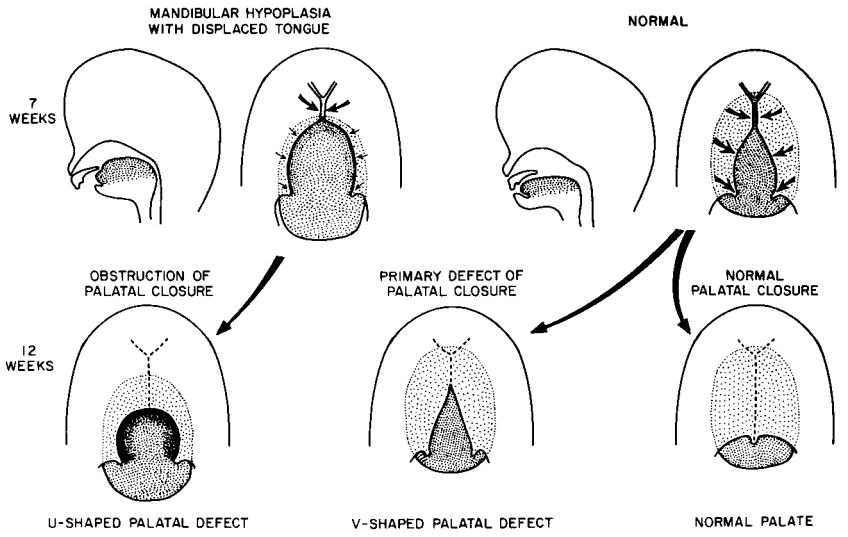


Fig. 20–14. *Robin sequence*. At left, small mandible results in posteriorly placed tongue partially interposed between palatal shelves. This prevents closure and posterior growth of soft palate, producing U-shaped cleft palate. V-shaped defect at right is frequently seen in primary defects of palatal closure not secondary to mandibular involvement. (From JW Hanson and DW Smith, J Pediatr 87:30, 1975.)

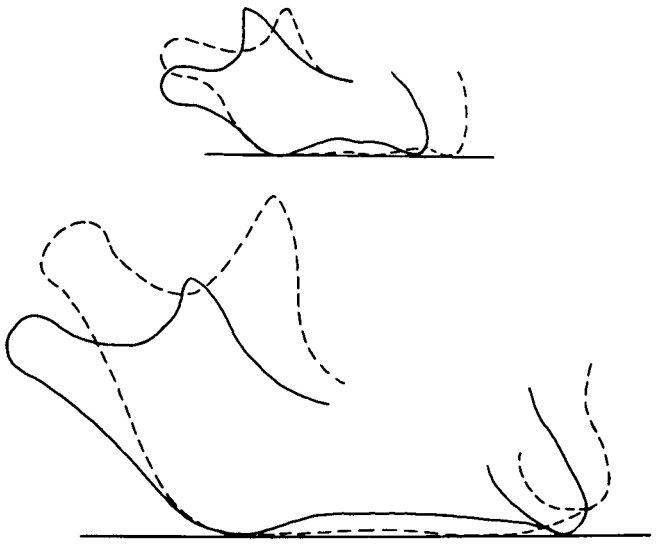


Fig. 20–16. *Robin sequence*. Superimposed tracings from normal (broken line) and Robin (solid line) mandibles. Note differences in height of ramus, length of body, gonial angle, and inclination of condyle to ramus. Note also catch-up growth. [From S Pruzansky, Birth Defects 5(2):120, 1969.]

has been recorded by a number of authors (18,28). Nasopharyngeal intubation or tracheostomy may reverse the signs of cor pulmonale.

Many striking abnormalities are features of the syndromes listed in Table 20–4. Other anomalies occur in unrecognized patterns. Ocular findings are particularly common. Smith and Stowe (57) found 13 eye anomalies in nine patients including esotropia, glaucoma, and microphthalmia. Saraux and Dhermy (48) and Ortlepp and Brandt (34) reviewed glaucoma and Robin sequence. Ear anomalies occur less frequently, but especially include low-set ears and malformed ears (23,57).

Limb anomalies may be particularly striking and occur with some frequency. Wood and Sandlin (65), in a review of eight patients with Robin sequence, found three cases with limb anomalies including syndactyly, hypoplastic digits, and Poland anomaly. Williams et al (64) noted that peripheral limb defects were particularly common. Congenital amputations, limb reduction defects, talipes equinovarus, and congenital hip dislocation have been reported as well as rib and sternal anomalies (4,7,23,31,38,46,57).

Glander and Cisneros (21) compared craniofacial measurements in velocardiofacial and Stickler patients, both groups having presented with a Robin phenotype.

Prenatal diagnosis has been carried out (27a).

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Robin sequence, congenital thrombocytopenia, agenesis of the corpus callosum, distinctive facies, and developmental delay

Braddock and Carey (1) reported a combination of Robin sequence, congenital thrombocytopenia, distinctive facies, agenesis of the corpus callosum, and developmental delay in two unrelated females.

Both exhibited pre- and postnatal growth retardation, microcephaly, mental retardation, sparse curly hair, large posteriorly rotated pinnae, high forehead, broad nasal root, inverted U-shaped mouth, Robin sequence, lack of facial expression, and hypoplastic tooth enamel.

Neonatal persistent thrombocytopenia with normal number of marrow megakaryocytes in one and a decreased number in the other were found. Agenesis of the corpus callosum was noted in both.

Ventricular septal defect was found in one child, multicystic kidneys in the other.

Both had clinodactyly/camptodactyly of the fifth fingers.

Reference (Robin sequence, congenital thrombocytopenia, agenesis of the corpus callosum, distinctive facies, and developmental delay)

1. Braddock SR, Carey JC: A new syndrome: Congenital thrombocytopenia, Robin sequence, agenesis of the corpus callosum, distinctive facies, and developmental delay. Clin Dysmorphol 3:75–81, 1994.

Robin sequence, unusual facies, and digital anomalies

Chitayat et al (1) reported two half brothers with the same mother. The forehead was high and broad with widow's peak and partial bossing. The nasal bridge was broad, flat, and wrinkled. The philtrum was long. The cleft palate was U-shaped.

The fingers and toes tapered with short distal phalanges and hyperconvex nails. Clinodactyly of the fifth digit was evident bilaterally. Delayed bone age was demonstrated.

Inheritance may be X-linked recessive.

Reference (Robin sequence, unusual facies, and digital anomalies)

1. Chitayat D et al: Robin sequence with facial and digital anomalies in two half-brothers by the same mother. Am J Med Genet 40:167–172, 1991.

Robin sequence, ventricular extrasystoles with syncopal episodes, and digital hypoplasia

Stoll et al (1) described hypoplasia or absence of the distal phalanges of the toes (perodactyly), ventricular extrasystoles with syncopal episodes, and Robin sequence in six individuals in three generations.

Four of the six had bilateral terminal transverse defects of the fingers and toes. Small stature was present in four patients. All exhibited ventricular extrasystoles, occurring more often as bigemini. Five of the six had sudden syncopal episodes. Retardation of mandibular growth, and glossoptosis, a constant feature, were more striking in younger patients. Submucous cleft palate was found in five of the six with a U-shaped cleft palate presented in the sixth.

Inheritance is presumably autosomal dominant.

Wood and Sandling (3) and Williams et al (2), in reviews of patients with Robin sequence, noted hypoplastic digits as a feature but no mention was made of other findings.

References (Robin sequence, ventricular extrasystoles with syncopal episodes, and digital hypoplasia)

1. Stoll C et al: Ventricular extrasystoles with syncopal episodes, periodactyly, and Robin sequence in three generations: A new MCA syndrome? Am J Med Genet 42:480–486, 1992.
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Robin sequence, short stature, vertebral anomalies, short neck, and mental retardation

Mathieu et al (1) reported a father and son with unusual facies (epicanthic folds, short nose with anteverted nostrils, thin upper lip, posteriorly

rotated pinnae), micrognathia, cleft palate, brevicollis, vertebral anomalies, and mental retardation. Stature was short (-4SD). Joints were hyperextensible. The hands appeared especially short.

Diaphragmatic hernia and ankylosis of the ankles were also documented.

Reference (Robin sequence, short stature, vertebral anomalies, short neck, and mental retardation)

1. Mathieu M et al: A familial syndrome with micrognathia, cleft palate, short neck and stature, vertebral anomalies, and mental retardation. Genet Couns 4:299–303, 1993.

Robin sequence, mental retardation, and brachydactyly

Gurrieri et al (1) reported a brother and sister with mental retardation, Robin sequence, and brachydactyly.

In addition, they had a somewhat unusual facial appearance: synophrys, short palpebral fissures, long philtrum, bowed-shaped upper lip, and severe micrognathia. In addition to the brachydactyly, there was considerable clinodactyly of the fourth and fifth fingers.

The mental retardation was mild to moderate.

Reference (Robin sequence, mental retardation, and brachydactyly)

1. Gurrieri F et al: New syndrome of mental retardation, Robin sequence, and brachydactyly. Am J Med Genet 100:49–51, 2001.

Noncleft palatal anomalies

The palate may or may not be highly arched, but this can only be known by measurement of palatal height. The term *highly arched palate* is most commonly used as a subjective description. Objective measurements often belie subjective clinical impression. For example, patients with trisomy 21 syndrome are commonly described as having highly arched palates. However, in the metric study of Shapiro et al (9), palatal height tended to be in the normal range and was not markedly high. Palatal width tended to be more narrow than in normal controls, resulting in the illusion of highly arched palate (Fig. 20–17). Surprisingly, palatal length was found to be dramatically shorter than normal, and in the overwhelming majority of cases, trisomy 21 syndrome patients and normal controls could be distinguished on the basis of this measurement (Fig. 20–18).

Prominent lateral palatine ridges (Fig. 20–19) are a nonspecific feature of various conditions (Table 20–5). Two types of disorders predominate: those with neuromotor dysfunction and those with primary palatal malformation. In both types, proper tongue thrust into the palatal vault is prevented. This may occur in patients with neuromuscular dysfunction of long standing or with malformation such as Byzantine arch palate. Hanson et al (4) suggested that long-standing deficit of tongue thrust is the common pathogenetic mechanism. In the Byzantine arch palate of Apert syndrome, lateral palatal swellings are present that increase in size with age (Fig. 20–20). These swellings have been shown to contain excess mucopolysaccharide content, predominantly hyaluronic acid, and to a lesser extent, sulfated mucopolysaccharides (2,10).

Acquired palatal groove (Fig. 20–21) has been observed in infants with prolonged orotracheal intubation. The palatal groove appears to be related to the duration of intubation and to vigorous sucking during that period of time (3,8).

An unusual palatal anomaly is found in anencephaly (5–7) and holoprosencephaly (1). Although the palate is closed, deep depressions are found extending the length of the hard palate. The abnormality appears to be caused by incomplete downgrowth of the central nasal process. The appearance of such a palate in a case of cyclopia is shown in Figure 20–22.

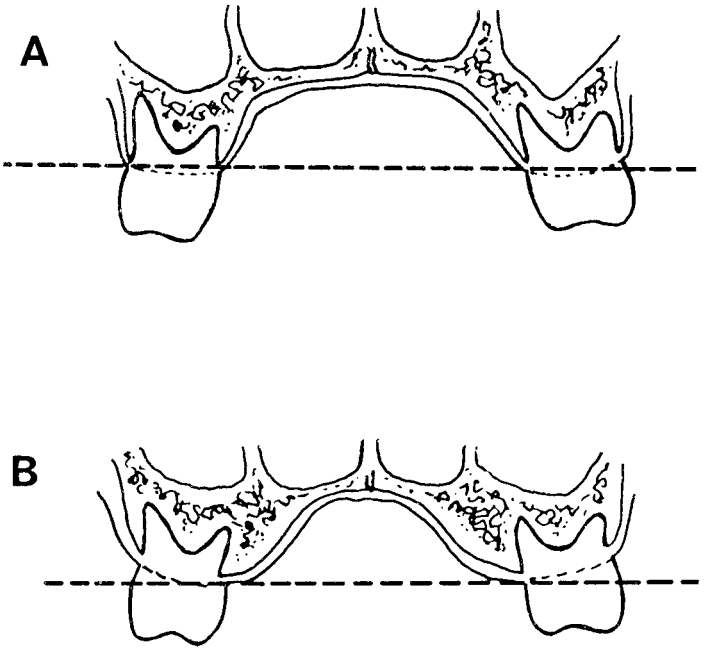

Fig. 20–17. *Noncleft palatal anomalies*. Cross-sections through palate. (A) Normal. (B) Narrow palate of trisomy 21 syndrome giving the illusion of being high. (From BL Shapiro et al, N Engl J Med 276:1460, 1967.)

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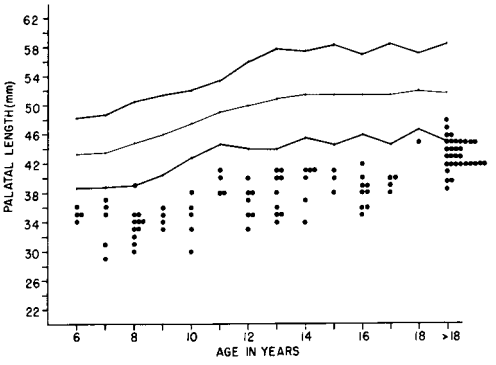
Fig. 20–18. *Noncleft palatal anomalies*. Palatal length of male trisomy 21 syndrome patients plotted on a graph with normal mean ± 2 standard deviations for reference. Palatal length is dramatically short. (From BL Shapiro et al, N Engl J Med 276:1460, 1967).



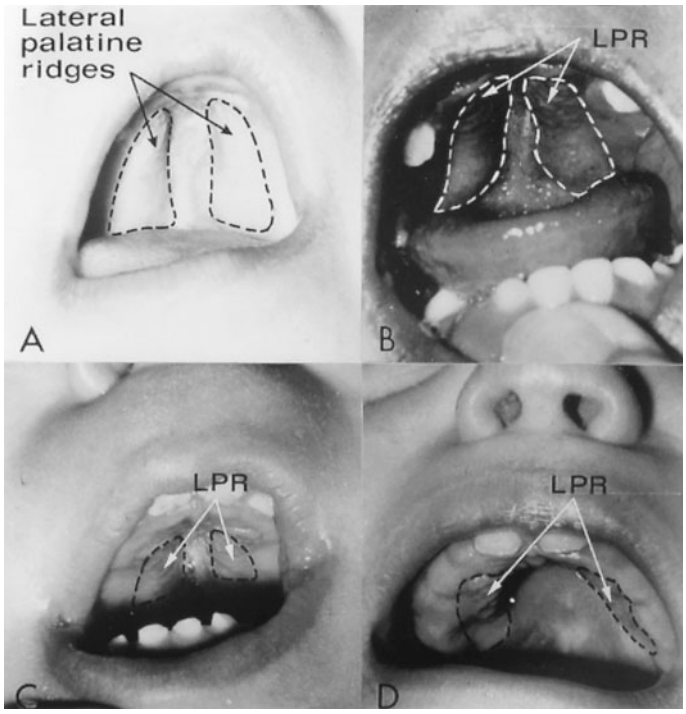


Fig. 20–19. *Noncleft palatal anomalies*. Examples of unusually prominent lateral palatine ridges. (A) Fetal alcohol syndrome (16 months). (B) Trisomy 21 syndrome (3 years, 9 months). (C) Sotos syndrome (10 months). (D) Smith-Lemli-Opitz syndrome (12 months). (From JW Hanson et al, J Pediatr 89:54, 1976.)

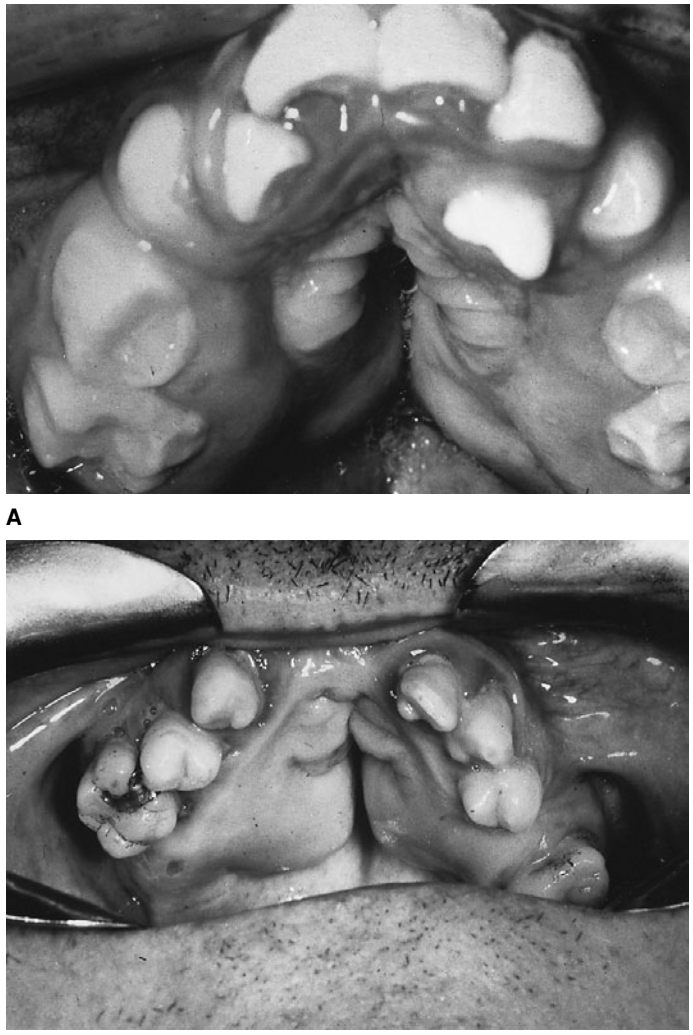
Tessier clefting system

Many classifications for orofacial clefting have been used (4,6,13) and more elaborate classifications have been proposed to deal with extensive craniofacial clefting (5,7,8–10). Tessier (11), in 1976, described a classificatory system in which clefts are situated along definite axes. His system assigns numbers to various sites of clefting, depending on their relationships to the sagittal midline (Fig. 20–23). Bone and soft tissues are both involved, but rarely to the same extent. From the sagittal midline to the infraorbital foramen, abnormalities of soft tissue predominate. From the infraorbital foramen to the temporal bone, however, osseous defects are more severe than those of soft tissue, a notable exception being the ear. Clefts through the orbit use the lower eyelid as an equator. Cleft numbered lines may be either northbound (cranial) or southbound (facial). Cranial numbered lines have facial numbered counterparts, yet these numbers are different to avoid the implication that they necessarily have the same etiopathogenesis.

Table 20–5. Conditions with altered neuromuscular function or malformations associated with prominent lateral palatal ridges

Clinical sign of neuromuscular dysfunction	Condition
Hypotonia	Trisomy 21 syndrome
	Prader-Willi syndrome
	Zellweger syndrome
Hypertonia	Smith-Lemli-Opitz syndrome
	Menkes syndrome
Other	Sotos syndrome
	Fetal alcohol syndrome
Syndrome	"Abnormality proposed to interfere with palatal molding by tongue"
Apert syndrome	Extremely narrow midpalate
Glossopalatine ankylosis syndrome	Mechanically immobilized tongue
Hypoglossia–hypodactylia syndrome	Small tongue

Modified from JW Hanson et al, J Pediatr 89:990, 1976.



A

B

Fig. 20–20. *Noncleft palatal anomalies*. Palatal swellings in Apert syndrome. (A) Younger patient. (B) Older patient. Note change in size of palatal swellings with age. (From MM Cohen Jr, Craniosynostosis: Diagnosis, Evaluation, and Management, Raven Press, New York, 1986.)

In some instances, overlying soft tissue defects predict the possibility of underlying bony clefts. Features such as colobomatous notching of the upper or lower eyelid and nostril or interruption of eyelashes and eyebrows have been referred to as Tessier signs (1). Such patients should be examined radiographically to rule out possible underlying bony clefts. Several types of osseous clefting are illustrated in Figure 20–24 and clinical examples of the Tessier clefting system are shown in Figures 20–25 to 20–27.

The Tessier classification is anatomic and descriptive, thereby avoiding terms that imply, often erroneously, etiopathogenetic mechanisms. The causes of most such clefts are unknown. The overwhelming majority occur sporadically. Many cannot be explained embryologically, suggesting the possibility of disruptive factors. David et al (3) have elegantly illustrated each type and have added three dimensional reconstruction. Thorne (12) and Cohen (2) also have illustrated each type. The reader is also referred to the sections on *oblique facial clefts, lateral (transverse) facial clefts,* and *median mandibular clefts.*

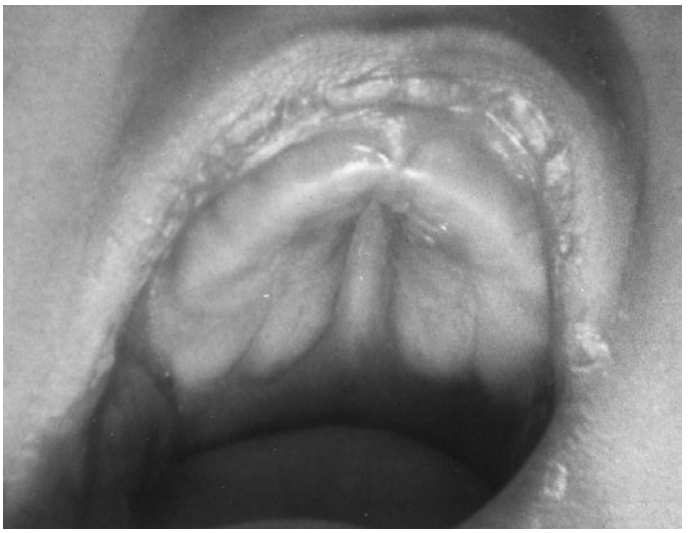


Fig. 20–21. *Noncleft palatal anomalies*. Acquired palatal groove from orotracheal intubation. Infant intubated for 70 days. (From BS Saunders et al, J Pediatr 89:988, 1976.)

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Fig. 20–22. *Noncleft palatal anomalies*. Unusual palatal form in cyclopia. Arrow demonstrates bifid uvula. [From MM Cohen Jr and RJ Gorlin, Birth Defects 5(2):113, 1969.]

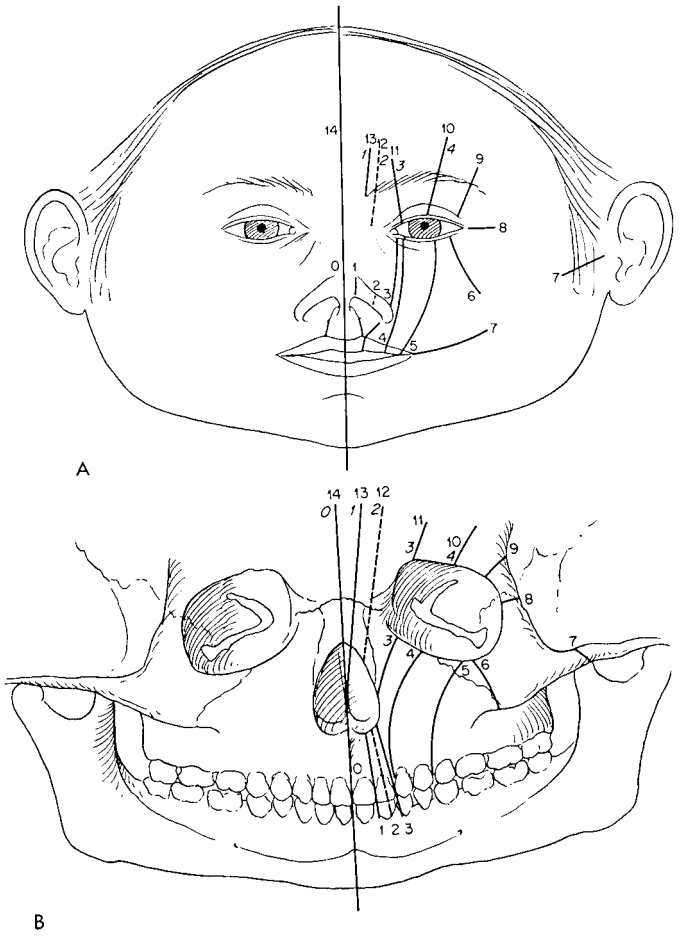

Fig. 20–23. *Tessier clefting system*. (A) Soft tissue clefts. (B) Bony clefts. Dotted lines represent uncertain localization or uncertain clefting. Note that northbound cranial line has different number than its counterpart southbound facial line. Thus, system is descriptive and anatomic, and avoids etiologic and/or pathogenetic speculation. For example, the cause of a No. 10 cleft may possibly be different than the cause of a No. 4 cleft. (From P Tessier, J Maxillofac Surg 4:69, 1976.)

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Lateral (transverse) facial clefts

Lateral facial cleft (macrostomia, Tessier type 7) may be an isolated phenomenon. More often, however, it occurs in association with other disorders: *mandibulofacial dysostosis, oculo-auriculo-vertebral spectrum, Nager acrofacial dysostosis, amniotic rupture sequence,* etc.

Various authors have estimated the frequency of isolated lateral facial cleft as 1/100 to 350 cases of cleft lip and/or palate, that is, approximately

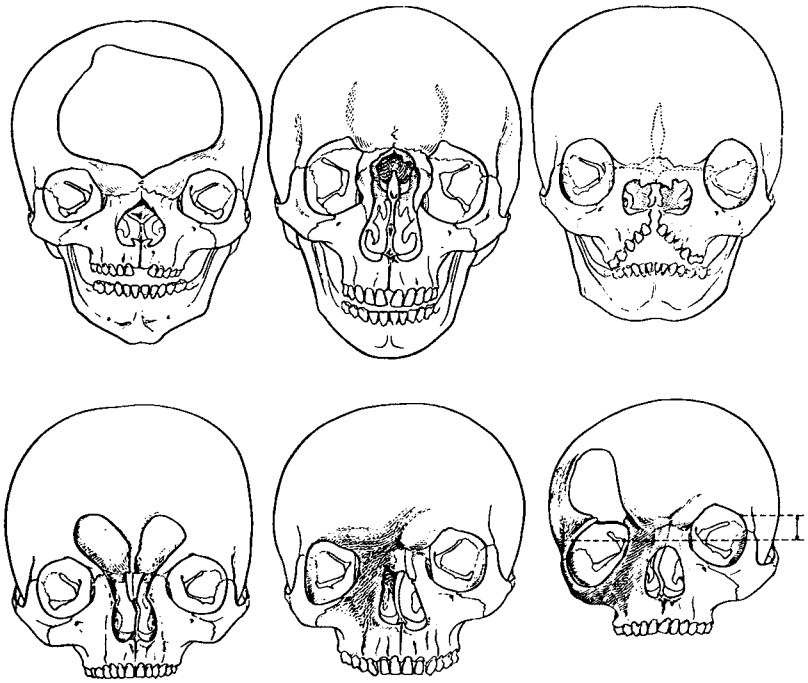


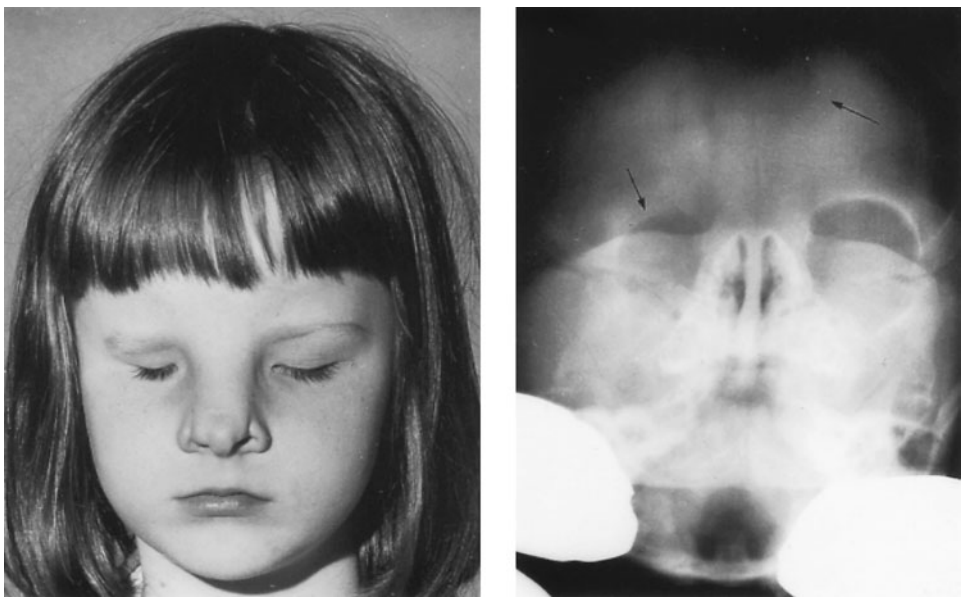
Fig. 20–24. *Tessier clefting system*. Upper left: Cleft Nos. 0, 14. Median craniofacial dysraphism involving encephalocele, hypertelorism, bifid nose, and diastema between maxillary central incisors. Upper middle: Cleft Nos. 0, 14. Median frontonasal encephalocele and dystopia canthorum. Note sparing of upper cranial region and tooth bearing part of maxilla. Upper right: Cleft Nos. 0, 14. Median craniofacial dysraphism with encephalocele or calcification of the falx cerebri or both, duplication of the crista galli, hypertelorism, bifid nose, absence of vomer, and keel-shaped maxillary dental arch. Lower left: Cleft Nos. 1, 13. Bilateral paramedian encephaloceles and hypertelorism. This case was associated with colobomatous notching of both nostrils. Lower middle: Cleft Nos. 2, 12. Unilateral involvement affecting facial component more severely than cranial component. Cleft is either through frontal process of maxilla or between maxilla and nasal bone. Note unilateral hypertelorism. Patient had cleft through medial part of the right nostril. Lower right: Cleft No. 10. Unilateral large defect of frontal bone involving supraorbital rim and orbital roof with encephalocele, unilateral hypertelorism, and dystopia with lateral rotation of the affected orbit. (From P Tessier, J Maxillofac Surg 4:69, 1976.)

1/50,000 to 1/175,000 live births (5,6,10,18). Like oblique facial cleft, the isolated lateral cleft does not appear to have a genetic basis. It has been reported in one of monozygous twins (12). Especially bizarre are the severe cases in sibs whose father had cleft lip and cleft palate (21) and in three half sibs, each having a different father (11).

The cleft may represent failure of penetration of ectomesenchyme between developing maxillary and mandibular prominences. Multiple growth centers are involved in each facial prominence. Failures of these centers to merge could eventuate in macrostomia. However, the variable placement of the lateral cleft in relation to the ear in different cases (Figs. 20–28 and 20–29) suggests the possibility of disruptive factors in many cases.

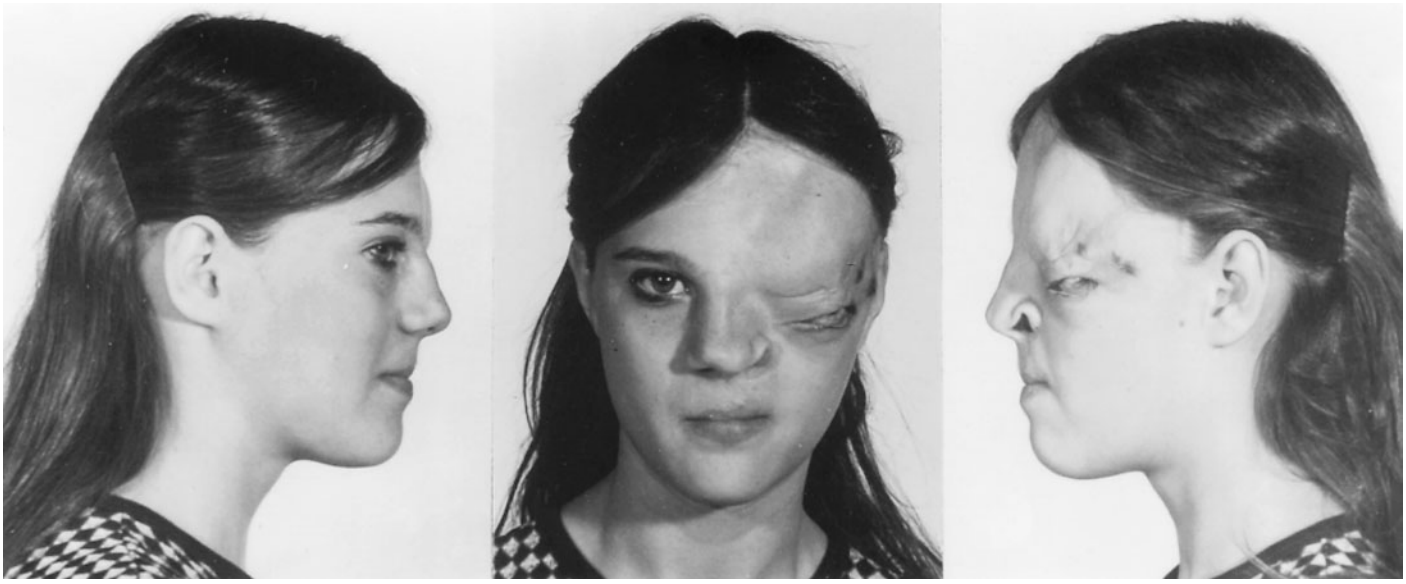
The lateral facial cleft may be unilateral or bilateral (10%–20%), partial or rarely complete, extending from the angle of the mouth to the ear (3,13,14,19). It appears to be somewhat more common in males, and, when unilateral, is more frequent on the left side. Minimally, it may involve only a groove-like thinning of the cheek or mild lateral displacement of the commissure (16). The external defect is always accompanied by an underlying muscle defect (Fig. 20–29). The reader is referred to *Tessier clefting system* (type 7).

Associated anomalies have been reported including micrognathia (4), nasal dermoid (5), tetralogy of Fallot and intestinal anomalies (16a), and epignathus (1). Bizarre clefts of all types may be associated with *amniotic band syndrome*. Transverse facial cleft may be associated with accessory maxillae (7–9,15,20,23). Patients with *Klippel-Feil syndrome* rarely have creases running from both commissures toward the ears (2,17,24,25). We suspect the patient of Shetty et al (22) has *oculo-auriculo-vertebral spectrum*.



A B

Fig. 20–25. *Tessier clefting system*. (A,B) Cleft Nos. 0, 14. Note midline cranium bifidum, hypertelorism, unilateral microphthalmia with small orbit, and colobomatous notching of nostrils. (From HO Sedano et al, J Pediatr 76:906, 1970.)



A B C

Fig. 20–26. *Tessier clefting system*. (A–C) Cleft No. 10. Note unilateral hypertelorism with downward displacement of the orbit, interruption of eyebrow on affected side, and repaired cleft lip (CCFA #1240, female, age 14 yrs, 7 mos). [From S Pruzansky. In: JF Bosma, Symposium on Development of the Basicranium, HEW Publication No. (HIN) 76–989, Bethesda, Maryland, p 278, 1976.]

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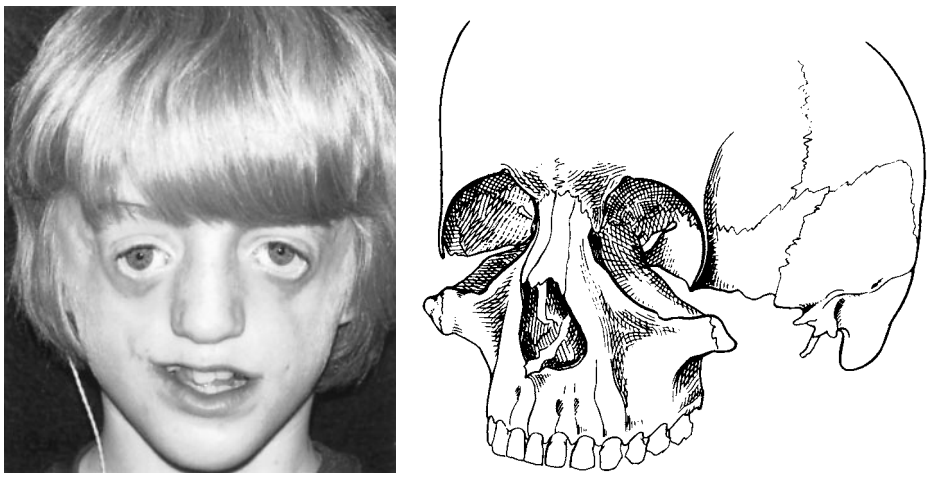

A B

Fig. 20–27. *Tessier clefting system*. Cleft Nos. 6, 7, 8. Mandibulofacial dysostosis. (A) Clinical appearance showing downslanting palpebral fissures and malar deficiency. Note abnormal shape of lower eyelids that often have missing lashes medially. (B) Bony clefting of ovoid-shaped orbits with absence of zygomatic arches. (A from MM Cohen Jr, The Child with Multiple Birth Defects, Raven Press, New York, 1982, p 106. B from P Tessier, J Maxillofac Surg 4:69, 1976.)

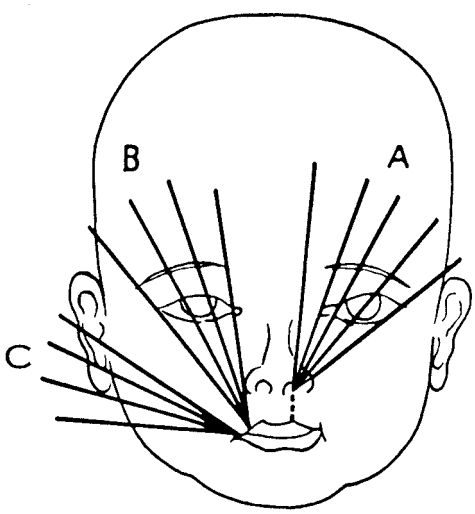

Fig. 20–28. *Lateral and oblique facial clefts*. The oblique facial cleft does not follow a uniform pattern. It may involve the nostril (A), or it may skirt the ala (B). Transverse facial cleft (macrostomia) is similarly variable (C). (From M Grob, Lehrbuch der Kinderchirugie, Georg A Thieme, Stuttgart, 1957, p 101.)

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Oblique facial clefts

Oblique facial cleft (meloschisis) is exceedingly rare. Fogh-Andersen (12) reported 1 case/1300 cases of facial cleft. Gunter (13) found 4 among 900 cases of facial cleft. Wilson et al (42) estimated that they represented 0.25% of clefts. Kawamoto (16) estimated that they occur in approximately 2–5 per 100,000 births.

From the approximately 225 published examples that we have tabulated, the cleft appears to be bilateral in approximately 20% (4,5,31) and more often on the right side when unilateral (3). The cleft is nearly always associated with cleft lip and palate. Occasionally lateral facial cleft is also present (3,9,38). There is no sex predilection. All known cases are sporadic. For historic discussion, see Morian (22) and Boo-Chai (3).

Oblique facial cleft is extremely variable in degree (4). It may extend through the upper lip to the nose (as a typical cleft lip) to involve the eye (producing microphthalmia or anophthalmia), at times even reaching the brow or temple (3,11,21,23,26,30), or it may arise lateral to the philtrum and extend to the eye by skirting the nose (Figs. 20–28,20–30 and 20–31). The more severe types are, not uncommonly, incompatible with life. A three-dimensional study is that of David et al (7).

An early attempt was made by Morian (22) to classify the oblique facial cleft into two types: (1) *naso-ocular cleft*, extending from the nostril to the lower eyelid border with possible extension to the temporal region, that is, along the line of closure of the nasolacrimal groove, and (b) *oro-ocular cleft*, extending from the eye to the lip. This latter form, the more common (60%) type, was subdivided into (b_1) oromedial canthal type and (b_2) orolateral canthal type (1,3,8,17,40). Tessier (36) proposed a more elaborate surgically oriented numerical classification of rare facial clefts. Oblique facial clefts include those of types 2–6. Those that involve the nostril are called type 3; the ones that skirt the nostril are type 4, and those that extend from the oral commissure to the eye are type 5. Type 9 extends to the temporal area. These classifications are important descriptive observations that do not consider etiopathogenesis. The reader is referred to *Tessier clefting system* for further discussion.

The cleft has been stated to represent failure of penetration of ectomesenchyme between the lateral nasal and maxillary prominences with resultant failure of coverage of the nasolacrimal groove. We believe that most examples are because of tears in the ectomesenchyme related to the *amniotic rupture sequence*. This appears to be clearly evident in those cases associated with constriction rings or bands, intrauterine amputation of digits, or aplasia cutis congenita (3,5a,8,12,17–20,29,30,38). In some cases, an amniotic strand is presumably swallowed and becomes attached to the pharynx, slicing the ectomesenchyme of the facial processes. See also *tetra-amelia* for discussion of another association.

Other so-called associated anomalies may be interpreted as being secondary to the cleft, such as abnormal eyebrow and/or hairline, facial asymmetry, choanal atresia, absence of nasal ala, agenesis of lacrimal puncta with or without formation of nasolacrimal duct, bifid nasolacrimal system, eyelid colobomas as well as sundry eye anomalies (choroid coloboma, microphthalmia, rarely anophthalmia), supernumerary teeth, jaw fusion, and dental malocclusion (2,8–10,15,16,24,25,27,28,32,33,35,38,39).

Various other associated anomalies may occur including hernia (25), genitourinary abnormalities (13), talipes (13,20), cutaneous tag (6), spinal and costal defects (9), encephalocele (14,17), and hydrocephalus (22). Mental retardation is a variable finding.

There is no evidence that the cleft has single gene inheritance (41).

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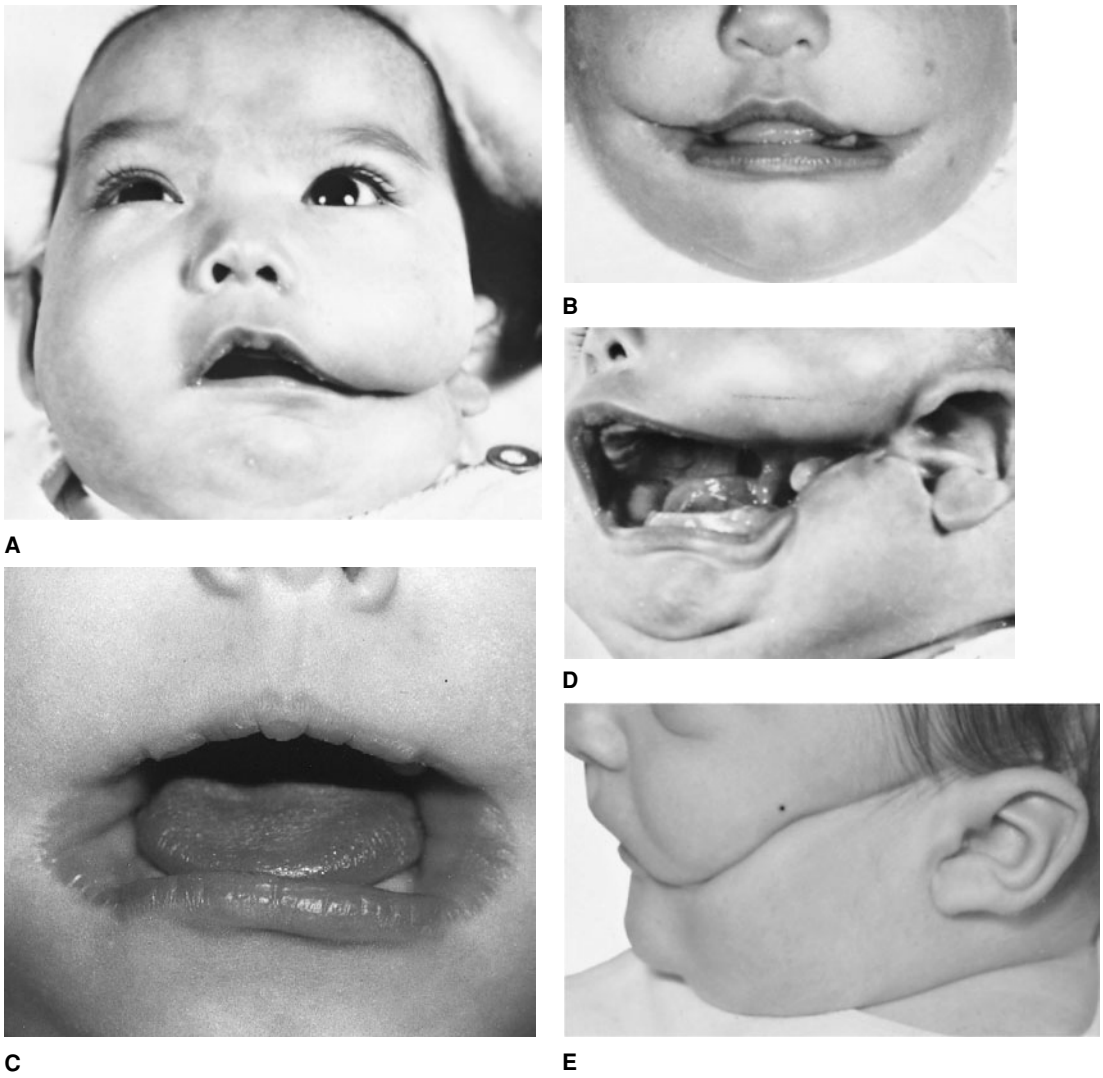
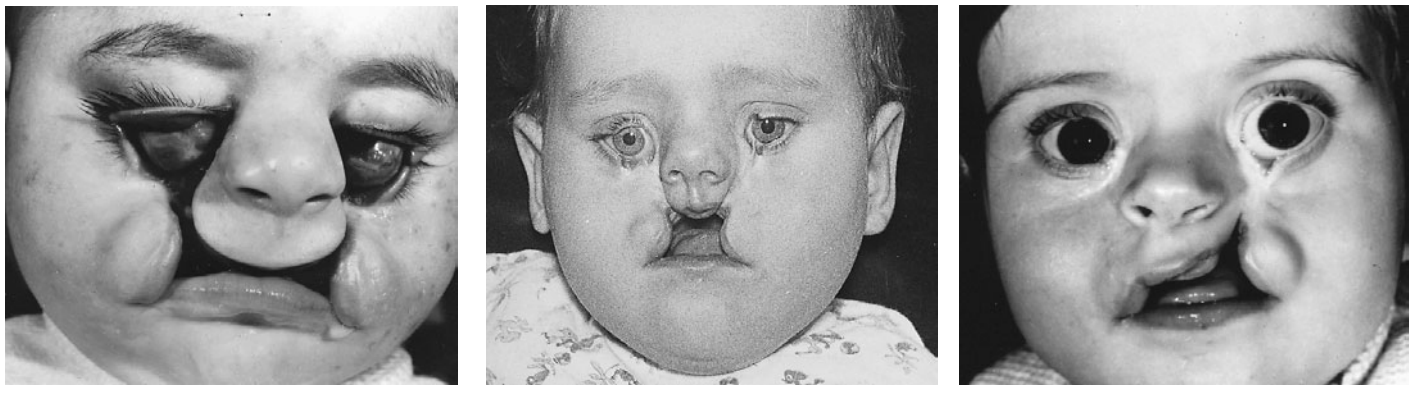


Fig. 20–29. *Lateral (transverse) facial clefts*. (A) Unilateral facial cleft. (B) Bilateral lateral facial cleft. (C) Bilateral macrostomia. (D) Unilateral lateral facial cleft extending to tragus. (E) Lateral facial cleft extending above helix of low-set, posteriorly angulated ear. (A,D from P Fogh-Andersen, Acta Chir Scand 129:275, 1964. B courtesy of K Schuchardt, Hamburg, Germany. C from BS Bauer et al, Plast Reconstr Surg 70:752, 1982. E from HM Blackfield and NJ Wilde, Plast Reconstr Surg 6:62, 1950.)

Fig. 20–30. *Oblique facial clefts*. Bilateral clefts (A,B) and unilateral cleft (C) bypass nostrils and extend roughly along line of closure of nasolacrimal canals. (A,C courtesy of P Tessier, Paris, France.)



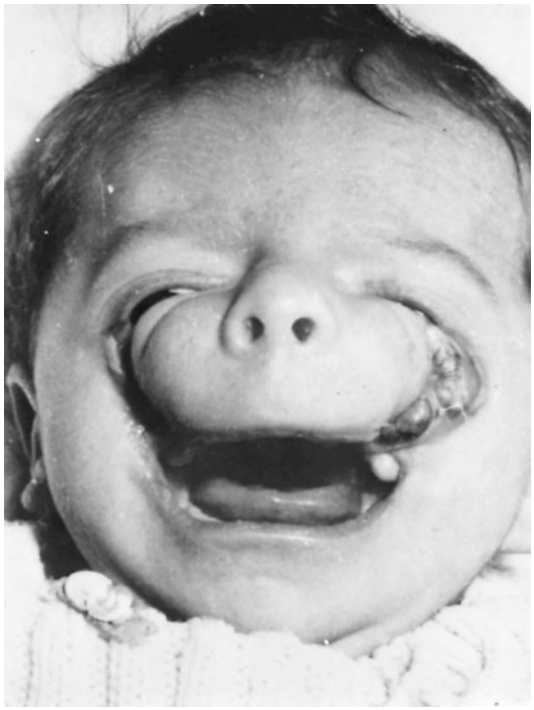


Fig. 20–31. *Oblique facial clefts*. Clefts extending from angles of mouth to outer canthi of eyes, following no line of embryonic fusion of facial processes. (From J Pintanguy and T Franco, Plast Reconstr Surg 39:569, 1967.)

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Median cleft of the upper lip

Most median clefts of the upper lip are not true median clefts. They represent agenesis of the primary palate associated with holoprosencephaly with or without trisomy 13.

True median cleft of the upper lip is because of failure of the lowest part of the median nasal prominences to approximate in the midline (14). It is among the rarest of facial clefts, constituting only approximately 0.2% (7). The median cleft usually involves only the vermilion of the upper lip but occasionally extends between the central incisors into the alveolar process (Fig. 20–32). Often there is duplication of the frenum of the upper lip with a small pit between the mucosal folds. The philtral columns are somewhat widened (1–6,8–14). Philtral pits have been reported in a few cases (5,13).

Median cleft of the upper lip may be associated with a number of syndromes such as the *oral-facial-digital syndromes, Ellis-van Creveld syndrome, Majewski syndrome*, and *median cleft of upper lip, double frenum, and hamartoma of columella and/or anterior alveolar ridge*.

Fogh-Andersen (7) very briefly reported male sibs with midline cleft of the upper lip and dysplastic terminal phalanges of the hands (digital amputation and syndactyly).

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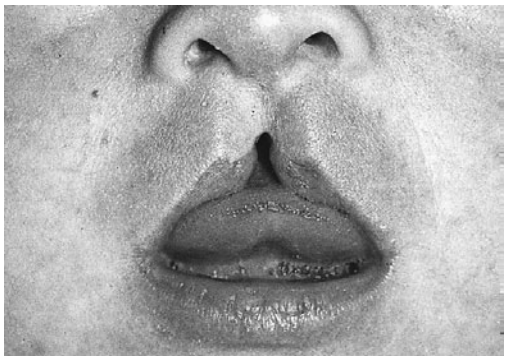
Fig. 20–32. *Median cleft of the upper lip*. Median cleft upper lip. [From W Hoppe, Arch Kinderheilkd 171(Suppl 52):1, 1965.]



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Lateral sinus of the upper lip

The lateral sinus of the upper lip is located along the line at the position of fusion of the median nasal and maxillary prominences, i.e., along the line of closure of the lip, and probably represents a microform of cleft lip (1–9). It may be in the vermilion and associated with minor salivary glands or even extend into a palatal cyst. Bilateral sinuses have been reported (6,8).

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Median cleft of upper lip, double frenum, and hamartoma of columella and/or anterior alveolar ridge

Approximately 25 authors (1–6,8–26) have described patients with (a) median cleft of the upper lip extending through the vermilion, (b) duplication of the maxillary median frenum, (c) pedunculated skin-covered club-shaped cylindrical mass presented through one nostril, its base attached to the nasal septum or columella, and (d) a similar mass attached to the mid-anterior alveolar process (Figs. 20–33 and 20–34). Not all patients have all four components present. In rare examples, the midline cleft of the upper lip extends into the nose (24). Striking examples are those of Kernahan (9) and Guion-Almeida (4), whose patients had a skin raphé, extending from the midline cleft lip along the nasal bridge to the bregma. In both there was hypertelorism. In one (9), a skin

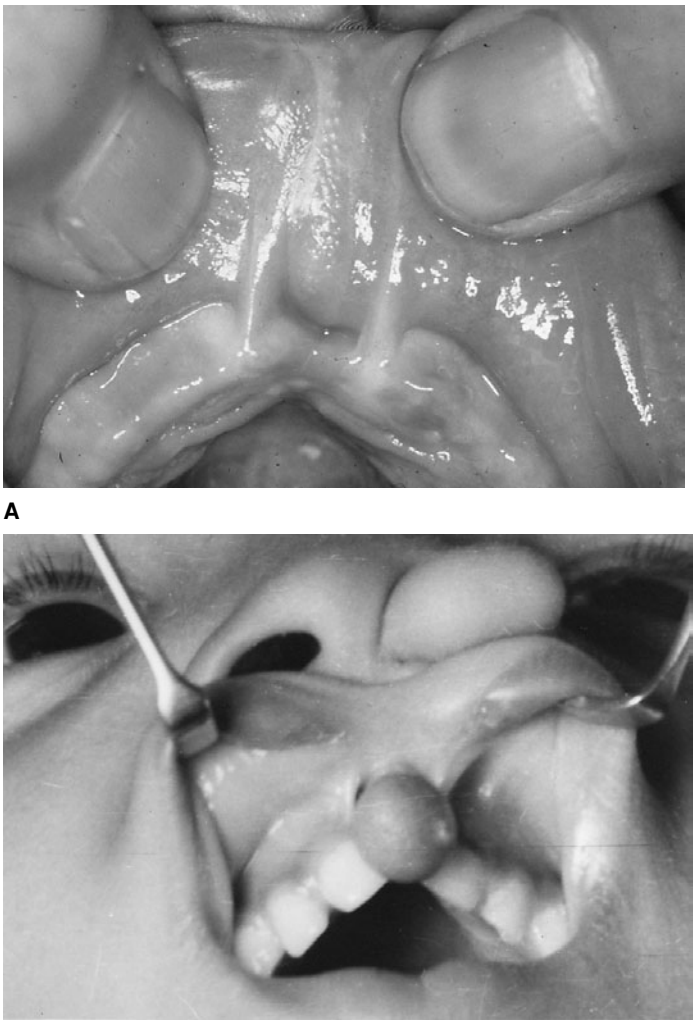

Fig. 20–34. *Median cleft of upper lip, double frenum, and hamartoma of columella and/or anterior alveolar ridge*. (A) Duplication of maxillary median frenum. (B) Pedunculated mass attached to frenum area. (A from J Nakamura et al, Plast Reconstr Surg 75:727, 1985. B courtesy of LK Sharma, Nagpur, India.)

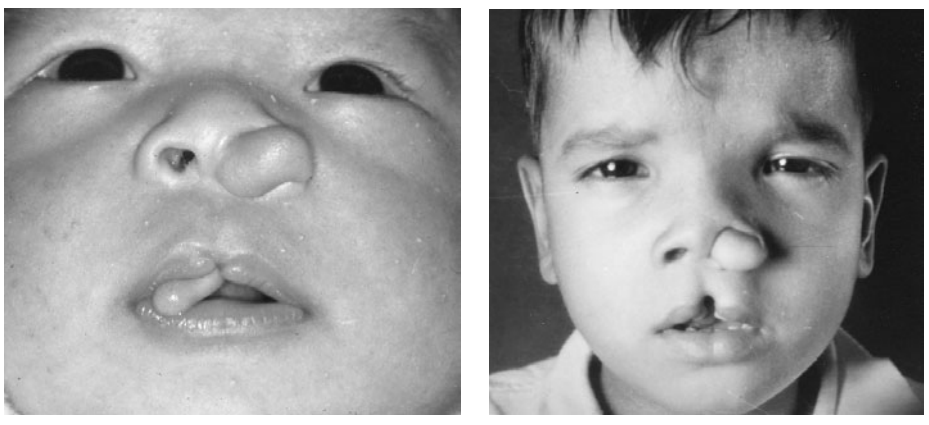

Fig. 20–33. *Median cleft of upper lip, double frenum, and hamartoma of columella and/or anterior alveolar ridge*. (A) Median cleft of upper lip, median mass extending from alveolar process, nasal mass extending from columella. (B) Compare anomalies seen in A with those seen in second patient. (A from J Nakamura et al, Plast Reconstr Surg 75:727, 1985. B courtesy of LK Sharma, Nagpur, India.)

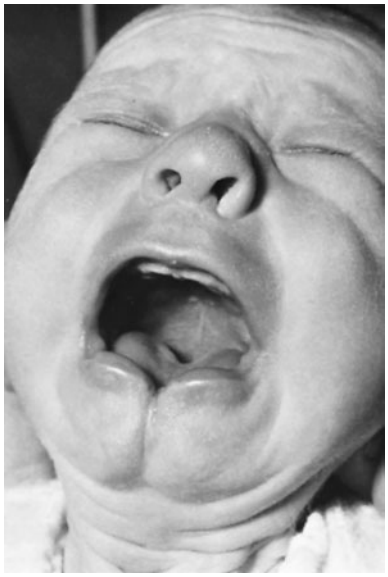

Fig. 20–35. *Median mandibular clefts. Incomplete cleft of lower lip and chin with complete cleft of mandible*. (From CC Knowles et al, Br Dent J 127:337, 1969.)

tag was present on the side of the nose near the glabella. No details were presented. Microscopically, it consists of skin and dermal appendages, fibrous connective tissue, adipose tissue, and striated muscle. This represents a malformation of the primary palate. In several cases, a lipoma was found in the corpus callosum (4,5,15,16,19,21,23) and in the spinal canal (18). Rarely, the nasal tip is bifid (25). Although the syndrome has been called Pai syndrome, a large number of examples had been described prior to the report of Pai et al (19) in 1987.

Midline clefts of the upper lip can be seen in other disorders such as *holoprosencephaly*, palate duplication, various *oral-facial-digital syndromes, Ellis-van Creveld syndrome, Majewski short-rib polydactyly syndrome*, and bifid nose (22).

Miscellaneous anomalies have included: mesodermal dysgenesis of the anterior eye (5,21), conjunctival lipoma (15), cartilaginous skin tag of glabella, mid-forehead, or lateral nose (8,19,23), bifid uvula (23), mental retardation and short stature (4), and clinodactyly of V (19). A similar skin tag was found in an infant who manifested no other sign of the syndrome.

The suggestion that the condition has autosomal dominant inheritance, we believe, is weak (23). The father had only a coloboma of the iris. There is a slight male sex predilection. Masuno et al (14) reported finding a translocation in a patient that involved either Xq28 or 16q11.2.

Lipoma of the corpus callosum can be found in *frontonasal malformation*.

References (Median cleft of upper lip, double frenum, and hamartoma of columella and/or anterior alveolar ridge)

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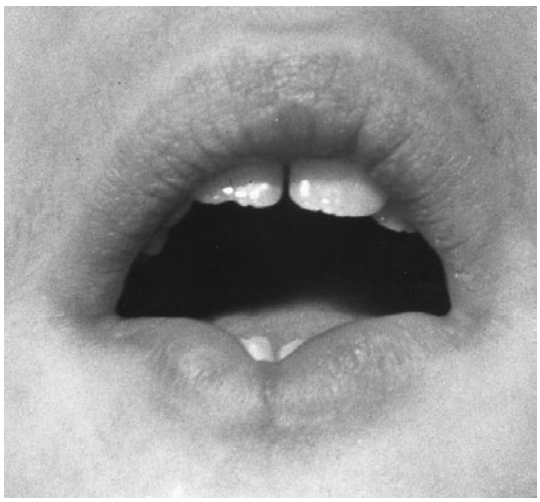

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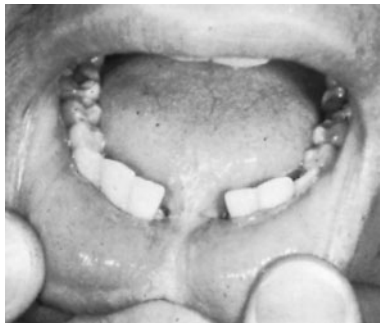

B

Fig. 20–36. *Median mandibular clefts*. (A) Median cleft of lower lip. Mild cleft involving only soft tissues. (B) Median cleft of lower lip with tongue tip attached to mandible. (A from R Ranta, Int J Oral Surg 13:555, 1983. B from HA Ecker, Am J Surg 96:815, 1958.)

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Median mandibular cleft (Tessier type 30)

The rare anomaly is usually an isolated finding. Redard and Michel (30) reviewed early examples. The earliest may be that of Couronné (11) in 1819. Although Rey et al (31), in 1982, listed 64 examples, they included a number we cannot accept. As of 1997, perhaps 80 true cases have been reported. The disorder is not hereditary and there is no sex predilection. Its frequency is approximately 4 to 5 cases/million births (27,28).

Some examples are mild, involving only the lower lip and essentially sparing the bone (23); approximately 70% are more extensive (2) (Fig. 20–35). In approximately 35%, the tongue is significantly cleft. In nearly all cases there is ankyloglossia, the tongue tip being attached to the median cleft by a broad frenum (8,13,18,20,21). In others, there is more extensive ankyloglossia. Rarely is the tongue spared. The cleft may be very severe, bifurcating the mandible, tongue, and structures of the midneck down to the region of the hyoid bone (19) (Figs. 20–35 and 20–36). The hyoid bone and occasionally the manubrium of the sternum are absent. Some patients have a midline cervical cord (14,24). Ranta (29) described 12 cases of minimal cleft of the lower lip with cleft palate in 7, Robin sequence in 3, and/or agenesis of lower central incisor teeth in 2 patients.

We do not agree that the anomaly results from failure of merging of the paired first and second arches (22). We agree with Oostrom et al (25) that there is a single branchial arch with two mandibular swellings separated by a groove in the midline. The groove is normally erased by ectomesenchymal growth (merging). Variable hypoplasia of the mandibular prominences within the first arch makes for the variable degrees of expression of this anomaly. Giroud and Martinet (15) reported an animal model.

Various associated congenital abnormalities include symbrachydactyly and contractures of digits (5.24), cleft palate (8,9,14,24,29), congenital heart anomalies (12,24,26,33,34), and ear tags. Fujino et al (14) described a midline cervical cord; Surendran and Varghese (35) and Chidzonga and Shija (8), and Armstrong and Waterhouse (3) found midline dermoid of the neck/chin area. Constantinides and Cywes (10) noted aplasia of the epiglottis. Other miscellaneous anomalies are cited by Fujino et al (14), Rey et al (31), Oostrom et al (25), and Lu et al (19). A *Klippel-Feil anomaly* has been described (36).

Cleft tongue can be seen in association with the *oral-facial-digital syndromes*. It may be an isolated phenomenon (17). It should not be mistaken for true doubling or replication of the tongue that can be associated with cleft palate. *Frontonasal dysplasia* can be associated with cleft palate, cleft lip, and midline dermoid (4,6,7,16,32). The reader is referred also to *oral duplication and cleft* palate. Complex clefting of the lower lip was reported by Abramson (1). The oft-cited patient of Braithwaite and Watson (5) clearly has *oculo-auriculo-vertebral spectrum*.

References [Median mandibular cleft (Tessier type 30)]

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Chapter 21
Orofacial Clefting Syndromes: Common and Well-Known Syndromes

Cerebro-costo-mandibular syndrome (rib-gap syndrome)

The syndrome originally described by Smith et al (28), in 1966, consists of both intrauterine and postnatal growth disturbance, cerebral maldevelopment or malfunction, bell-shaped thorax, variable rib-gap defects, respiratory distress, cleft palate, and micrognathia. Although approximately 55 cases have been reported, it is possible that the correct diagnosis of other examples may not have been made because of failure to perform autopsy or to take a radiograph of the chest.

The inheritance pattern is unknown (26). There is no sex predilection (24). McNicholl et al (18) and Trautman et al (32) reported affected sibs. Leroy et al (16) described the disorder in a mother and in her two children by different fathers. Merlob et al (20) reported the disorder in a father and daughter. Schrander-Stumpel et al (25) described an affected mother and daughter. Van den Ende et al (33) reported two examples of affected mother and daughter. Hennekam et al (8) noted affected sibs, one of them having only mild expression. In three cases, relatives had some stigmata (6,22). Duval et al (4) reported two female sibs with severe intrauterine growth retardation, severe microcephaly, prominent eyes, large nose, small mouth with full lips and severe micrognathia, severe brain hypoplasia, severe rib gaps, contractures of joints and hypoplasia of several bones. Kirk et al (12) described male and female sibs with severe micrognathia, cleft palate, absent olfactory tracts, and abnormal rib development. A similar case is that of Hennekam and Goldschmeding (7). Two pairs of dizygous twin sibs have been described (3). There was extremely variable expression. All other examples have been isolated. Consanguinity was noted in only one case (2). Chromosome studies have been normal (23,32). We are not certain how to classify one example (22). The child, the product of an incestuous union, exhibited cleft palate, hypoplasia of the sternum, clavicles and pubis, semirudimentary ribs, and porencephalic cyst.

Polyhydramnios has been reported in a few cases (3,6,18,20). Approximately 50% die prior to the first year of life (11,24).

Microcrania has been reported in approximately 35% (19,24,25), and mental retardation, ranging from moderate to severe, has been documented in approximately 35% of those that have survived. Normal intelligence has been described in most cases (15,17,19,23), but asphyxia, seen in a few examples, may contribute to retardation in approximately 30% of those that have survived (24).

The mandible is small in all cases, some patients requiring tracheostomy (Fig. 21–1A,B). Cleft palate (65%), short palate (15%), and glossoptosis (65%) have been noted and several infants were classified as having Robin sequence (19,23,34).

The upper thorax is very narrow (Fig. 21–1A). The constant feature is bilateral posterior rib gaps. They vary in number but are most frequent between the third and seventh thoracic segments, although all 12 levels have been affected (27). Rudimentary ribs may occur at the second level with absent twelfth ribs in approximately 70% of the cases (19,24) (Fig. 21–1C). Other lower ribs may be missing (25). The gaps represent pseudoarthroses (10,14). Follow-up reveals that the gaps are ultimately joined by bony bridges.

Respiratory distress is evident in nearly 100% in early infancy (31). The lungs are hypoplastic and with age, the chest width is greatly reduced (25).

Miscellaneous findings have included pterygium colli (5,13,20,25,26, 28) and an assortment of orthopedic anomalies: clubfoot, scoliosis (21,25), hip dislocation, stippled epiphyses (1), absence of external auditory canals (33), choanal atresia (33) and elbow dysplasia (6,13,15, 18,29,33,35). Conductive hearing loss (5,16,26,32), microstomia (20), ventricular septal defect (14), and cystic renal changes (22) have also been noted.

Prenatal diagnosis has been made (9).

Differential diagnosis would include an autosomal dominant syndrome of Robin sequence, rib dysplasia, scapular hypoplasia, and pectus excavatum (30). *Robin sequence, unusual facies, and digital anomalies* must also be excluded for pectus excavatum was also noted. Some patients with *del22q* have a similar phenotype.

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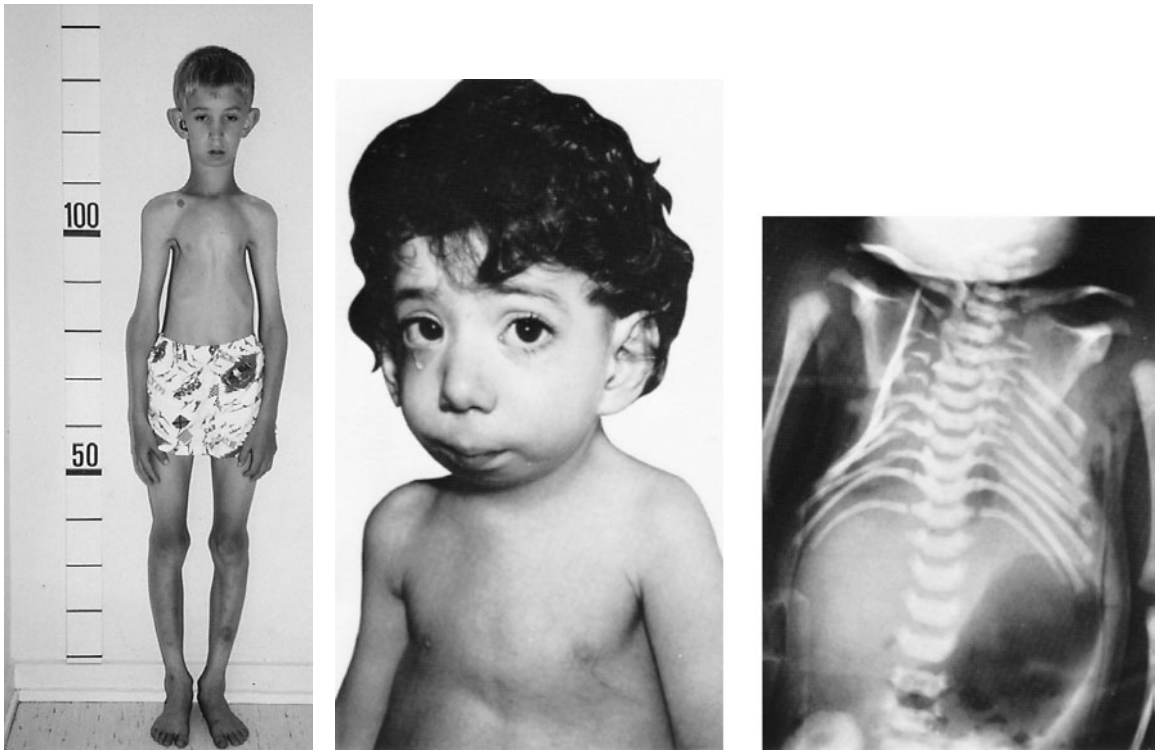

Fig. 21–1. *Cerebro-costo-mandibular syndrome (rib-gap syndrome).* (A) Severe narrowing of upper thorax in 12-year-old boy. (B) One of three sibs with microcephaly, thoracic deformity with rib gaps, and vertebral anomalies. (C) Radiograph showing severely narrowed upper part of the thorax and bizarre vertebral and rib anomalies. (A from JJ van den Ende et al, Clin Dysmorphol 7:87, 1998. B,C from B McNicholl et al, Arch Dis Child 5:421, 1970.)

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EEC syndrome (ectrodactyly-ectodermal dysplasia-clefting syndrome)

The first report of the syndrome of ectrodactyly (lobster-claw anomaly) of the hands and feet, lacrimal duct anomalies with ocular complications, and cleft lip-palate was likely that of Eckholdt and Martens (19) in 1804. Another early nineteenth century description was that of Cruveilhier (17). In excess of 250 cases have been reported (42,74,76). EEC syndrome is present in 1/50,000 live births. The acronym, EEC syndrome, was coined by Rüdiger et al (79). Most reports are sporadic but the syndrome has autosomal dominant inheritance with reduced penetrance and variable expressivity (49,62,75,80,89).

Approximately 50% are sporadic examples (76). Pedigrees with skipped generations have been noted (16,21,35,96). Penetrance has been estimated as somewhat less than 80% (74). One ectrodactyly gene, *EEC1*, has been mapped to 7q11.2–q21.3 (2,24,28,29,69). A second gene, *EEC2*, maps to 19p13–q13 (59), while a third, *EEC3*, is at 3q27. The last gene is *p63*, where missense mutations are responsible for the EEC syndrome (5a). These are due to amino acid substitutions. *p63* is the homologue of the archetypal tumor suppressor gene *p53* (52,97a). However, *p63* mutations have been found in only 85% of EEC patients. Prenatal diagnosis has been accomplished (9). A comprehensive literature review is that of Roelfsma and Cobben (76).

There is marked overlap among Rapp-Hodgkin and Hay-Wells syndromes and a child with EEC syndrome (52a,53).

Birth weight may be somewhat low (10th–25th centiles) (4,10,11).

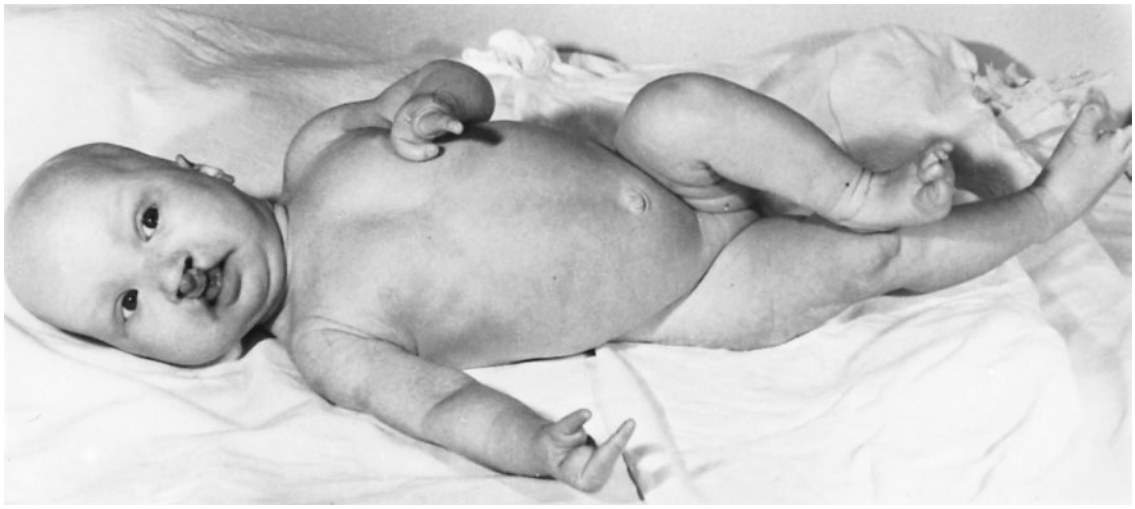


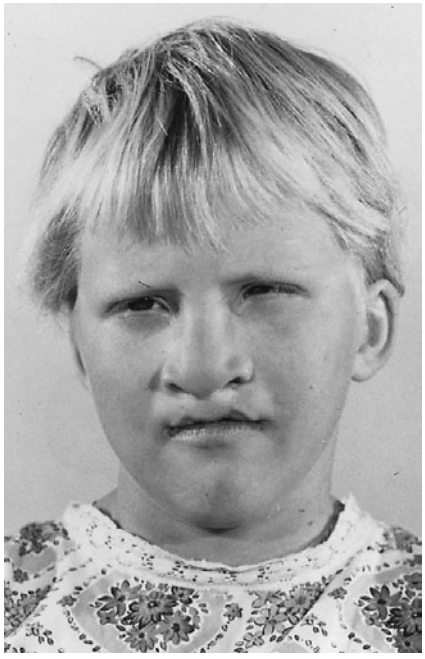
Fig. 21–2. *EEC syndrome*. Bilateral cleft lip-palate and ectrodactyly. (From RA Rüdiger et al, Am J Dis Child 120:160, 1970.)

Facies. The facies is characterized by dacryocystitis, keratoconjunctivitis, tearing, photophobia, and cleft lip. Scalp hair, lashes, and eyebrows are nearly always sparse (15,78). (Figs. 21–2 and 21–3).

Extremities. Limb anomalies affect approximately 85%–90%, with tetramelic involvement in 60%. Approximately 40% have asymmetric anomalies. The classic central ray deficit may be present in the hands with only syndactyly present in the toes (Fig. 21–4). However, some patients have been described without ectrodactyly (12,23,42,49,60,66), a single extremity may be normal (14). Occasionally, soft tissue syndactyly, especially of the toes or preaxial polydactyly or duplication of part of a digit occurs (4,7,89).

Eyes. Absent lacrimal punctas, usually bilateral and noted in approximately 90%, are associated with tearing, blepharitis, dacryocystitis, keratoconjunctivitis, and pannus with photophobia (10,11) (Fig. 21–4C).

Fig. 21–3. *EEC syndrome*. Patient has photophobia, clefting, and sparse hair.



These conditions often cause chronic corneal ulcers and scarring, which result in severe visual impairment. The irides are often blue in white patients as part of the pigment dilution. The number of Meibomian orifices is reduced (54,60,66,88).

Skin, hair, and nails. Pigmentary dilution of the skin and hair has been noted in most white patients (1,7,12,22,60), but black patients have normal pigmentation. Scalp hair, eyebrows, and lashes are silvery blond, coarse, and dry in 80%. The scalp hair is sparse in approximately 20% and slow growing (12,22,60,79,86). Light microscopic examination has shown the hair to be normal (60). Nails are dysplastic in 80% (7,11,38,71,78,86). They are also slow growing and transversely ridged or pitted. Absence or sparse sebaceous glands have been observed on skin biopsy (60,66,88). Approximately 12% have many pigmented nevi (12,22,41,60,66), and widespread comedone nevi have been described (45). Opitz (58) described a large kindred with clefting and ectrodactyly but no ectodermal defects as in the ECP (ectrodactyly-cleft palate) syndrome. Hypohidrosis is rare (10%). In one patient, the scalp was ulcerated as seen in *Hay-Wells syndrome* (82).

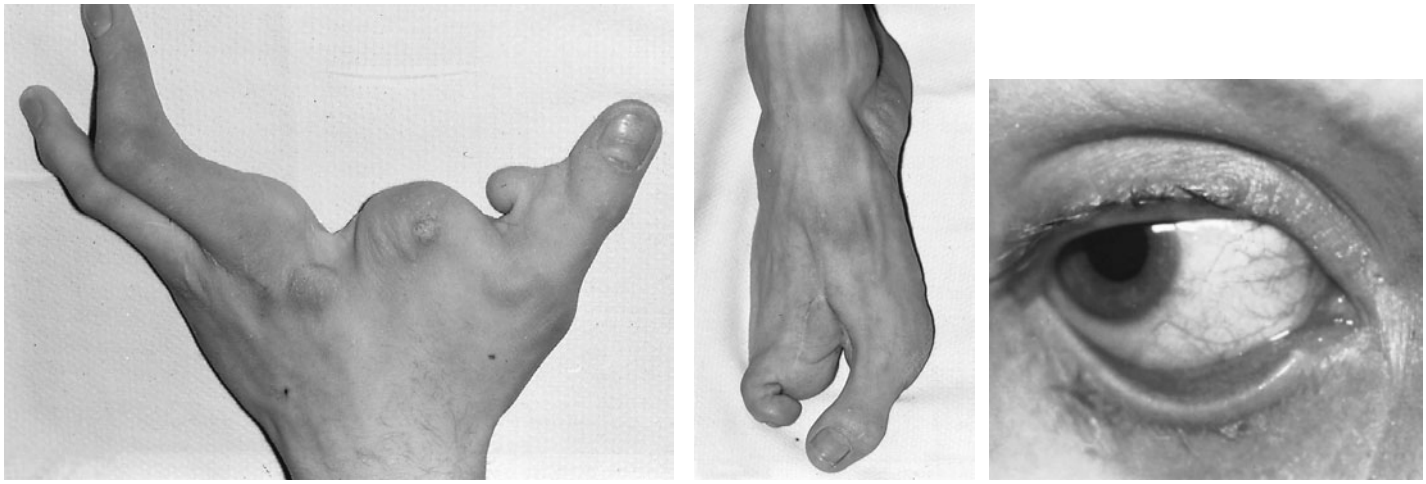
Central nervous system. Microcephaly and mental retardation have been reported in approximately 10% (1,6,7,22,60,79) but there may have been ascertainment bias. Growth hormone deficiency has been noted (40).

Genitourinary system. Kidney and ureter malformations (duplication of the kidney, collecting system and ureter, absent kidney, recurrent urinary tract infections, small dysplastic kidney, hydronephrosis, and hydroureter) have been described in at least 45% (3,8,34,38,74,86,88,96) as has hypospadias (11,55). Cryptorchidism (3,30), prune belly (34), and anal atresia (18,50) have been documented. One form may be related to having a thin atrophic bladder (48).

Endocrine system. Hypogonadotrophic hypogonadism has been reported (25,94) as well as growth hormone deficiency (40). Thymic aplasia has been described (36).

Otolaryngologic manifestations. Conductive hearing loss has been reported in approximately 30% (11,12,38,46,64,66,70,86,90). Absence of the stapes and part of the incus was found in one patient (12). Breathy voice has been observed in some patients (63). Choanal atresia has also been noted (14,91). Non-Hodgkin lymphoma was diagnosed from peritonsillar masses (56a).

Oral manifestations. Cleft lip-palate, bilateral in approximately one-half the cases, is described in 60%–75% (7,12,16,22,38,45,60,64,79,



A B C

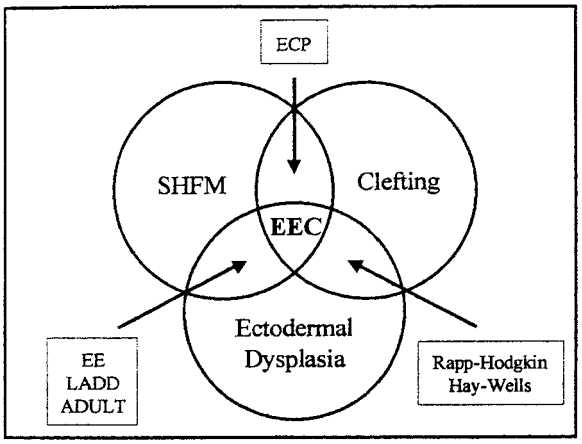
Fig. 21–4. *EEC syndrome*. (A,B) Ectrodactyly of hands and feet. (C) Absence of lacrimal point.

86,88). In possibly 10%, cleft palate without cleft lip is noted (11,63,64). Clefting is absent in other patients (15,22,49,62,65,97). Congenitally missing permanent teeth and teeth with coniform crowns (45) are common and, rarely, may be the only manifestation of the syndrome (15). The deciduous teeth are usually normal in number (68) but rarely the maxillary deciduous first molars are missing (62). Taurodontism has been noted (11). Xerostomia and enamel dysplasia may contribute to high dental caries rate. Parotid duct atresia has been documented (60,66). A deep anteroposterior furrow in the midline of the dorsum of the tongue has also been described along with candidal cheilitis and candidal perleche (60,66).

Differential diagnosis. Ectrodactyly is most commonly an isolated finding. At least three genes (100) have been mapped for isolated ectrodactyly, the most common being a deletion at 7q21.3 (33,51,72,73), but others have been located at 10q24 (26), Xq26 (27), and 3q27.

The number of ectrodactyly syndromes is legion: Wildervanck (99) described two sibs with severe sensorineural hearing impairment and ectrodactyly of the hands and feet, born to presumably normal parents; no other abnormalities were recorded. The *Patterson-Stevenson-Fontaine syndrome* (61) is characterized by ectrodactyly of the feet and craniofacial findings reminiscent of *mandibulofacial dysostosis*. Reed et al (71) described a mother and daughter with ectrodactyly, lacrimal duct obstruction, early graying of hair with pili torti, subtotal alopecia, and atrophic pigmented macules on the extensor surfaces of the body. Propping and Zerres (67) suggested an *ADULT syndrome* composed of autosomal dominant inheritance of ectrodactyly, pigment anomalies, nail dysplasia, and hypodontia. No clefting was evident. *Cleft lip-palate, hypohidrosis, thin, wiry hair, and dystrophic nails (Rapp-Hodgkin syndrome)* (84), when combined with ankyloblepharon filiform adnatum, is called *Hay-Wells syndrome*. Both (if they are indeed separate disorders) have autosomal dominant inheritance. Some authors have suggested that there is identity among these two and EEC syndrome (53) (Fig. 21–5). We suspect that some examples are EEC syndrome without ectrodactly. We also suggest that *Bowen-Armstrong syndrome* (8) *is Hay-Wells syndrome*. The *odontotrichomelic syndrome (cleft lip-palate, tetraperomelia, deformed pinnas, and ectodermal dysplasia)* (13) appears to have autosomal recessive inheritance. Patients with *craniosynostosis, severe asymmetrically malformed extremities, and cleft lip-palate (Herrmann syndrome)* resemble those with EEC syndrome. Stewart et al (83) reported cleft lip-palate with ectrodactyly and hypomelanosis of Ito which indicates mosaicism. Ohdo et al (57) reported a kindred with ectrodactyly, syndactyly, sparse thin hair, and macular dystrophy; inheritance was autosomal recessive. There is overlap with of EEC syndrome with *LADD syndrome* with which it may be identical (31,43). Ohdo et al (57) described the EEM syndrome, an autosomal recessive disorder consisting of sparse hair. ectrodactyly, and macular dystrophy. Differential diagnosis of many of these conditions has been extremely well discussed by Rodini and Richieri-Costa (74). Additional ectrodactyly syndromes has been reviewed by Schroer (81) and Buss (11). One must exclude the autosomal recessive syndrome of *cleft lip/palate, cardiac anomalies, genital anomalies and ectrodactyly*.

Fig. 21–5. *EEC syndrome*. Relationship among EEC and overlapping conditions. (From D Everman, 2001.)



The limb-mammary syndrome, an autosomal dominant syndrome mapping to 3q27, is characterized by hypoplasia of the mammary gland and nipple, variable ectrodactyly, lacrimal duct atresia, nail dysplasia, hypohidrosis, hypodontia, and cleft palate (92).

Lacrimal duct obstruction occurs in 1%–2% of the general childhood population, it has been found in approximately 10% of patients with isolated cleft lip-palate. Hoyme et al (32) described autosomal dominant ectrodactyly and absence of long bones of upper and lower extremities. Oğur and Yüksel (56) described two male sibs, the product of a consanguineous union, with tetramelic syndactyly, ectodermal dysplasia, cleft lip and palate, renal anomalies, and mental retardation. Atkin and Patil (5) reported a male infant and his maternal uncle with microphthalmia, cloudy corneae, and a CNS anomaly. The infant also had ectrodactyly, cleft lip, brain cyst, renal anomaly, hypospadias, and cryptorchidism. Conditions such as *de Lange syndrome, focal dermal hypoplasia*, and various ectodermal dysplasias with clefting by Fosko et al (20) can easily be excluded. Jones et al (37) reported ectrodactyly with aplasia cutis congenita, cleft palate and epidermolysis bullosa. Kasznicka et al (39) described ectrodactyly with abnormal pinnae and congenital

heart anomaly. Landy and Donnai (44) noted ectrodactyly with duplication of halluces, and hydrops. Van den Ende (93) reported ectrodactyly, congenital heart anomalies, and unusual facies. Viljoen and Smart (95) and Suthers and Morris (85) described ectrodactyly, microphthalmia, cleft palate, and mental retardation.

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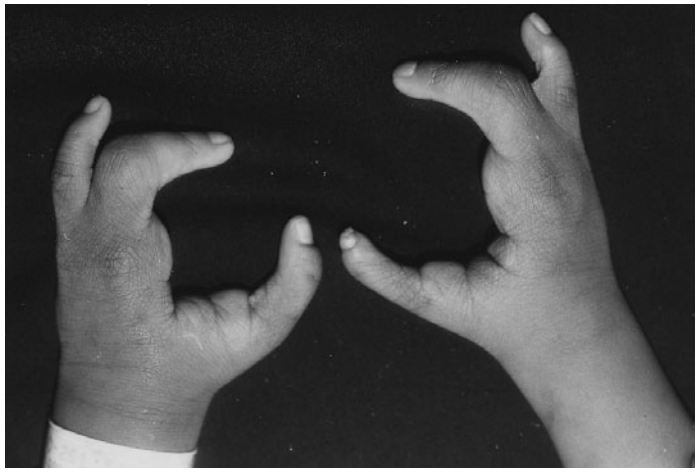
Fig. 21–6. *ECP syndrome*. (A) Ectrodactyly of the hands. (B) Ectrodactyly of the feet. (Courtesy of JM Opitz, Helena, Montana.)



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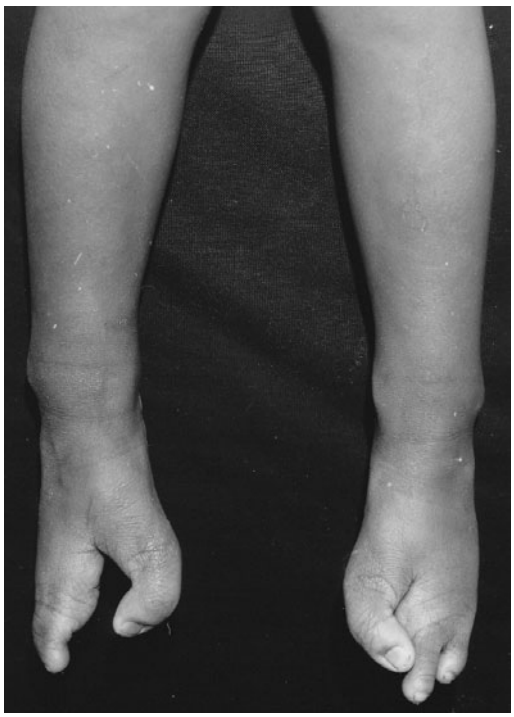

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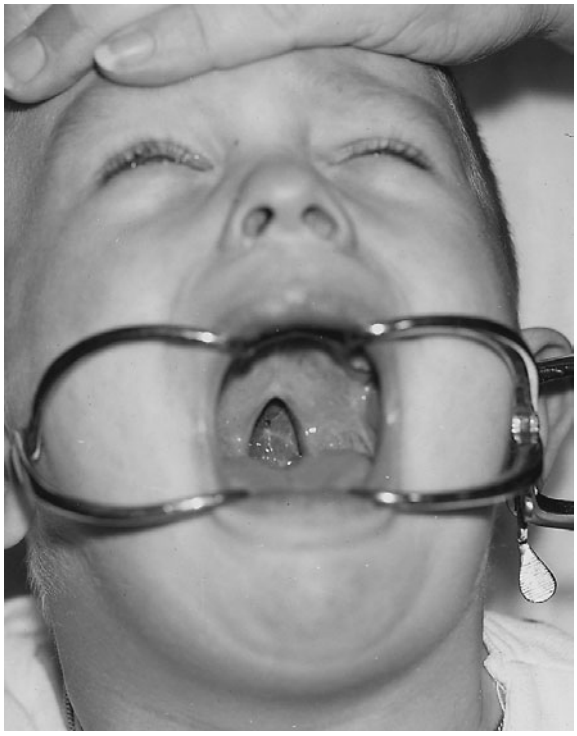

Fig. 21–7. *ECP syndrome*. Cleft palate. (From JM Opitz et al, Eur J Pediatr 133:217, 1980.)

ECP syndrome (ectrodactyly-cleft palate syndrome)

In 1980, Opitz et al (2) reported an autosomal dominantly inherited syndrome of cleft palate and ectrodactyly involving the hands and feet in a large five-generation pedigree (Figs. 21–6 and 21–7). Features of the *EEC syndrome* such as cleft lip, hypotrichosis, nail dysplasia, and defects of the lacrimal canal were not observed. Other less common manifestations of the EEC syndrome such as mental retardation, microcephaly, conductive hearing loss, renal anomalies, and cryptorchidism were also not observed. The ECP syndrome is, in addition, distinct from *Patterson-Stevenson-Fontaine syndrome* consisting of ectrodactyly of the feet, micrognathia, submucous cleft palate, dysplastic ears, mental deficiency in some instances, and autosomal dominant inheritance (1). This must be differentiated from *acro-cardio-facial syndrome*.

References [ECP syndrome (ectrodactyly-cleft palate syndrome)]

1. Fontaine G et al: Une observation familiale du syndrome ectrodactylie et dysostose mandibulofaciale. J Genet Hum 22:289–307, 1974.
2. Opitz JM et al: The ECP syndrome, another autosomal dominant cause of monodactylous ectrodactyly. Eur J Pediatr 133:217–220, 1980.

Ectrodactyly of the feet and cleft palate (Patterson-Stevenson-Fontaine syndrome)

Patterson and Stevenson (2) in 1964 and Fontaine et al (1) in 1974 described an acrofacial dysostosis characterized by cleft palate, unusual pinnae, sensorineural hearing loss and variable oligosyndactyly of the feet. Another case from the Patterson-Stevenson family was added by Willkie and Goodacre (3).

In the kindred described by Fontaine et al (1), one of four exhibited moderate mental retardation and seizures whereas two had mild retardation. Microretrognathia has been evident in all.

Autosomal dominant inheritance is evident with variable penetrance and expression (1–3). One must exclude the *EEC syndrome*.

References [Ectrodactyly of the feet and cleft palate (Patterson-Stevenson-Fontaine syndrome)]

1. Fontaine G et al: Une observation familiale du syndrome ectrodactylie et dysostose mandibulo-faciale. J Genet Hum 22:289–307, 1974.
2. Patterson TJS, Stevenson AC: Craniofacial dysostosis and malformations of the feet. J Med Genet 1:112–114, 1964.
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Cleft lip/palate, cardiac anomalies, genital anomalies, and ectrodactyly (acro-cardio-facial syndrome)

Richieri-Costa and Orquizas (3) reported a male with ectrodactyly, cleft lip/palate, VSD, micropenis, and mental retardation. Giannotti et al (1) described male and female sibs with low birthweight, cleft palate, ASD, VSD, coarctation of aorta, cryptorchidism, cleft hand, and mental retardation. They may have the same syndrome. Another example is that of Guion-Almeida et al (2).

Inheritance is probably autosomal recessive.

References [Cleft lip/palate, cardiac anomalies, genital anomalies, and ectrodactyly (acro-cardio-facial syndrome)]

1. Giannotti A et al: An autosomal recessive syndrome of cleft palate, cardiac defect, genital anomalies, and ectrodactyly (CCGE). J Med Genet 32:72–74, 1995.
2. Guion-Almeida ML et al: Cleft lip/palate, abnormal ears, ectrodactyly, congenital heart defect, and growth retardation. Definition of the acro-cardio-facial syndrome. Clin Dysmorphol 9:269–272, 2000.
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Cleft lip/palate, ectodermal dysplasia with [Hay-Wells (AEC) syndrome] or without [Rapp-Hodgkin syndrome] ankyloblepharon filiforme

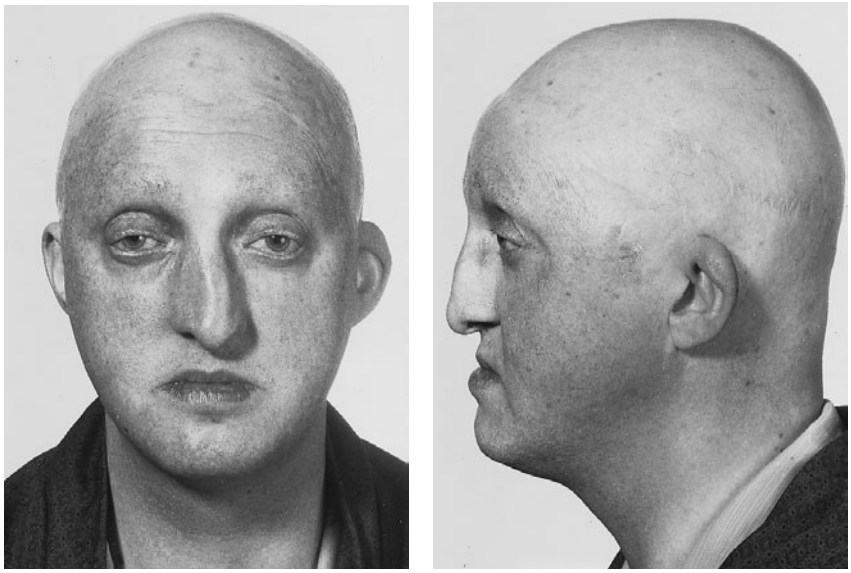
In 1976, Hay and Wells (16) described seven patients from four families with autosomal dominant inheritance of congenital ankyloblepharon, principally involving the lateral lid margins, atresia of the lacrimal ducts or absence of lacrimal punctae, absent or dystrophic nails, coarse wiry sparse hair, pili torti, scalp infections, sparse to absent eyelashes, cleft palate, cleft lip, deficient teeth and teeth with conical crown form, maxillary hypoplasia, and mild hypohidrosis (Figs. 21–8 and 21–9). Numerous additional examples with ankyloblepharon have been published (13–15, 20,22,29,31,33,35).

The syndrome described by Rapp and Hodgkin (23) in 1968 consists of cleft lip and/or palate, sparse hair, small mouth, and hypospadias in males. Several other families (3,5,7,9,10,14–21,25,27,28,30,34,36,37,40,41), and isolated examples (11,12,18,19) have been described (Figs. 21–10 and 21–11). The condition reported by Bonafé et al (4) probably represents this syndrome.

Missense mutations have been found in the SAM protein-protein interaction domain of the *p63* gene on 3q27 (19a). A family seen by R. Gorlin maps to a 3′ splice site exon located between the DNA binding site and the SAM. This family greatly resembled that of Hay and Wells (16).

We do not believe that the former group is clearly separable from so-called *Rapp-Hodgkin syndrome*. Clinical findings in both groups of patients are roughly comparable (8). Only ankyloblepharon filiforme separates them. Autosomal dominant inheritance with variable expressivity is evident (25), but there may be genetic heterogeneity. We await molecular evidence. There have been a few cases of affected sibs with presumably normal parents (7,21,32,41).

Clinical findings. Stature, although often cited as short, has seldom been documented (37,40).



A B

Fig. 21–8. *Hay-Wells syndrome*. (A,B) Frontal and lateral facial views of 38-year-old male patient showing lack of scalp hair, eyebrows, and lashes, midfacial hypoplasia, dysmorphic left pinna. Patient has cleft palate. (From RJ Hay and RS Wells, Br J Dermatol 94:277, 1976.)

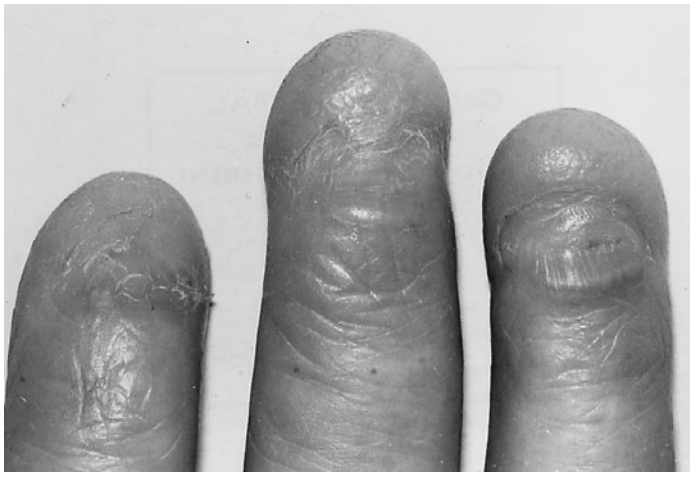
Craniofacial findings. High forehead, midface hypoplasia, narrow nose, short philtrum, thin vermilion, and small mouth characterize the face. There is midfacial hypoplasia (15). Approximately 50% have cleft lip and palate and 50% have cleft palate. The teeth are usually deficient in number, and the incisors have conical crown form (12). Ear canals may be atretic (12,27,35,37).

Skin. Scalp and body hair is generally sparse as are eyebrows and eyelashes. The hair is generally slow growing, blond, and wiry. However, it may be abundant and uncombable (36). Microscopic study reveals pili torti and/or pili canaliculi (34). Nails are typically narrow, dystrophic, and brittle. There is hypohidrosis but never to the degree seen in hypohidrotic ectodermal dysplasia (10,27,30). There are reduced numbers of sweat pores (10). Scalp dermatitis, especially in infants, is seen in 15%–50% (10%) and appears to be more common in those with ankyloblepharon. Mild 3–4 syndactyly has been described (12). The breasts may not develop in females (38).

The hair is triangular or ellipsoidal in cross-section. SEM has demonstrated canal-like grooves along the axis (5,7,12,27,32) (Fig. 21–12).

Ocular system. Approximately 30% have ankyloblepharon filiforme. These patients have been classified as having Hay-Wells (AEC) syndrome. Agenesis or atresia of lacrimal punctae has been noted (3,12,14,16,23,30,35–37,40), resulting in blepharitis and photophobia.

Fig. 21–9. *Hay-Wells syndrome*. Congenitally absent fingernails. (From RJ Hay and RS Wells, Br J Dermatol 94:277, 1976.)



Genitourinary system. Hypospadias has been noted in most males (4,7,12,23,37,39).

Other. Thymic aplasia has been noted (6).

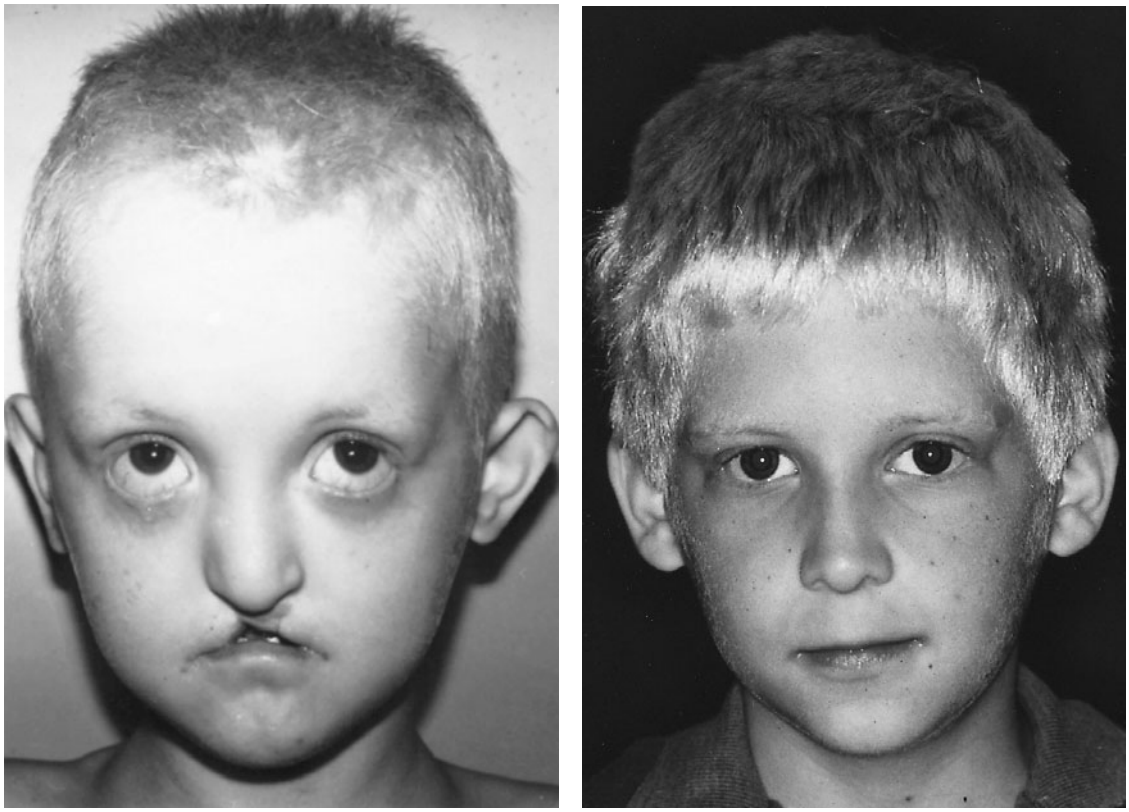
Diagnosis. Ankyloblepharon may be a dominantly inherited isolated finding, or found in binary combination with cleft lip and/or cleft palate in *popliteal pterygium syndrome*, in *van der Woude syndrome*, and in CHANDS (curly hair and nail dysplasia) and with trisomy 18 (2).

Seres-Santamaria et al (31) reported male and female sibs with coarse wiry hair, ankyloblepharon, cleft palate, dystrophic nails, soft tissue syngnathia, and pits of the lower lip. This bridges *van der Woude syndrome*.

Rosselli and Gulienetti (26) described what is probably a unique syndrome. Their cases 2 and 3 had wooly hair, cleft lip and palate, dystrophic nails, subungual keratoses, dystrophic facial skin, a papulofollicular dermatosis of the trunk, and hypoplasia or aplasia of the thumbs and popliteal pterygia.

Abramovits-Ackerman et al (1), in 1992, reported 20 patients from 7 families with an autosomal recessive syndrome of pili torti, scalp follicular plugging, scalp keloids (15%), keratosis pilaris, xerosis, eczema, palmoplantar keratoderma, mild syndactyly of fingers (65%), nail dysplasia, typical facies (unfortunately not illustrated), anteverted pinnae (75%), malar hypoplasia, and cleft lip/palate (35%). They stated that dental anomalies were found in all patients, but they were neither illustrated nor described.

There is probably etiologic heterogeneity and molecular studies should solve this dilemma. Some studies may represent the EEC syndrome without ectrodactyly that maps to 7q21.21. Watson and Hardwick (41) described a girl with bilateral cleft lip-palate, hypoplastic pinnae, total anodontia, and dystrophic nails. A sib who died soon after birth had cleft lip-palate and congenital heart anomalies. The mother and a sister exhibited oligodontia. The parents were consanguineous. Shelley and Shelley (32) described sibs with uncombable sparse blond hair, scarring alopecia of the scalp at the occiput, absence of tears, sparse eyelashes, cup-shaped pinnae, dysplastic ridged nails, and short palate with bifid uvula or cleft palate. The nose was narrow. The incisors were anomalous. One sib had clubfoot and another mesodermal dysgenesis of the anterior segment of both eyes. Their father had syndactyly of the right index and middle fingers without a nail on the middle finger. The child described by Crawford et al (10) had hypoplastic nasal alae, absent lacrimal



A B

Fig. 21–10. *Rapp-Hodgkin syndrome*. (A) Sparse wiry hair, absent lashes and lacrimal puncta, ectropion of lower lids, hypoplasia of nasal alae, abnormal pinnae, bilateral cleft lip-palate. (B) Boy has cleft palate and blond, wiry hair. [A from RL Summitt and RL Hiatt, Birth Defects 7(8):121, 1971. B courtesy of C Salinas, Charleston, South Carolina.]

puncta, epiphora, photophobia, cleft soft palate, sparse eyebrows, coarse kinky scalp hair, dysplastic nails, reduced sweat pores, hypoplastic dermal ridges, and oligodontia. Moynahan (21) reported sibs with what he called XTE (*X*eroderma, *T*alipes, and *E*namel defect) syndrome. The parents were consanguineous. The syndrome consisted of cleft palate, hypohidrosis, dry skin, dry coarse hair, nail deformities, evanescent cutaneous bullae, absence of eyelashes, small lacrimal puncta, talipes, and defective enamel. We believe that these patients can be classified in this group.

It is interesting to note that the mother in one family had the syndrome although her child appeared to have EEC syndrome (20). Filiform adhesions were found between the eyelids. There is obvious overlap with the disorder reported by Zlotogora et al (43), but mental retardation was found. We are not convinced that the condition described by Richieri-Costa et al (24) is different from the syndrome in spite of alleged autosomal recessive inheritance. Mild syndactyly (2–3 and 3–4) was evident. We, too, believe that *Bowen-Armstrong syndrome* is the same as Hay-Wells (AEC) syndrome (42). Hay-Wells syndrome and CHAND syndrome seem to overlap as does limb-mammary syndrome.

References [Cleft lip/palate, ectodermal dysplasia with (Hay-Wells [AEC] syndrome) or without (Rapp-Hodgkin syndrome) ankyloblepharon filiforme]

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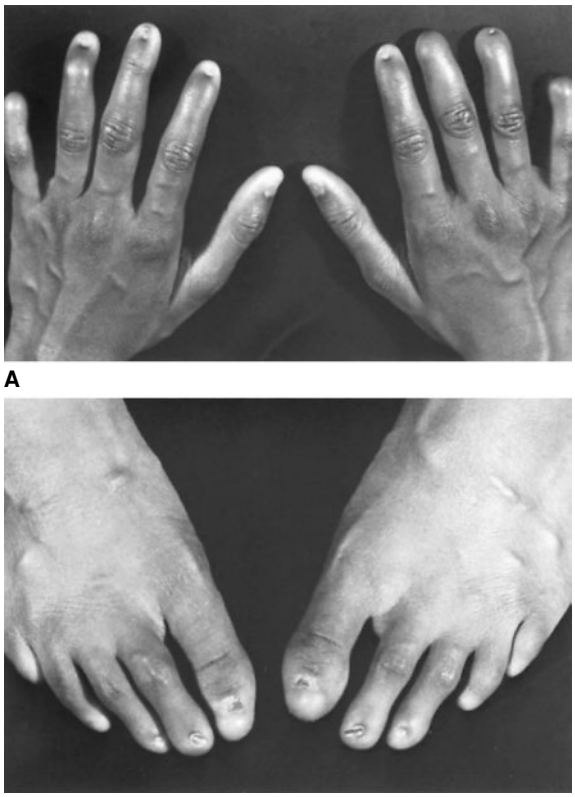

A

B

Fig. 21–11. Rapp-Hodgkin syndrome. (A,B) Hypoplastic nails of fingers and toes. (From RM Watson and CE Hardwick, Br Dent J 130:77, 1971.)

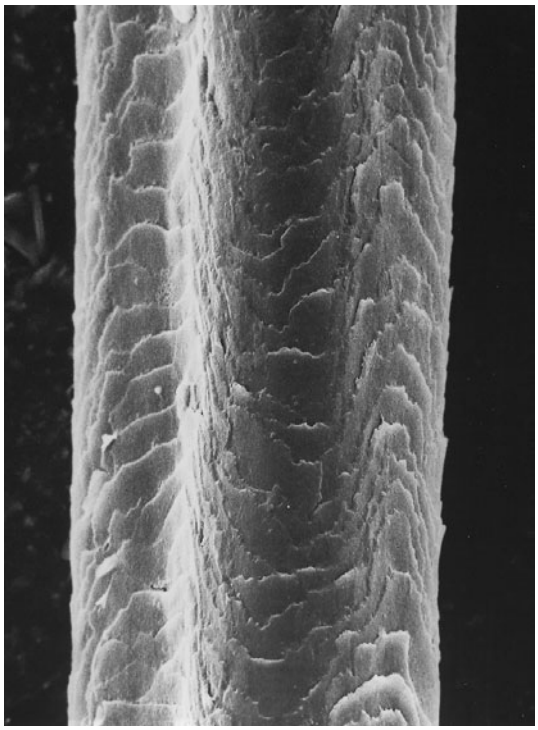

Fig. 21–12. *Rapp-Hodgkin syndrome*. SEM of hair showing characteristic grooving.

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Bowen-Armstrong syndrome (cleft lip-palate, ectodermal dysplasia, and mental retardation)

Bowen and Armstrong (1) described three female sibs with mild to moderate mental retardation, ectodermal dysplasia, and cleft lip and/or palate. It is uncertain whether these children had incomplete expression of the *EEC syndrome*, had the *AEC (Hay-Wells) syndrome*, or represented a unique disorder (2).

The hair was sparse and fair, with the brows and lashes absent (Fig. 21–13A). One child had congenital skin defects on the buttocks (Fig. 21–13B). Mottled brown pigmentation subsequently appeared on

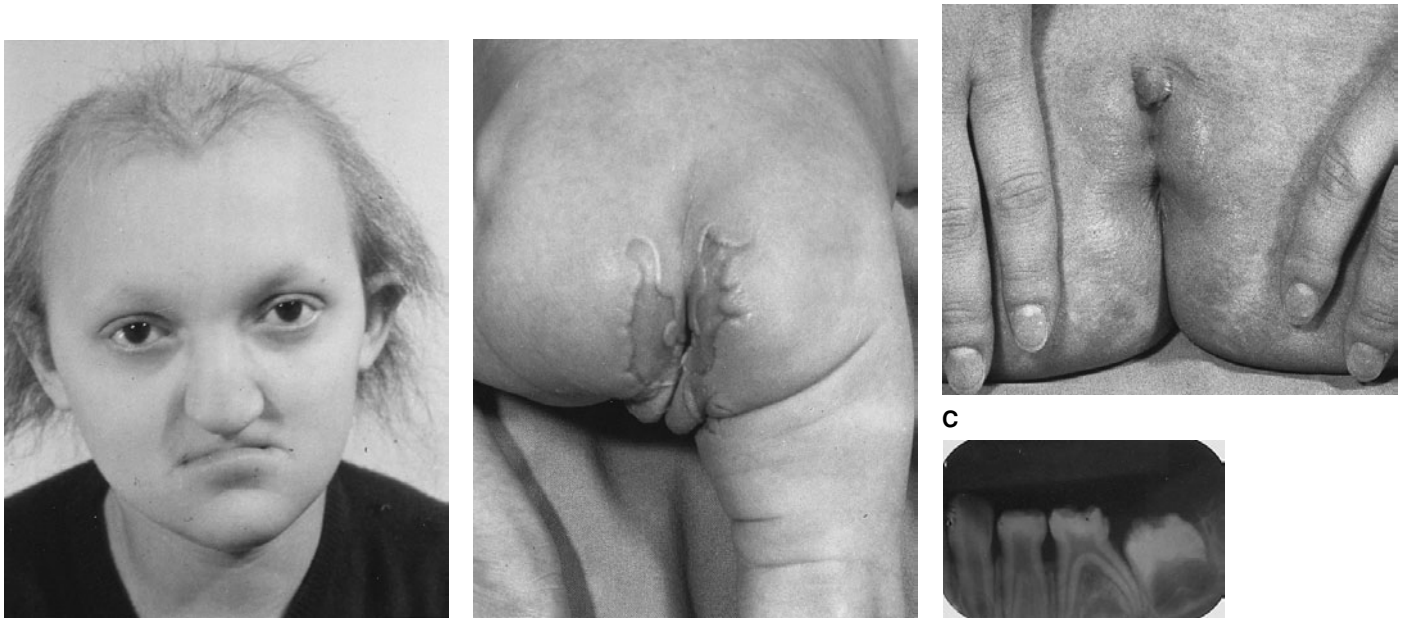

Fig. 21–13. *Bowen-Armstrong syndrome*. (A) Note unusual facies, wiry, scaly hair, sparse eyebrows and lashes. (B) Congenital skin defects on buttocks. (C) Absence of labia and vaginal introitus and mottled pigmentation of area. (D) Thin dysplastic enamel. (From P Bowen and HB Armstrong, Clin Genet 9:35, 1976.)

the genital area, axillae, and buttocks (Fig. 21–13C). Blepharitis and photophobia were present in one child and ankyloblepharon filiforme adnatum in two of the sibs. The extremities exhibited variable soft tissue syndactyly of the feet. There was some degree of bony syndactyly. The nails were somewhat hypoplastic. Genital anomalies included hypoplasia of the labia minora with absence of vaginal opening. Dental abnormalities were absence of primary and secondary maxillary incisors and canines and enamel hypoplasia (Fig. 21–13D).

References [Bowen-Armstrong syndrome (cleft lip-palate, ectodermal dysplasia, and mental retardation)]

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Filiform adhesions of the eyelids and cleft lip-palate

The association of cleft lip with or without cleft palate and congenital filiform fusion of the eyelids (ankyloblepharon filiforme adnatum) appears to be inherited as an autosomal dominant trait with extremely variable expressivity (1–23). In several families, there were relatives with facial clefting but no eyelid anomalies (6,12,14,20,21). There has been one association with isolated cleft palate (5). The disorder may be more common in India. Syngnathia was noted in two patients (16,22).

Multiple connective tissue bands, 0.3 to 5.0 mm in width, extend from the white line of one lid to that of the other lid, posterior to the cilia and anterior to the meibomian orifices (Fig. 21–14). No associated anomalies are found in the eyeballs. The filiform adhesions may be an isolated finding or in combination with the *cleft lip-palate and paramedian lower lip pits*, in the *popliteal pterygium syndrome* and in the *Hay-Wells (AEC) syndrome*. They have been found in patients with trisomy 18 (3,7) and in CHANDS, an autosomal recessive disorder of curly hair, ankyloblepharon, nail dysplasia, and ataxia (4). Associated anomalies that appear to be aleatory are spina bifida, superior adherence of pinna, and syndactyly of fourth and fifth toes. Imperforate anus has been described in several patients. (2,5,10,11).

The orofacial findings have been attributed to defects in inductive influences or terminal differentiation in cephalic neural crest cells (23).

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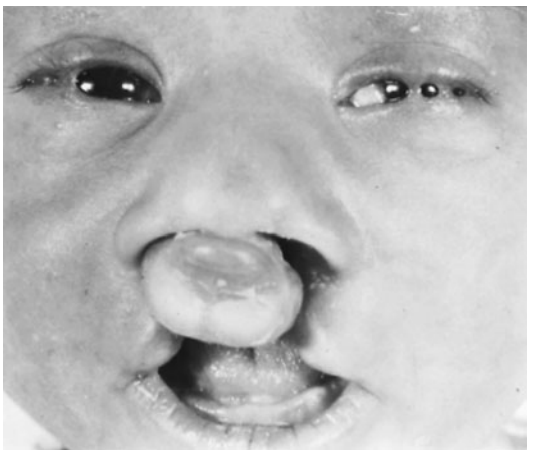
Fig. 21–14. *Filiform adhesions of the eyelids and cleft lip-palate*. Note bilateral involvement of eyes and lip. (From JC Long and SE Blandford, Am J Ophthalmol 53:126, 1962.)



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Larsen syndrome

Recognized as an entity in 1950 by Larsen et al (25), the syndrome consists of flattened facies, multiple congenital joint dislocations, clubfoot deformities, and, frequently, cleft palate. Earlier cases date back to Drehmann (10) and many others (21,33,34,49). Among the Buang of New Guinea, there are examples (31). At least 150 patients have been reported to date. The frequency has been estimated to be approximately 1 per 100,000 births (2).

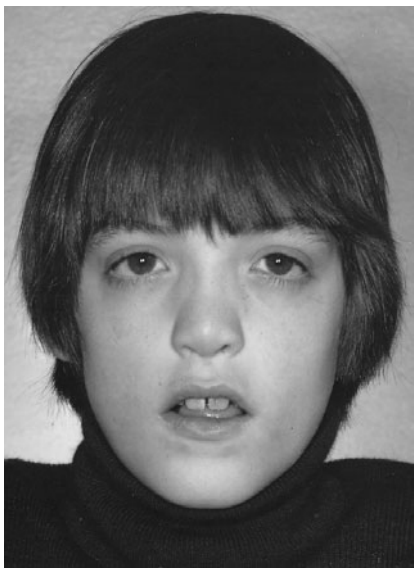
The syndrome is heterogeneous. Examples of Larsen syndrome have been reported in affected sibs with normal parents (3,5,38,44,49,59), but many more have been found in two or more generations (12,14,26, 34,40,46,47,51,56,60,62). Differentiation of the autosomal recessive form from the autosomal dominant form is not possible in the individual case. In general, among "recessive cases," increased parental consanguinity has not been found (13) with rare exception (23), although a recessive form has been seen with high frequency (38 cases) in the island of La Réunion in the Indian Ocean (4,27). Fourteen of the 38 patients died in childhood from dislocation of the cervical spine, tracheomalacia, congenital heart disease, or severe respiratory infections. All were short (−5 SD). Larsen syndrome has been shown not to be a collagen disorder (4). Petrella et al (42) reported what appeared to be sibs with the recessive form. One of them subsequently had an affected child, thus raising the possibility of gonadal mosaicism. Strisciuglio et al (55) suggested that the recessive form is more often associated with cardiac and respiratory complications than the dominant form, but this has never been confirmed. Short stature was also emphasized by Topley et al (59) in the recessive form. Le Marec et al (29) opined that cervical malformations were more common in the recessive form.

The gene for the dominant form has been mapped to 3p21.1–p14.1 (63).

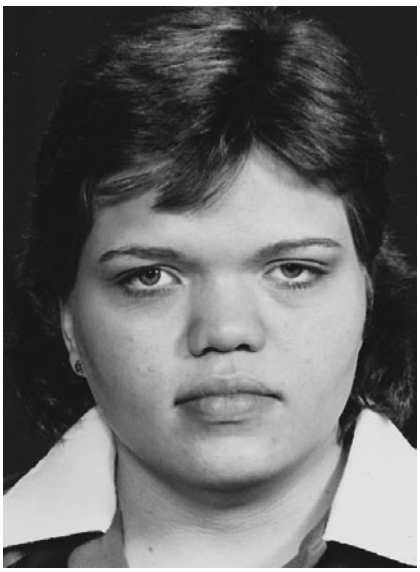
Facies. The facies is typically flattened and there is depressed nasal bridge. The eyes appear widely spaced. Frontal bossing may be marked (Figs. 21–15 and 21–16A).

Skeletal system. Bony alterations include bilateral anterior dislocation of the radial head (70%), bilateral anterior dislocation of the tibia on the femur (80%), hip dislocation (80%), and talipes equinovarus or equinovalgus (85%). The patella is often dislocated laterally. Joint dislocations become less frequent with age. Adult height is reduced, the patient usually being less than 152 cm tall (Fig. 21–16). The fingers are long and cylindric (pseudoclubbing) with extra creases in approximately 75% (Fig. 21–17). The thumb is spatulate. Mild thoracolumbar scoliosis is absent at birth but becomes evident during infancy (11,12,21,24,26,28,34,45,52,60). Pectus excavatum is present in 10% (9).

Radiographic changes include dislocations, as previously noted. The distal phalanges are abbreviated. The metacarpals and metatarsals are relatively shortened. Bone age is retarded. When the carpal bones appear, they are irregular. There are from one to four supernumerary carpal bones in 75% (Fig. 21–18A). Abnormal segmentation and/or hypoplasia of

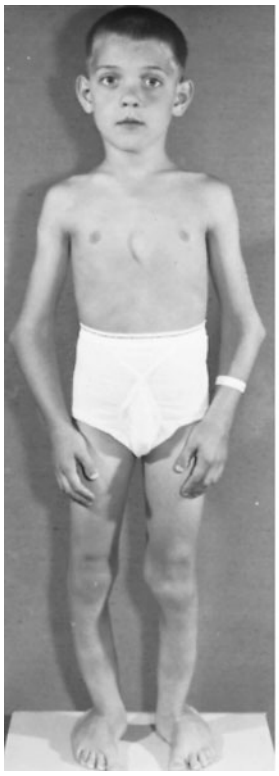


A



B

Fig. 21–15. *Larsen syndrome*. (A,B) Flattened midface with broad nasal bridge in male and female patients.



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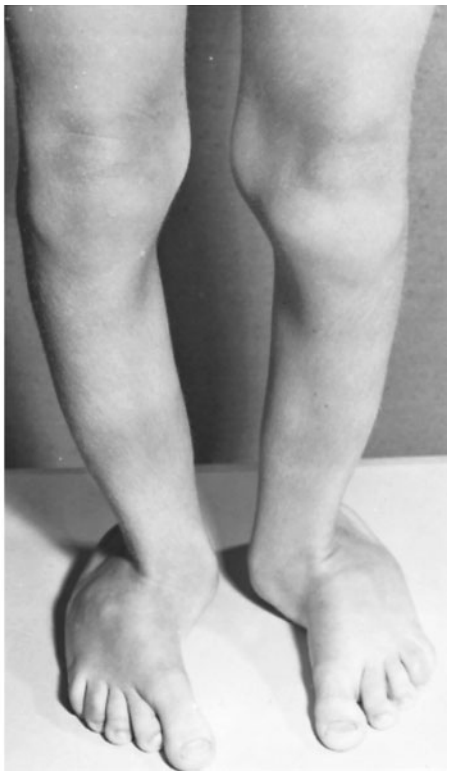


B

Fig. 21–16. *Larsen syndrome*. (A,B) Note similar facies, subluxation of radial heads, sternal anomaly, dislocated knees, "windmill" feet, spatulate thumbs.

cervical and thoracic vertebrae are common (2,12,21,24–26,29,35,36,40, 52,56,58,60). This may be associated with marked cervical kyphosis (19,58). In some cases, cervical vertebral instability has led to quadriplegia or death (35,39). The vertebral bodies may be flattened (24,26,56). A juxtacalcaneal accessory bone is present within the first four years of life in approximately 40% (25,48,56). It coalesces with the calcaneus by 5–8 years of age forming a bifid calcaneus that is evident in lateral view (Fig. 21–18B). Additional centers of ossification may be seen at the elbow (13,19,39,49,54). The proximal tibial epiphysis is often cone-shaped during development. Approximately 60% of the La Réunion group exhibited proximal radioulnar synostosis (27).

Cardiovascular anomalies. ASD and VSD as well as aortic dilatation and valvular anomalies are seen in approximately 10% (9,22,33, 45,55,57).

Central nervous system. Mental retardation has been noted in approximately 15% (9,47). Sensorineural, mixed, and conduction hearing loss has been described in 20% (16,44,50,62), the last because of deformity or dislocation of the malleus, incus, or stapes footplate (18,20,30).

Oral manifestations. Oral changes are essentially limited to cleft palate, which occurs in approximately 30% (9,54). This may be limited to the soft palate or uvula. Some patients have laryngotracheomalacia (11,26,46). Collapse of the flabby laryngeal cartilages may lead to death. Others may have laryngeal stenosis (8,17,58). Cephalometric study has been reported (61).

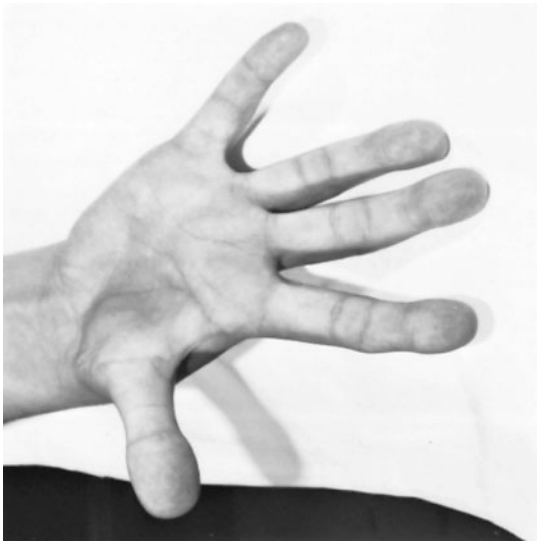
Differential diagnosis. *Otopalatodigital syndrome* is most often mistaken for Larsen syndrome. In contrast, these patients exhibit a pugilistic facies, hearing loss, paddle-shaped metatarsal bones, no juxtacalcaneal bone, and no supernumerary carpal bones. Differential diagnosis also includes arthrogryposis, *fetal akinesia sequence, monosomy 21, Ehlers-Danlos syndrome, types VII and XI, COFS syndrome, cleft palate, short stature, depressed nasal bridge, and sensorineural hearing loss* (19), *spondyloepimetaphyseal dysplasia, Desbuquois syndrome, SPONASTRIME dysplasia,* and lethal Larsen-like syndrome (6,7,37,64).

Multiple congenital dislocations may occur as an isolated finding (15).

Schröder (48) reported a syndrome in five sibs. There were bizarre pinnae, bilateral luxation of the radius, radiohumeral ankylosis, dislocation of hips, shoulders, and knees, genua valga, and camptodactyly. Matsoukas et al (32) described an autosomal dominantly inherited syndrome of joint dislocations (hips, elbows, wrist), short stature, mental retardation (IQ-65), and various ocular anomalies (myopia, microphthalmia, corneal sclerosis).

Pavone (41) described a patient with multiple dislocations, unusual facies, and decreased production of procollagen.

Fig. 21–17. *Larsen syndrome*. Note extra flexion creases of fingers, spatulate thumb.



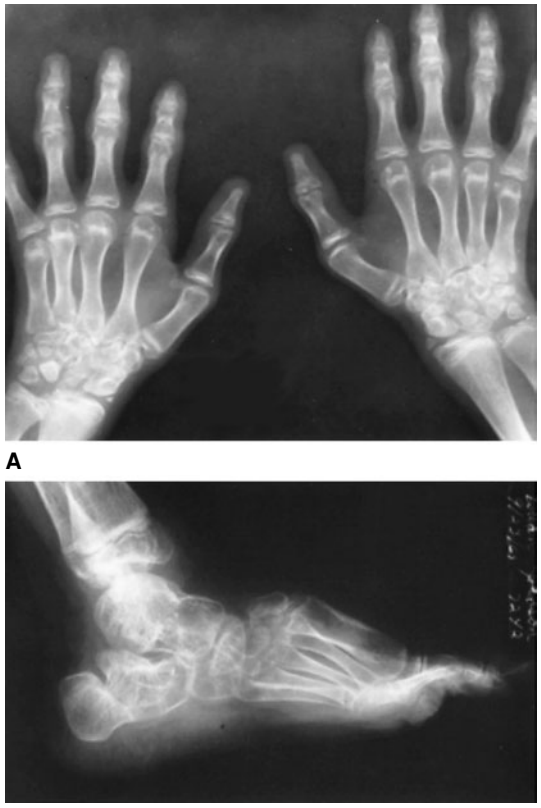


Fig. 21–18. *Larsen syndrome*. (A) The carpal bones, late to appear, are supernumerary. (B) Juxtacalcaneal bone fuses with calcaneus just prior to puberty. Also note unusual relationship of metatarsals to tarsal bones.

Anderson et al (1) reported sibs with what we suspect is SEM dysplasia.

Phoake et al (43) noted a patient with multiple joint dislocations, metaphyseal dysplasia, deficient calcification of the skull vault, growth retardation, natal tooth, lymphedema, and unusual facies. The child died during the neonatal period.

Steel et al (53) reported a syndrome of dislocated hips and radial heads, carpal coalition, scoliosis, cavus feet, and short stature. Three of 23 Puerto Rican patients had an affected sib but inheritance was not clearly recessive.

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Meckel syndrome (Gruber syndrome, dysencephalia splanchnocystica)

Meckel (25), in 1882, delineated a lethal syndrome of microcephaly, encephalocele, microphthalmia, congenital heart defects, postaxial polydactyly, polycystic kidneys, and clefts of the lip and/or palate. The condition has been forgotten, and periodically rediscovered. We refer the reader to several comprehensive historical reviews of cases published prior to 1970 (8,15,24,26,28,31).

Inheritance is autosomal recessive (15,21,42). Parental consanguinity has been noted in approximately 30% of cases. The gene has been mapped to 17q21–q24 (32) in Finnish families. A second gene has been identified at 11q13 in Middle Eastern and African families (40,56). There may be a third gene responsible (33). Nelson et al (29) reported postaxial polydactyly as an expression of the carrier state, but we are dubious. Estimates of frequency in various parts of the world range between 1 in 1500 to 1 in 50,000 births (21,42,44,52,55). In Finland, birth prevalence is 1 in 9000 births (18a). Perhaps 300 cases have been reported to date.

Breech presentation occurs in approximately half of the cases. Oligohydramnios has been noted in over 60%. The thorax is short and bell-shaped and the abdomen bulges. The syndrome is lethal, death usually occurring at birth or in the first few hours of life. The placenta is grossly enlarged in approximately 25%.

It should be emphasized that there is extreme variability from case to case and from affected sib to affected sib (6,10). There appears to be no obligatory feature of the syndrome (19).

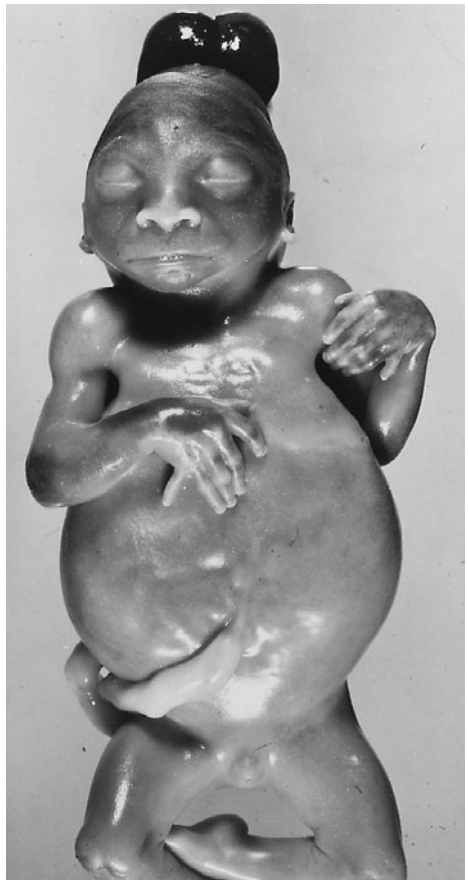
Craniofacial findings. Microcephaly, sloping forehead, sunken eyes, occasional Potter facies, large low-set dysmorphic pinnae, macrostomia, clefting, and micrognathia present a striking appearance (Figs. 21–19 and 21–20).

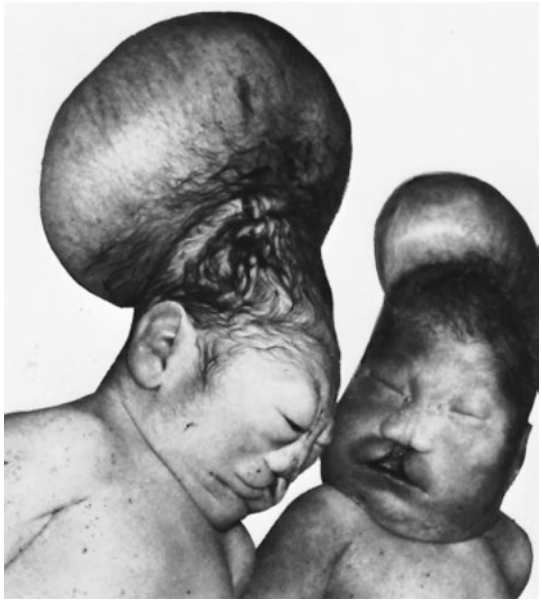
Ocular findings. Various eye anomalies, seen in approximately 30%, include sclerocornea, microcornea, partial aniridia, cataract, anophthalmia, microphthalmia, iris coloboma, retinal dysplasia, and hypoplasia of optic nerves (22,26).

Central nervous system. Microcephaly/anencephaly (50%–65%), absent olfactory bulbs (80%), and double occipital encephalocele (65%–90%) are striking (Figs. 21–19 and 21–20) (50). The larger encephalocele occurs rather high in the occipital bone. The smaller is low in the basal occipital bone resulting in a cleft in the occipital foramen magnum and extending onto the first vertebral arches (cerebellar encephalocele) (34). It is covered by a focal depression of skin. It has been estimated that Meckel syndrome may account for 5% of neural tube defects. Microgyria or polygyria, heterotopias, fusion of frontal lobes, agenesis or hypoplasia of the optic tracts, olfactory lobes, corpus callosum and septum pellucidum, cerebellum and brain stem, Dandy-Walker malformation, neurorosettes, and internal hydrocephalus have been found in 15%–20% (1,14,35,51,53). Cervical rachischisis occurs in approximately 5% (18,27). Craniosynostosis is a rare finding. Hydrocephalus is seen in 10%–20% (50).

Kidney, liver, pancreas, and lungs. Huge cystic and dysplastic kidneys (10–20 times larger than normal) are a constant feature (38). The spherical cysts, ranging in size from 1 to 10 mm, are smallest in the subcapsular area and largest near the renal pelvis. Glomeruli are grossly deficient in numbers, interstitial fibrosis is marked, and the finding of cartilage is frequent (4). The renal pelves, calices, ureters, and urinary bladder are often hypoplastic (2,3,7,12,20,27,37,39,41) (Fig. 21–21). Urethral atresia and/or obstructive uropathy have been described in a few patients (13,41,54).

Fig. 21–19. *Meckel syndrome*. Male fetus at 23 weeks gestation. Note occipital encephalocele, microcephaly, polydactyly, enlarged abdomen due to polycystic kidneys. (From NC Nevin et al, Clin Genet 15:1, 1979.)





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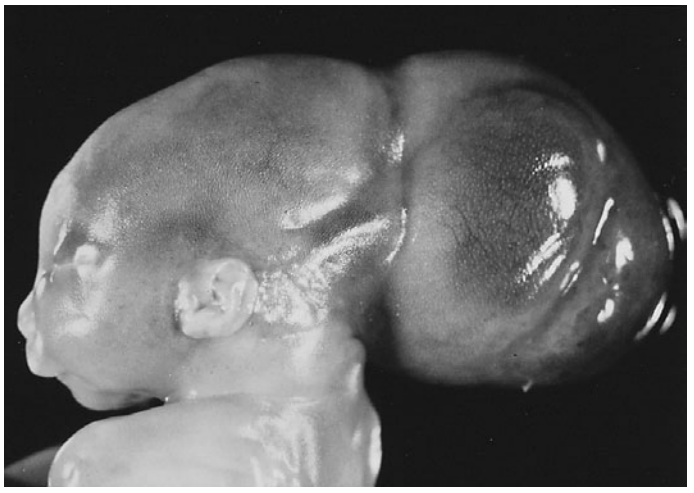
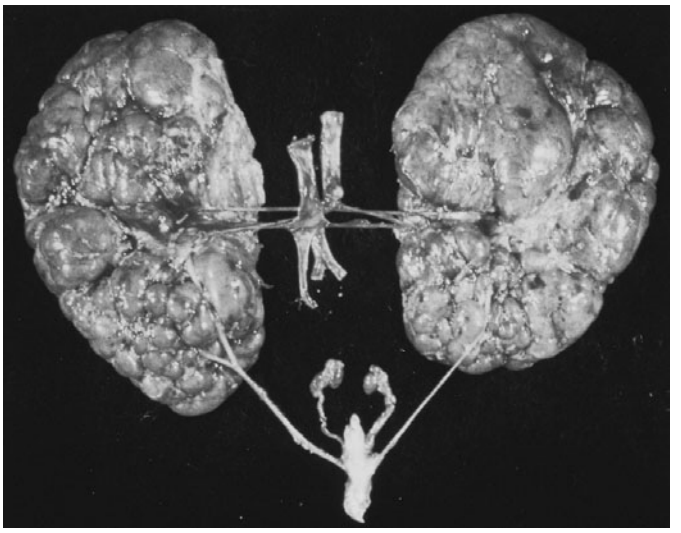


B

Fig. 21–20. *Meckel syndrome*. (A) Microcephaly, occipital exencephalocele, microphthalmia, ocular hypotelorism, premaxillary agenesis in twins. (B) Note microcephaly, occipital encephalocele, dysmorphic pinna. (A from YE Hsia et al, Pediatrics 48:237, 1971.)



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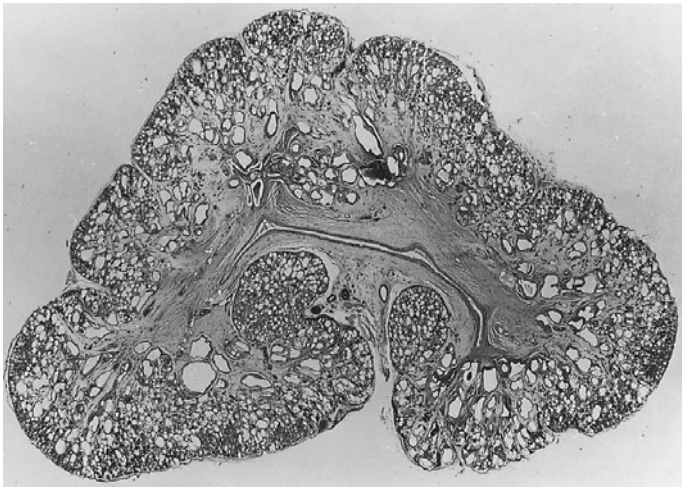


B

Fig. 21–21. *Meckel syndrome*. (A) Huge multicystic dysplastic kidneys. Note tiny ureters and hypoplastic bladder. (B) Multicystic dysplastic kidney. (A from P Moerman et al, Hum Genet 62:240, 1982. B from U Friedrich et al, Clin Genet 15:278, 1979.)

The liver exhibits macroscopic cysts in 15% with fibrotic changes in the portal areas due to hamartomatous proliferation and dilatation of bile ducts in nearly all patients (4). The pancreas is fibrotic and the ducts dilated in 30% (3,7,20,37,38). The lungs are uniformly hypoplastic.

Musculoskeletal findings. The most common skeletal alteration is bilateral postaxial polydactyly (55%–80%) (18). Rarely, there is preaxial polydactyly (23,53,54). The hands are more often involved than the feet. There may be six or more digits (Figs. 21–19 and 21–22). There are usually six metacarpal bones or, if five, the middle one is often bifurcated. Talipes equinovarus, probably due to oligohydramnios, has been noted in 30%–50%. The tibiae may be short and angulated and the upper extremities are shortened in approximately 15% (7,15,17,23,27,36,41,45,47). The cranial base is malformed, as noted earlier (18). The lumbar vertebral bodies may also be cleft (18).

Genital anomalies. Hypoplastic penis and cryptorchidism in males are almost constant features and may lead to erroneous gender assignment (38) (Fig. 21–23). Males often have Müllerian duct remnants (20%) and epididymal cysts (40%) (37). Septate vagina and hypoplastic or bicornuate uterus in females have been observed in 20%–25% (3,7,27,30,41,46). On occasion, ambiguous external genitalia have been noted (31).

Other findings. Malrotation of the intestines, situs inversus, and a wide array of congenital/cardiac anomalies (VSD, ASD, common atrium, absent mitral valve, preductal coarctation, persistence of left superior vena cava) have been found in 30% (7,20,27,41).

Oral manifestations. Cleft lip (20%) and/or, more often, cleft palate (45%) and various malformations of the tongue (ankyloglossia, bifid tongue, anterior marginal hamartomas) have been noted (8,27,39). The larynx is frequently hypoplastic (41).

Differential diagnosis. Marked variability makes for difficulty in diagnosis. Meckel syndrome may be confused with *trisomy 13* and occasionally severe *Smith-Lemli-Opitz syndrome, C syndrome,* and *hydrolethalus syndrome* (19). Although not obligatory, the triad of occipital encephalocele, postaxial polydactyly, and polycystic kidneys is persuasive

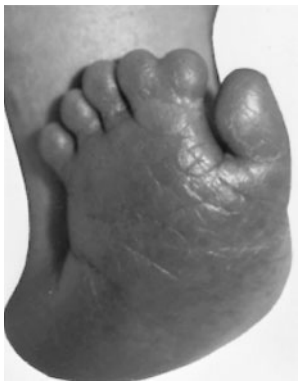


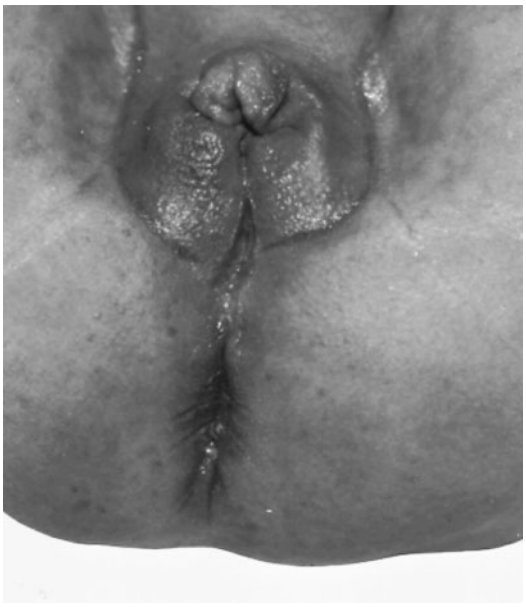
Fig. 21–22. *Meckel syndrome*. Polydactyly, syndactyly, abbreviation of hallux, talipes. [From JM Opitz and JJ Howe, Birth Defects 5(2):167, 1969.]

in making a diagnosis of Meckel syndrome. Seller (46) indicated that the triad is present in 60%–70% of the cases. In approximately 15%, there is binary combination of either encephalocele or polydactyly with polycystic kidneys. Among the remainder, there is only a single component present. In studies of affected sibs, approximately 50% have identical anomalies whereas the other half do not. The *short rib-polydactyly syndromes* (Majewski type, Saldino-Noonan type, Naumoff type, etc.) can easily be separated from Meckel syndrome.

The so-called cerebro-reno-digital (Meckel-like) syndrome with Dandy-Walker malformation of Genuardi et al (11), we view as an example of Meckel syndrome. A number of cases with Dandy-Walker malformation have been considered to be other syndromes. These have been elegantly reviewed by Al-Gazali et al (1). We cannot accept these as representing other than the variable expression of Meckel syndrome.

Laboratory aids. Chromosome studies will exclude *trisomy 13*. Prenatal diagnosis may be made by ultrasonography (oligohydramnios, microcephaly, anencephaly, occipital encephalocele, internal hydrocephalus, large kidneys, empty bladder, reduced femur length). Ultrasonography should be employed from the 11th to 12th weeks of pregnancy serially (10,34,48). Amniotic fluid α-fetoprotein levels are elevated in approximately 70% (open CNS lesions, cystic kidneys) at around week 17–18 of pregnancy. Various other backup tests may be employed: study of amniotic fluid for acetylcholinesterase levels, elevated pregnancy specific β_1-glycoprotein, positive β-trace protein, human chorionic gonadotropin levels, and amniotic cell culture (5,9,16,30, 39,45).

Fig. 21–23. *Meckel symdrome*. Hypoplastic penis, hypospadias. [From JM Opitz and JJ Howe, Birth Defects 5(2):167, 1969.]



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Hydrolethalus syndrome

Salonen et al (15), in 1981, reported 28 patients from 18 families in Finland with a lethal syndrome characterized by polyhydramnios, variable degrees of hydrocephalus, crossed polydactyly, talipes, congenital heart anomalies (most frequently VSD and common arteriovenous canal), and severe micrognathia. Salonen and Herva (14) estimated a frequency of approximately 1 per 20,000 births. Approximately 70 patients have been described to date (2,8,19). A mild example was reported (3). Nearly all have been aborted or stillborn.

Preterm delivery is common. Polyhydramnios is present in over 90% (14).

Inheritance is clearly autosomal recessive (2,8). The gene maps to 11q23–q25 (20). To date, almost all certain reports emanate from Finland (13). It is possible that the patient described by Fitch and Pinsky (5) may have the disorder, but one cannot exclude *Meckel syndrome* or, more likely *Smith-Lemli-Opitz syndrome*. The sibs reported by Adetoro et al (1) appear to have some new form of short rib-polydactyly syndrome. We believe that the child reported by Bachman et al (4) has *pseudotrisomy 13 syndrome*.

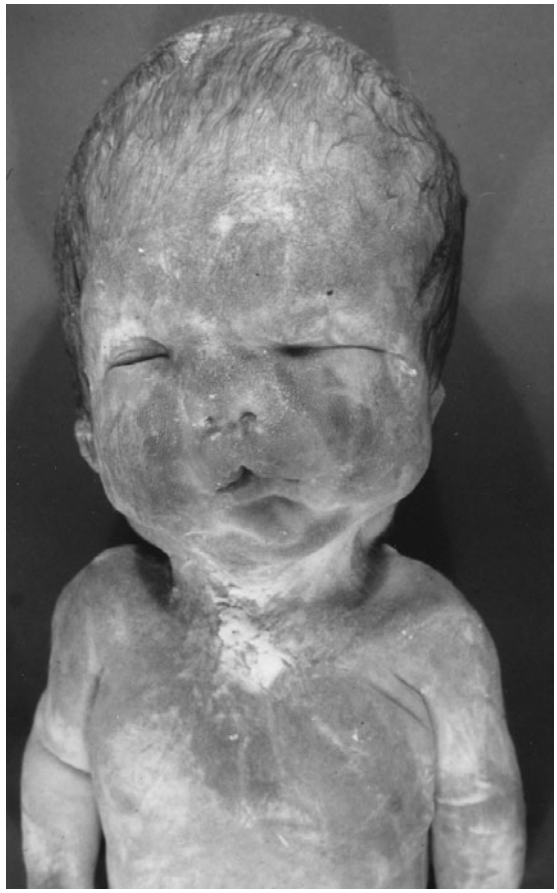


Fig. 21–24. *Hydrolethalus syndrome*. Small wide set eyes, malformed nose, midline cleft of upper lip, micrognathia. (From R Salonen, The Meckel and Hydrolethalus Syndromes. Diagnostic, Genetic, and Epidemiologic Studies. Academic Dissertation, Med. Fac. of Helsinki, 1986.)

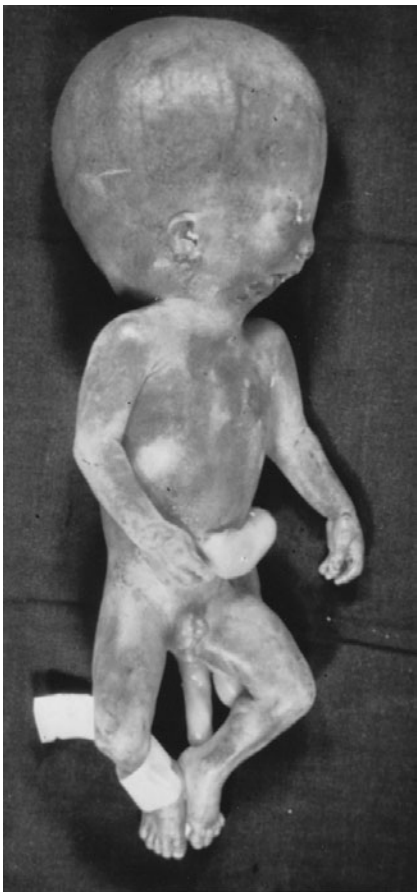
The face is rather striking. The nasal root is wide. The neck is broad. The eyes are deeply set (95%) and occasionally may be microphthalmic. The tongue is occasionally malformed, small, or absent. Approximately 40% have cleft palate. An equal number have smaller clefts of the mid-upper and lower lip. Cleft lip-palate has been noted in 50% (2,3,7). Micrognathia is marked in nearly all examples (Fig. 21–24).

In addition to hydrocephalus (85%), various other brain abnormalities found in approximately 25% include widely separated hemispheres and agenesis of the corpus callosum and septum pellucidum and, occasionally, the pituitary gland (Fig. 21–25) (10). Dandy-Walker anomaly has been described (11,12,18,19).

The larynx, trachea, and/or bronchi are stenotic or, less often, dilated in 60%. There is reduced lobation of the lungs in 60%. Various other abnormalities include incomplete rotation of the gut (25%), accessory spleens (15%), cryptorchidism (75%), and bicornuate or duplicated uterus (50%). Congenital heart anomalies are seen in 50%.

Radiographically, there is obvious hydrocephalus with a midline defect in the occipital bone posterior to the foramen magnum. Non-fusion of one of the dorsal arches of the first few cervical vertebrae has been noted. This "keyhole" defect seen in 75% in the base of the skull has been termed occipitoschisis (9,16,17). Approximately 20% have short limbs. Among those with polydactyly (80%), the extra digits are postaxial in the hands (50%) and preaxial in the feet, a characteristic hallux duplex (40%). Rarely, there are postaxial toes. The upper limbs are short in approximately 15%. The tibiae exhibit proximal hypoplasia. The feet are clubbed in 50%. Prenatal diagnosis by ultrasound is possible (6).

In hydrolethalus syndrome, in contrast to the *Meckel syndrome*, one finds hydrocephaly rather than microcephaly and/or occipital encephalocele. The polydactyly is crossed. The kidneys and liver are normal, the



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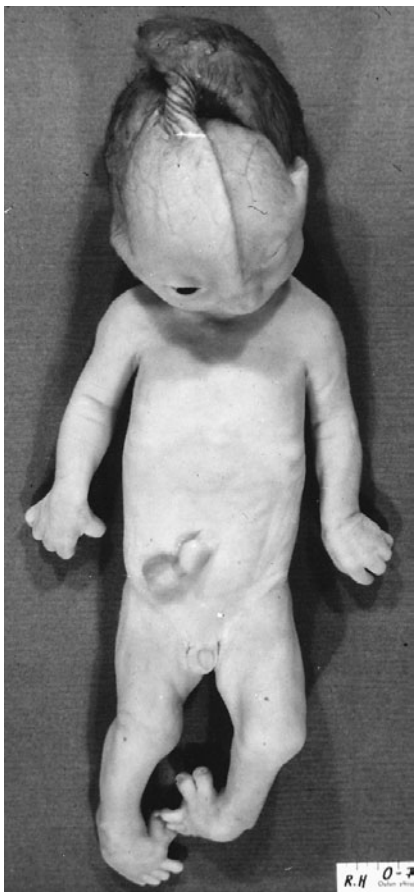

B

Fig. 21–25. *Hydrolethalus syndrome*. (A,B). Hydrocephalus, small mandible, short lower limbs, and polydactyly. (From R Salonen, The Meckel and Hydrolethalus Syndromes. Diagnostic, Genetic, and Epidemiologic Studies. Academic Dissertation, Med. Fac. of Helsinki, 1986.)

tibiae exhibit proximal hypoplasia, and there is polyhydramnios rather than oligohydramnios. Macrocephaly, hallucal duplication, and postaxial polydactyly of the hands are seen in the *acrocallosal syndrome* but hydrocephalus does not occur. Hydrocephalus, cerebellar hypoplasia, cardiac and genital anomalies, cleft palate, and polydactyly are seen in severe *Smith-Lemli-Opitz syndrome*, and hydrocephalus and agenesis of midline structures are found in *Walker-Warburg syndrome*. Other disorders such as *pseudotrisomy 13 syndrome* and *oral-facial- digital syndromes* IV and VI *must be excluded*. Excellent discussions of differential diagnosis are those of Krassikoff et al (10) and Morava et al (11).

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Branchio-oculo-facial (BOF) syndrome

A syndrome of cervical aplasia cutis congenita, cervical thymus, pseudocleft of the upper lip or cleft lip-palate, congenital nasolacrimal duct obstruction, and conductive hearing loss has been reported by a number of authors (1–9,11–23). The earliest example appears to be that of Harrison (9) in 1957. Fujimoto et al (4), in 1987, coined the term

branchio-oculo-facial syndrome. The reader is referred to a detailed review of 43 cases of the syndrome by Lin et al (14) in 1995.

Autosomal dominant inheritance has been demonstrated (2,7,11). The parents of two sibs were normal in two reports, suggesting gonadal mosaicism (6, C. Oley, personal communication). The gene does not map to the branchio-oto-renal area (14a).

Prenatal growth retardation has been noted in 45% whereas postnatal growth is slowed in 40% (14,16).

Craniofacial findings. The scalp hair begins to gray in late adolescence in 25% although it may begin as early as the age of ten (7), and there may be subcutaneous scalp cysts in 10% (7). A white forelock may be evident (17). The lack of hair pigment has been demonstrated microscopically (18). The nose may be broad and misshapen with a wide bridge and an indented or flattened nasal tip (7,20). The philtrum is often short (6,8,11,16) and prominent with thick fibrous vertical ridges producing a pseudocleft seen in 40%. Another 40% have cleft lip and/or palate (2,3,5,13,17–22). Paramedian upper lip pits, seen in 20%, correspond to the fusion sites of the median nasal and maxillary prominences (2,7) (Fig. 21–26). Approximately 15% have small sites of aplasia of the skin of the scalp above the ear (9,13,14,16,17,22). The mastoid bones may be hypoplastic (16) (Fig. 21–26).

Ocular system. Various eye anomalies have included unilateral microphthalmia (30%), anophthalmia (10%), myopia (30%), cataracts (25%), strabismus (30%), ptosis (30%), colobomas of iris, choroid, retina, and optic nerve (45%), orbital cysts (6), and upslanting palpebral fissures (50%). Nasolacrimal duct, seen in approximately 75%, results in dacryocystitis, which, in turn, eventuates in thickened lower eyelids (22).

Auditory system. The pinnae are almost always posteriorly angulated with a hypoplastic helix, prominent anthelix, and upturned lobules (5,7–9,11,16). Microtia is noted in 20% (16). Pre- and post-auricular and/or lobular pits have been documented in 25% (7,12,14,21). Conductive hearing loss of mild to moderate degree has been reported in 40% (7–9,11,16).

Neck. Bilateral cervical aplasia cutis congenita with thinned epidermis and underlying cervical thymus extending along the sternocleidomastoid muscle is a constant feature (Fig. 21–26A–C and Fig. 26–27A).

Skin. Small sites of aplasia cutis congenita may be seen over the sternum (14,16).

Microscopically, a ciliated epithelium representing the pharyngeal epithelium of the third pouch is located between the thymus and the skin (1,2,4,13,21,22) (Fig. 21–27B,C).

Extremities. Fifth finger clinodactyly has been seen in 20%.

Central nervous system. Developmental delay or mental retardation has been noted in 40% with microcephaly in 10%. Agenesis of the cerebellar vermis has been observed (15).

Renal system. Unilateral renal agenesis or renal multicystic dysplasia is found in 35% (12,13,21,22).

Diagnosis. Microscopic differential diagnosis of the neck lesions would include thymic cyst, ectopic hamartomatous thymoma, and benign lymphoepithelial tumor of the skin (2,5). Hing et al (10) reported an infant with holoprosencephaly and branchial cleft fistulae.

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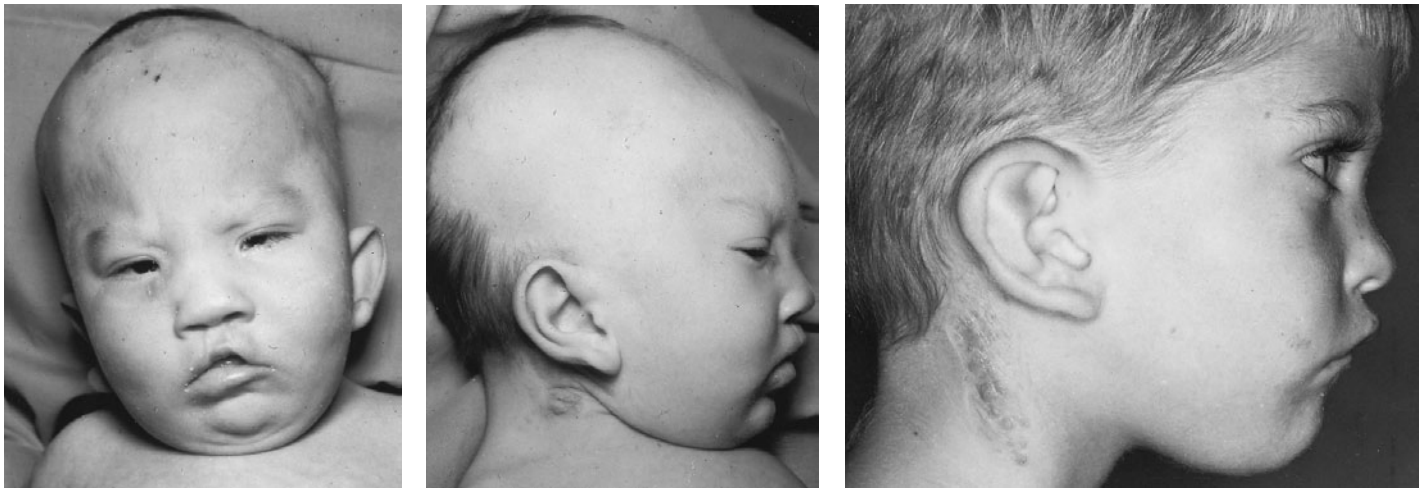
Fig. 21–26. *Branchio-oculo-facial (BOF) syndrome*. (A,B) Apparent hypertelorism, pseudocleft in upper lip, branchial cleft covered by thinned skin, posteriorly angulated pinna. (C) Note pouting upper lip due to pseudocleft-ing and aplasia cutis congenita of lateral neck. (A,B from A Fujimoto et al, Am J Med Genet 27:943, 1987.)



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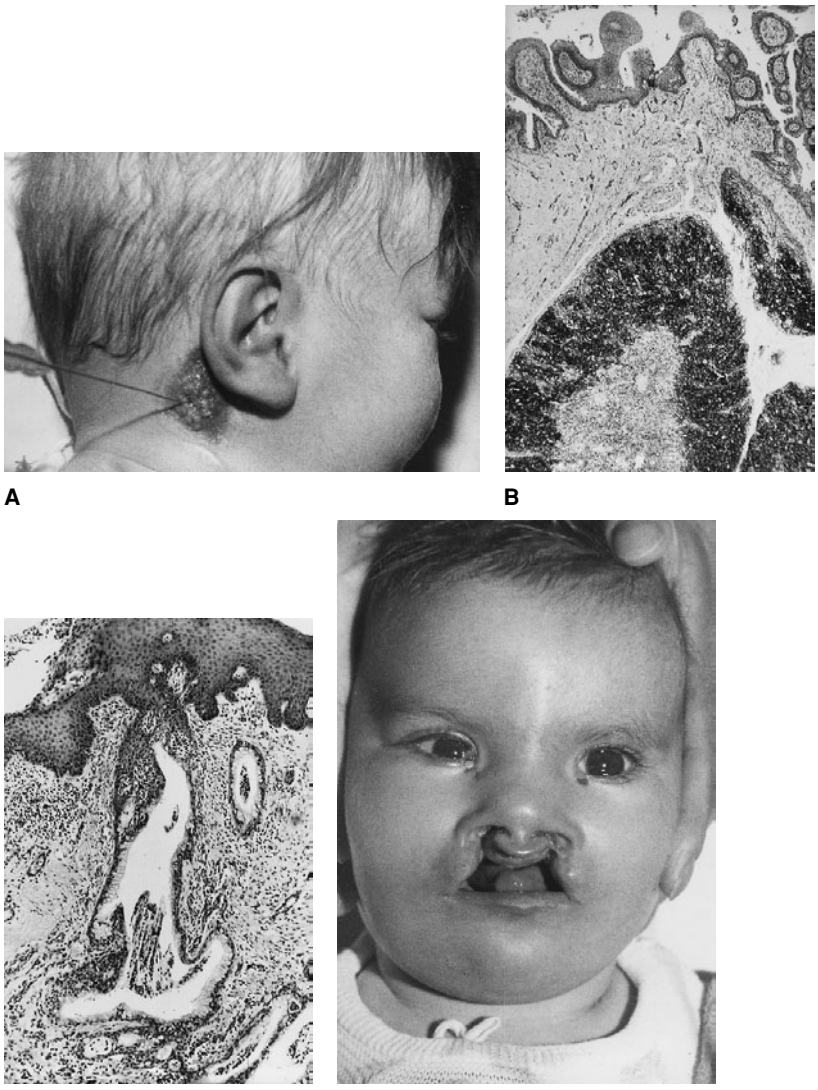

Fig. 21–27. *Branchio-oculo-facial (BOF) syndrome*. (A) Lateral cervical thymus. Child had similar lesion on opposite side. Helix is somewhat hypoplastic. (B) Section taken from neck showing underlying thymus. (C) Section from neck showing mucus-producing epithelia that lined original third pharyngeal pouch. (D) Bilateral cleft lip-palate, nasolacrimal obstruction, and almond-shaped upslanting palpebral fissures. (From W Schweckendiek et al, Laryngorhinootologie 56:795, 1977.)

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Femoral hypoplasia-unusual facies syndrome (femoral facial syndrome)

Daentl et al (7), in 1975, defined the femoral hypoplasia-unusual facies syndrome. However, a number of other authors reported earlier examples (1,2,10,20,26). Approximately 35% of those with the syndrome are examples of *diabetic embryopathy*. (15,19,27,28), thus making the syndrome analogous to caudal regression (sacral agenesis) with which one can also find cleft lip and/or cleft palate (4,10). However, 65% of the cases result from other causes. Although the condition has been reported in two generations (21), its inheritance pattern, if any, would more likely be multifactorial than autosomal dominant (22). We cannot accept the example of Robinow et al (28). At least 60 examples have been documented.

The facies is characterized by upward slanting palpebral fissures (35%), short pointed nose with hypoplastic alae (65%), mildly dysmorphic pinnae (45%), long flat philtrum, thin vermilion of upper lip (65%), and micrognathia (80%) (6,8,9,11,14,17,30,34). The pinnae may be deformed or low-set and overfolded (3,12,13,27). The ear canals may be narrowed . Cleft palate is common (80%); cleft lip-palate is rare (18,33) (Fig. 21–28).

Stature is markedly reduced due to abbreviation of the lower extremities (Figs. 21–29 and 21–30A). Arrest of femoral growth has been noted on ultrasound between 24 and 32 weeks of gestation with normal subsequent growth (31). The upper extremities and shoulder girdle

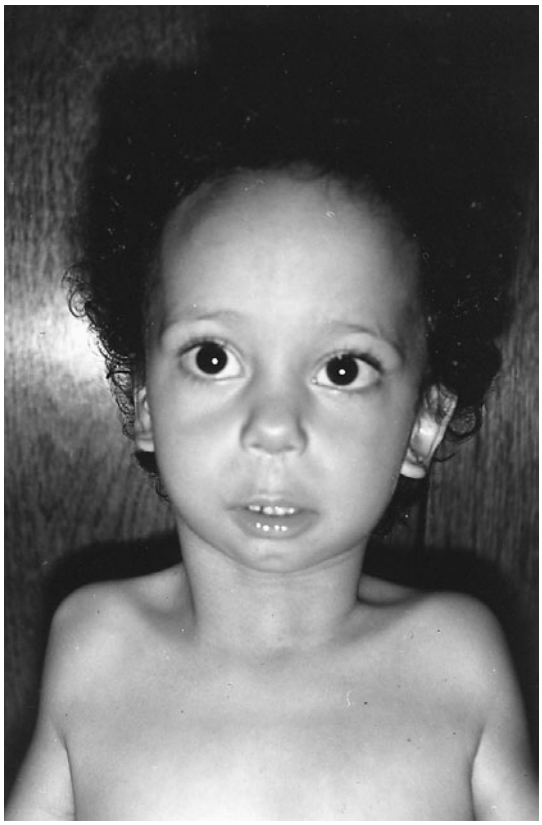

Fig. 21–28. *Femoral hypoplasia-unusual facies syndrome*. Note shortened nose, long philtrum, and micrognathia. (From RB Goldberg et al, Cleft Palate J 15:386, 1978.)

are affected in 75%. The humerus may be mildly shortened and there is limited motion of the shoulders and elbows. Sprengel deformity is rather frequent (1,12). Absent fibula has been reported (30). Syndactyly of toes and broad or bifid halluces have been noted as well as polydactyly (3,12,13,27). Inguinal hernia is common. Cardiac anomalies, documented in 20%, include VSD, pulmonary stenosis, and persistent truncus arteriosus.

Genitourinary anomalies have been noted in 60% (absent or hypoplastic labia, cryptorchidism, hypoplastic penis, macrophallus, polycystic kidneys, absent kidney, abnormal collecting system) (5,7,13,15,16,18,30) (Fig. 21–30A).

Radiographic changes are usually asymmetric. The femora, fibulae, and acetabulae range from being hypoplastic to aplastic (Fig. 21–30B). Vertebral anomalies, seen in 35%, include scoliosis, hemivertebrae, anterior synostosis of lumbar vertebrae, spina bifida occulta, and malsegmentation of the sacrum. The ribs may taper, and some may be fused or missing. Pelvic anomalies include small iliac wings and hypoplastic or absent acetabuli. Derangement of elbow joints (radiohumeral synostosis: radioulnar synostosis) and talipes are frequent. The great toes may be bifid and, rarely, there is polydactyly or agenesis of a toe (3,12,13,27,30). It should be noted that preaxial polydactyly is increased in the offspring of diabetic mothers (24).

Long bone histology has shown disorganization of the growth plate with vacuolization and binucleation of chondrocytes (32).

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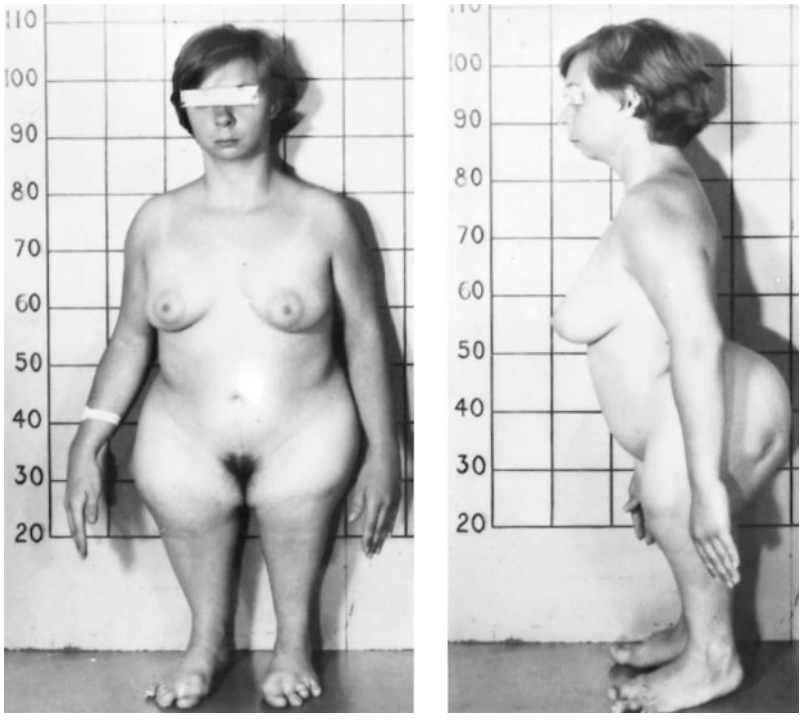
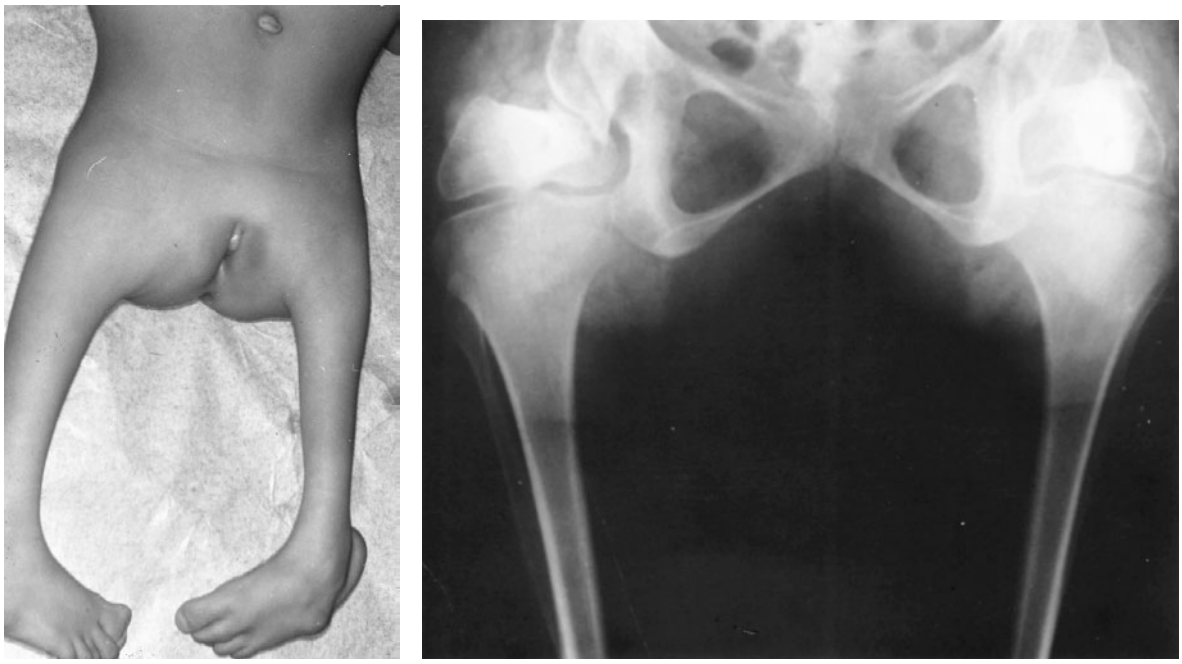


A B

Fig. 21–29. *Femoral hypoplasia-unusual facies syndrome*. (A,B) Severe abbreviation of lower limbs. Patients had dislocated and hypoplastic patellas, abnormal toes. (From JA Bailey and P Beighton, Clin Pediatr 9:668, 1970.)



A B

Fig. 21–30. *Femoral hypoplasia-unusual facies syndrome*. (A) Lower torso showing hypoplastic external genitalia, shortened legs, residual varus deformity, and polysyndactyly. (B) Radiograph showing miniscule femurs, absent acetabula, hypoplastic pelvis. (A from RB Goldberg et al, Cleft Palate J 15:386, 1978. B from JA Bailey and P Beighton, Clin Pediatr 9: 668, 1970.)

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Fryns syndrome (cleft palate, diaphragmatic hernia, coarse facies, and acral aplasia)

Fryns (11), in 1979, described an essentially lethal syndrome of diaphragmatic hernia, coarse facies, acral hypoplasia, and cleft palate. The infant reported by Fitch et al (10) in 1978 appears to have had the disorder. Inheritance is clearly autosomal recessive (1,2,20,23,24,30,31). Duplication of 1q24–q31.2 has been described, but its significance has yet to be determined (5). Aymé et al (1) estimated the prevalence as 0.7/10,000 births. It is seen in 4%–10% of infants with congenital diaphragmatic hernia (9). Approximately 50 cases have been reported (1–5,7,10–18,20–27, 30,37). The syndrome has been noted in MZ twins with variable expression (34a).

Polyhydramnios developing in the second trimester has been present in approximately 60% of the cases (1,2). Death often occurs at approximately 30 weeks gestation. Birth length, weight, and OFC tend to be normal. Of the 15% that survive, there are less diaphragmatic hernia, better lung development, and absence of complex heart anomalies (13,15). Neurologic impairment is, however, common (27,34).

Craniofacial findings. The face is coarse and hirsute with narrow palpebral fissures, broad flat nasal bridge, large upturned nose, large dysplastic pinnae with hypoplastic attached lobes, short upper lip, macrostomia, microretrognathia, and short broad neck (12) (Fig. 21–31). Dandy-Walker malformation and agenesis of the corpus callosum have been noted in 70% (26). Arhinencephaly and agenesis of olfactory bulbs have been described (1). The corneae are cloudy in approximately 15%, and retinal dysplasia has been noted (1). Scalp defects have been reported (14).

Chest and abdomen. Diaphragmatic defects are found in 90% (1,35,36). They are often large, allowing herniation of the abdominal contents into the thoracic cavity. They are usually unilateral (85%) and left-sided (70%). Fryns et al (11) suggested that the diaphragmatic hernia was secondary to the primary defect in lung development. Rarely, there is no diaphragmatic hernia (2,7,17,20,31,36). The thorax is narrow with hypoplastic widely spaced nipples in approximately 50% (26). Digestive tract anomalies, secondary to the diaphragmatic defect, are found in 60%. They include intestinal malrotation, anomalous attachment of the gut, omphalocele, duodenal atresia, and esophageal atresia. The lungs are usually hypoplastic and abnormally lobulated. The anus may be imperforate, atretic, or especially anteriorly displaced. Agangliosis of the bowel and bladder has been found (2).

Genitourinary findings. Various renal abnormalities (renal agenesis, cystic kidney, hydronephrosis, ureteral cysts, misplaced megaureters, duplicate and atretic ureters) have been reported in 55%. Genital anomalies, noted in 60%, consist of bicornuate uterus, hypoplastic upper vagina, hypoplastic ovaries, cryptorchidism, and saddle scrotum (1,2,11,16,20,23,24,31).

Cardiovascular system. Assorted cardiac defects (VSD, ASD, overriding aorta) were noted in 85% (26).

Musculoskeletal system. Distal limb hypoplasia (brachytelephalangy) with nail deficiency is found in 75%. The terminal digits may be broad. Camptodactyly of the fifth finger is frequent. Other fingers may be axially deviated. Other skeletal changes are minimal, consisting of broad medial ends of the clavicles (2), delayed ossification of basiocciput and cervical vertebrae (18).

Oral findings. Isolated cleft palate has been present in 30% (1,2,24,31), and cleft lip with cleft palate has been found in 25% (1–3, 20,23,32). Macrostomia is a constant feature. Natal teeth have been described (21).

Differential diagnosis. Prenatal diagnosis has been made at 19–20 weeks by ultrasonographic demonstration of diaphragmatic hernia and elevated alphafetoprotein levels (1,2,4,13,15,21,24,25).

Diaphragmatic hernia is ordinarily considered to be a multifactorial trait with a 3:1 male predilection occurring in 1 in 2000 births. In a study of associations among 143 cases of diaphragmatic hernia, David and Illingworth (8) noted two patients with cleft palate and micrognathia (Robin sequence) and three with cleft lip in association with diaphragmatic hernia. Crane (6) reported a different, probably X-linked lethal syndrome of cleft lip-palate, polyhydramnios, diaphragmatic hernia, and various urogenital anomalies. Lowry and MacLean (19) described a female child with cleft palate, proptosis of eyeballs, divergent squint, glaucoma, multiple congenital heart defects, mental retardation, diaphragmatic eventration, and craniosynostosis (*Lowry-MacLean syndrome*). Saal et al (29) reported monozygotic twins with cleft palate, agenesis of hemidiaphragm, and ambiguous genitalia but no distal limb anomalies.

Also to be excluded are *trisomy 18* and *Zellweger syndrome*. There appears to be considerable overlap with *Rüdiger syndrome* and *Pallister-Killian syndrome* (22,28,33). Diaphragmatic defects are also seen in *de Lange syndrome*.

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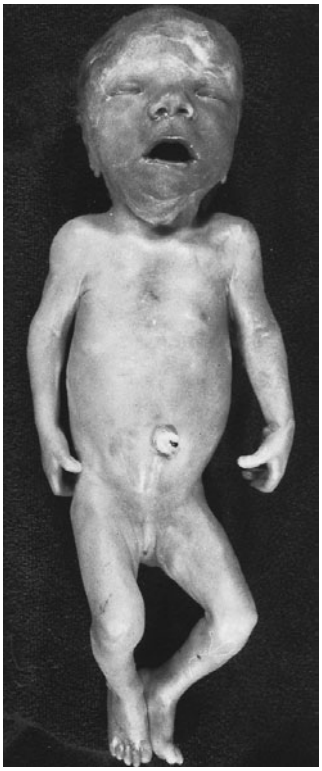

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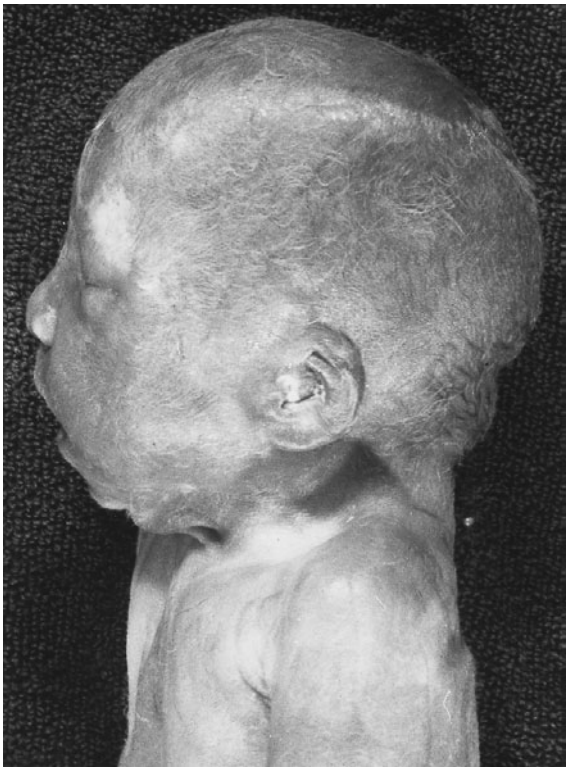

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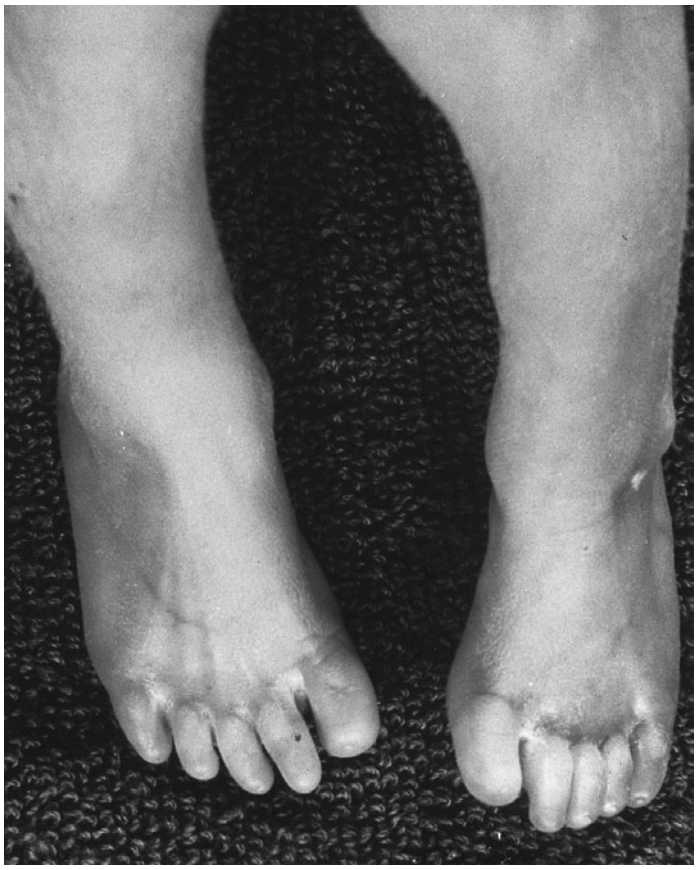

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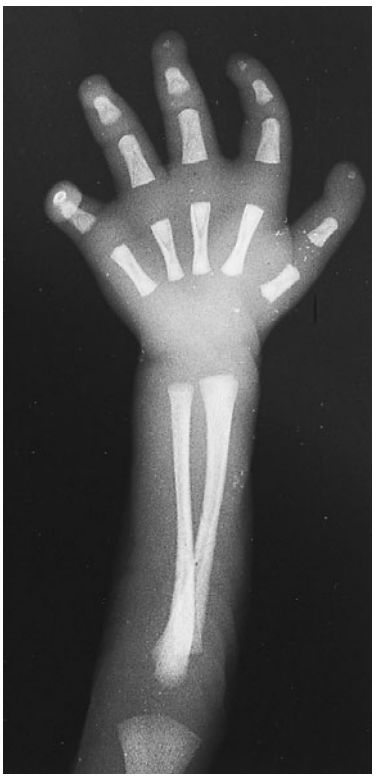

D

Fig. 21–31. *Fryns syndrome*. (A) Infant showing coarse facies, small eyes, flat nasal bridge, large upturned nose, short upper lip, and macrostomia. The thorax is small, the nipples hypoplastic. The thumbs are digitalized and proximally implanted. (B) The pinnae are low set, poorly lobed, and posteriorly rotated. (C) The terminal digits are hypoplastic. (D) Radiograph showing agenesis of terminal phalanges. (From JP Fryns et al, Hum Genet 50:65, 1979.)

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Roberts-SC phocomelia syndrome

The syndrome of cleft lip-palate and tetraphocomelia was discovered independently by a number of authors. The first classic description was that by Roberts (39) in 1919. However, there were earlier and later scattered reports until 1966 (6,12,14,22,24,33,43,46,48,52,54). The condition was largely forgotten until Appelt et al (1), in 1966, rediscovered it. Meanwhile, Herrmann et al (17), in 1969, reported the pseudothalidomide or SC syndrome, believing it to be a separate entity. Several authors (8,13,16,32,41,56) provided convincing evidence that the two disorders represent extreme ends of a phenotypic spectrum of a single syndrome. Very mild expression has been documented (32,34,36,44). A single complementation group has been demonstrated regardless of severity (32a).

Inheritance is autosomal recessive. Parental consanguinity and occurrence in sibs have been reported in approximately 50% of the cases (50). It has been described in identical twins (9). Over 100 cases have been reported (50). The reader is referred to the comprehensive review of Van den Berg and Francke (50) for analysis of each case and proposal of a rating system.

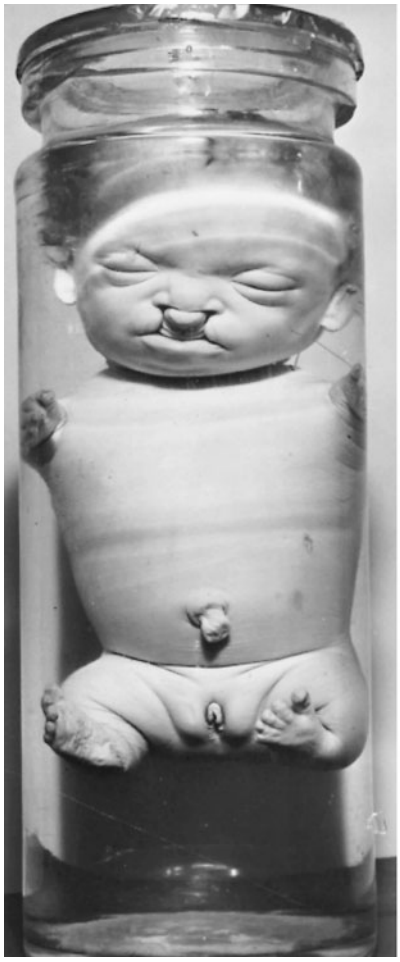
Prenatal growth retardation is a constant feature—full-term infants weighing less than the 3rd centile. Postnatal growth retardation can range from mild to very severe (20,32,40,41,47). Those with most severe growth retardation have the most severe limb reduction and craniofacial malformations. The minority who reach adulthood have been mildly growth retarded. Life expectancy is often short. At least 20% are stillborn.

Facies. Approximately 80% have microcephaly. Among those that die within the first month of life, there is hypertelorism (90%) and exophthalmos because of shallow orbits (70%). The nasal bridge is wide (80%) and the nostrils are small (30%) (Figs. 21–32 and 21–33). The pinnae are low-set, posteriorly angulated, dysmorphic, and lobeless (Fig. 21–34).

Facial clefts are present in 80%. In a few severe examples, the clefts are combined with encephalocele (7,8,32,51). Most are bilateral cleft lip-palate whereas isolated cleft palate occurs in only 10% (9,12, 13,17,21,35,37) (Figs. 21–32A).

In those that survive early infancy, the scalp hair is often sparse and silvery blond (13,15,28,37), but it may be dark initially (2). The nasal bridge is narrow. Hypoplastic alar cartilages producing thin nares and a pointed tip are more often found in milder cases.

Also, in milder cases, there are superficial capillary hemangiomas on the lip, nose, forehead, and ears in 85% (2,4,8,15,17,19,25,29,55,56). Cataracts and corneal opacities resulting in blindness have been observed more in those that survive infancy, but can be found in both groups (8,25,56).



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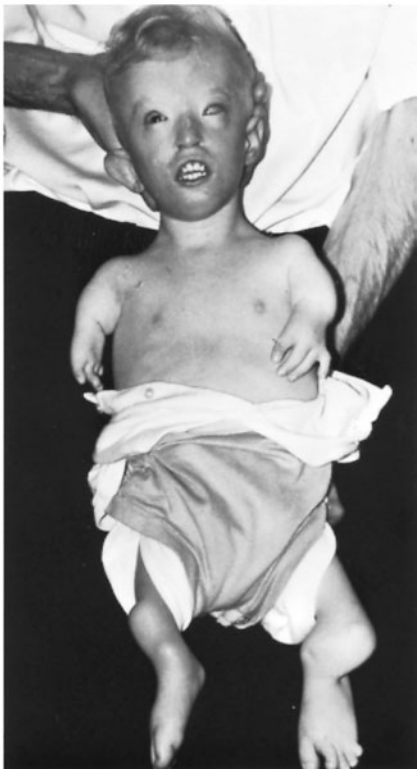
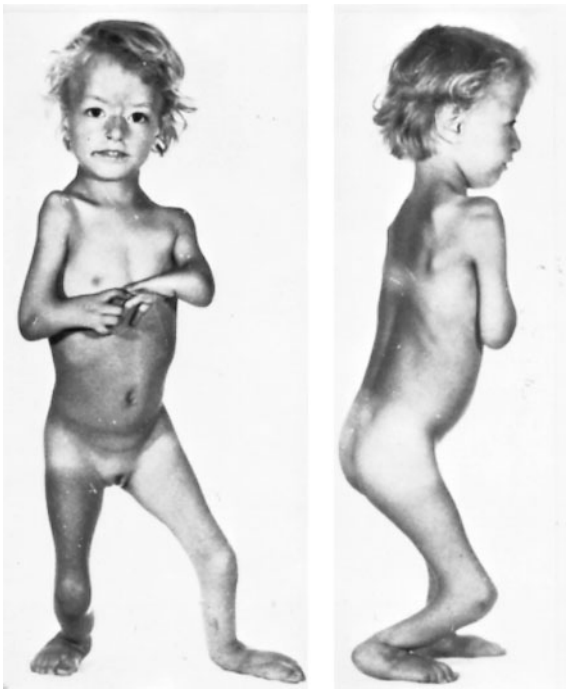


B

Fig. 21–32. *Roberts-pseudothalidomide syndrome*. (A) Ocular hypertelorism, reduction in digits, clitoral enlargement, bizarre pinnae. (B) Thin, pinched nose, abnormal pinnae, convergent strabismus, symmetric reduction of arms and legs with decreased number of fingers. [A from J Appelt, Padiatr Padol 2:119, 1966. B from J Herrmann et al, Birth Defects 5(3):81, 1969.]



A B

Fig. 21–33. *Roberts-pseudothalidomide syndrome*. (A,B) Compare with other cases. (From BD Hall and MH Greenberg, Am J Dis Child 123:602, 1972.)

Musculoskeletal system. The skull tends to be microbrachycephalic. There are asymmetric reduction anomalies of variable degree in the tubular bones of all extremities (90%), ranging from complete absence of arms and legs with rudimentary digits to mild reduction (Figs. 21–32 and 21–33). Only rarely is there symmetry. In general, the humerus is proportionately shorter than the femur. The radius is shorter than the ulna. The upper extremities are more often involved than the lower extremities. In several cases, the lower limbs are not affected (4,17,19,29,45). The hands may be radially clubbed and single palmar creases are common. The length and number of digits is reduced in 80%, more frequently in the hands (75%) (thumb, fifth finger) than in the feet (25%). The index fingers may be clinodactylous. Rarely polydactyly of toes (8) has been reported. Various joints, especially the knees, ankles, wrists, and elbows, exhibit flexion contractures in 50% (Fig. 21–33). Talipes and soft tissue syndactyly (40%) are common. The bones of the arm or leg are fused in approximately 10%. Tetra-amelia has been reported in association with splenogonadal fusion (5).

Radiographically, Wormian bones may be seen in the lambdoidal sutures. There are more severe skeletal anomalies among those that die in early infancy. Absence or severe hypoplasia of the radius, ulna, tibia, fibula, or femur is seen. The thumb phalanges and first and fifth metacarpals are hypoplastic or missing. The carpal bones are irregular and reduced in number. Humeroradial or humeroulnar synostosis, talipes, calcaneovalgus, and absence or posterior displacement and/or bilateral deformity of the fibulae are commonly reported (4,9,19) (Fig. 21–35). Less frequently, shortened or curved humerus and tibia, fusion of the fourth and fifth metacarpals, and femorotibial synostosis have been described in approximately 10% (2,17,29,38). The ribs are occasionally reduced in number (9).

Central nervous system. Among those that survive, approximately 50% are mentally retarded. Miscellaneous findings include hydrocephalus (8), calcification of basal ganglia (20), seizures (17), encephalocele (8,31,32,51), absent olfactory lobes (31), and cranial nerve paralysis (34).

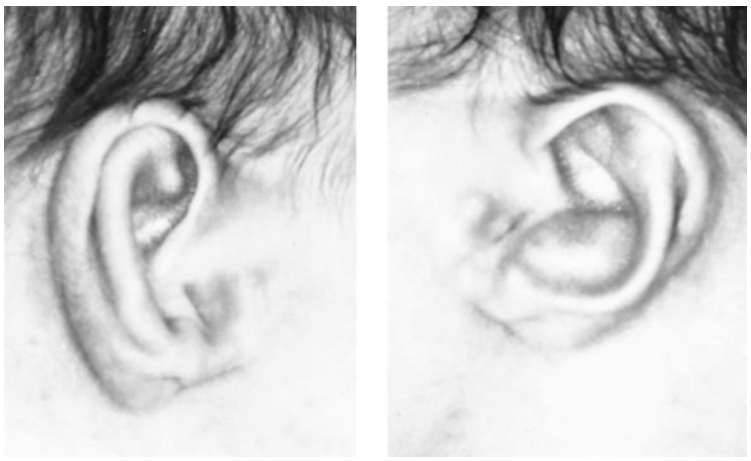
Urogenital findings. Various findings include enlarged penis (4,8, 12,31,39,52) or clitoris (1,31,39,43,55), ambiguous genitalia (31), hypospadias (53), enlarged or cleft labia minora (1), septate vagina (8), and bicornuate uterus (8). Cryptorchidism is a frequent feature in males.

Polycystic kidney, hydronephrosis, ureteral stenosis, and horseshoe kidney have been described (8,31,53).

Cardiac anomalies. Miscellaneous anomalies include VSD (21, 28,53), ASD (6), and PDA (8,53,55).

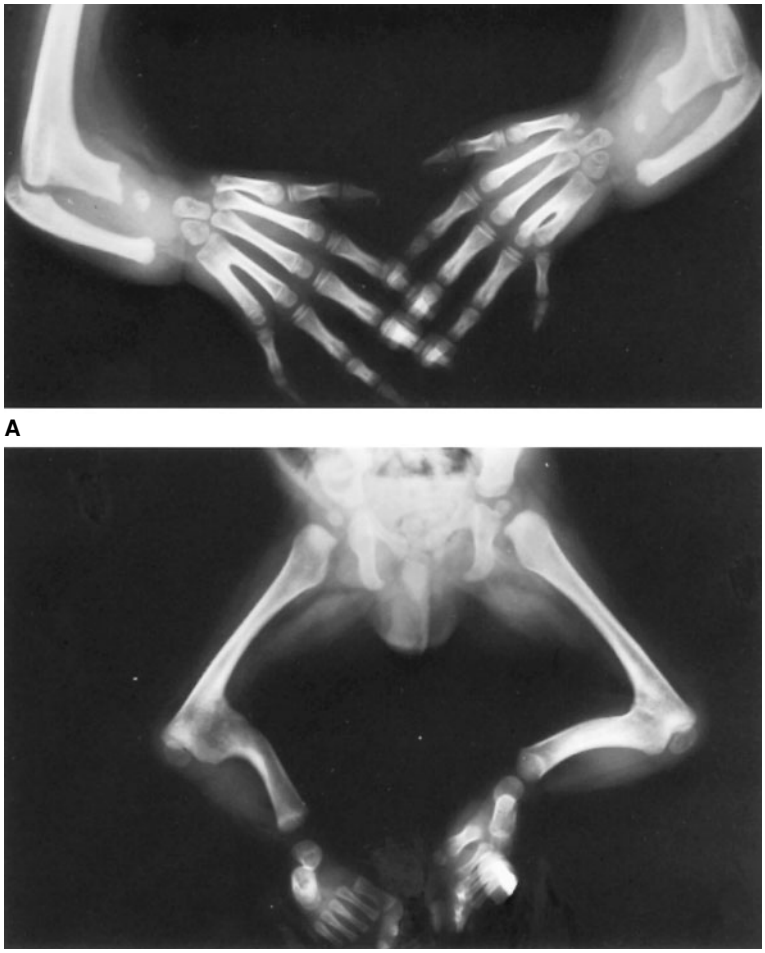
Miscellaneous findings. Thrombocytopenia has been reported in a few cases (4,53). Melanoma (34) and splenogonadal fusion (5) have also been noted.

Differential diagnosis. Reduction anomalies occur in a number of disorders: *thalidomide embryopathy*, DK-phocomelia (encephalocele and urogenital anomalies), Holt-Oram syndrome, thrombocyte aplasia radius (TAR) syndrome, VACTERL association, Fanconi anemia, *Baller-Gerold syndrome, trisomy 18, Nager syndrome*, etc. (37). Urban et al (49) pointed out the overlap with TAR syndrome. A case having some similarities was reported by Ladda et al (26), which we suspect is a mild form of Roberts-pseudothalidomide syndrome. This is discussed further under *Herrmann syndrome*. An X-linked lethal disorder (tetra-amelia, hydrocephalus, facial clefts, eye anomalies) has some overlap (57). Schinzel phocomelia is a recessive syndrome characterized by phocomelia, diaphragmatic hernia, agenesis of uterus and vagina, and hypoplasia of sacrum and pelvic bones (42).



A B

Fig. 21–34. *Roberts-pseudothalidomide syndrome*. (A,B) Close-up of ears in affected child. (Courtesy of S Pruzansky, Chicago, Illinois.)



A

B

Fig. 21–35. *Roberts-pseudothalidomide syndrome*. (A,B) Radiohumeral synostosis with marked shortening of humerus, synmetacarpalism, femorotibial fusion. (From M Levy et al, Ann Pediatr 19:313, 1972.)

Laboratory aids. Approximately 80% of the patients exhibit a striking chromosomal change involving the heterochromatic C-banding regions of most chromosomes (2,8,9,11,20,28,30,31,38,49,55,56) regardless of the degree of severity. The heterochromatic regions around the centromeres, especially of chromosome 1,9, and 16, have a puffed appearance. The heterochromatin of the long arms of the Y chromosome and the short arms of acrocentric chromosomes are often widely separated in metaphase spreads (30). Chromatid repulsion or, more accurately, constitutive heterochromatic repulsion has been demonstrated (32), the chromosomes looking like railroad tracks because of absence of centromeric constriction (Fig. 21–36). Fibroblasts exhibit unusual growth characteristics. Their mitotic processes are also altered (48). Prenatal diagnosis has been accomplished by ultrasound and by heterochromatic repulsion (10,40,41,45,51). Heterozygotes may occasionally show heterochromatic repulsion (32,35).

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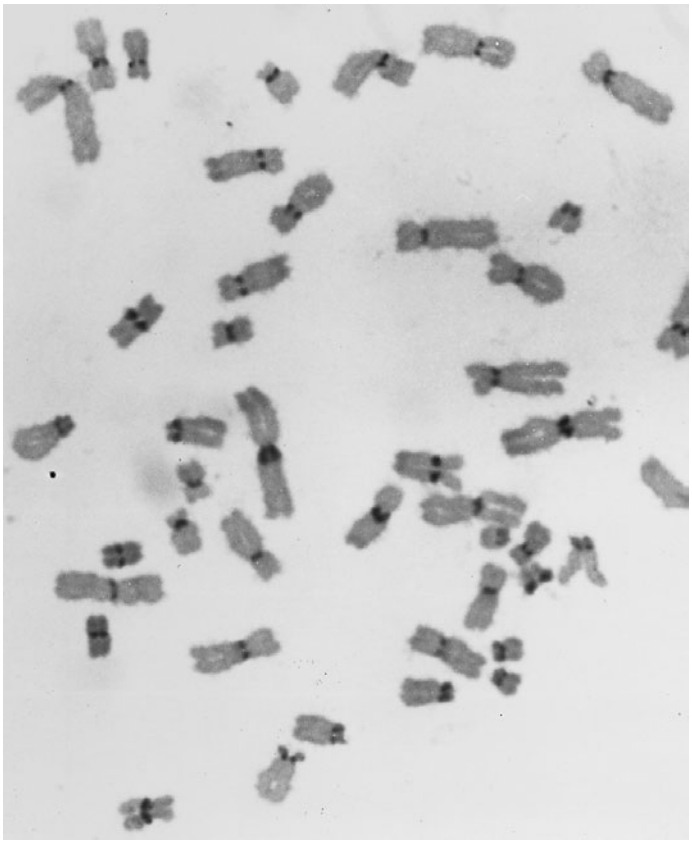

Fig. 21–36. *Roberts-pseudothalidomide syndrome*. Note centromeric separation with C-banding. (Courtesy of W Wertelecki, Mobile, Alabama.)

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Van der Woude syndrome (cleft lip-palate and paramedian sinuses of the lower lip)

The first report of congenital sinuses of the lower lip in combination with cleft lip and/or cleft palate appears to be that of Demarquay in 1845 (5). It was reported independently by Murray in 1860 (16). Over 900 cases have been published (3). The syndrome occurs in roughly 2% of patients with facial clefts (3,22,29) or roughly 1:35,000 to 1:100,000 in the white population (2,4,22). Numerous authors (4,8,10,13,19,39,42) have carried out extensive reviews and analyses of published cases. The most complete survey is that of Burdick et al (3).

The syndrome has autosomal dominant inheritance with variable expressivity. Penetrance ranges between 0.89 and 0.99 (2,3,11,33). The estimate of 80% penetrance (4) is too low, probably because of failure to include submucous cleft palate in the calculations. Between 30% and 50% represent new mutations (29). The mutation rate has been calculated to be 1.8×10^{-5} (3). After a deletion was demonstrated at 1q32–q41 (1,26,30), linkage to the renin gene was found (17,25,27). Sertié et al (32) suggested that mutation at 17p11.2 enhances the expression of cleft palate at the van der Woude locus.

Manifestations of the syndrome in other than the oral or facial areas are unusual.

Oral manifestations. Usually bilateral, often symmetrically placed depressions are observed on the vermilion portion of the lower lip, one on each side of the midline (Fig. 21–37A,B). The dimples are usually circular

but they may be transverse slits or sulci (22). On occasion, they may be located at the apex of nipple-like elevation (36). Rarely, the elevations may fuse in the midline, producing a snoutlike structure. The depressions represent blind sinuses that descend through the orbicularis oris muscle to a depth of 1 mm to 2.5 cm and communicate with the underlying minor salivary glands through their excretory ducts. The sinuses often transport a viscid saliva to the surface, either spontaneously or on pressure.

They may be so small as barely to permit a hair probe, or they may be as wide as 3 cm or more. Nipple-like processes occasionally occur without demonstrable fistulas (40). Although usually bilateral and symmetrically placed, an asymmetric single pit (37,40,41), a central single pit (21,40), or bilateral asymmetric pits (21) may occur. The appearance of the pits may be remarkably subtle (15).

Microforms exist such as transverse mucosal ridges of the lower lip and bilateral somewhat conical elevations of the lower lip mucosa (22). The latter are associated with cleft palate but not with cleft lip (24).

Sicher and Pohl (34) and Warbrick et al (41) suggested that the congenital fistulas arise from arrested development, that is, persistence of a median and/or lateral sulcus or sulci that normally are evanescent structures. These median and lateral grooves appear in the 5–6 mm embryo and disappear at the 10–16 mm stage (Fig. 21–37C). It should be pointed out that the grooves disappear at approximately the same time that fusion occurs between several facial prominences. This probably accounts for the simultaneous occurrence of sinuses and facial cleft. Although surveys have differed considerably because of various biases (4,11,22,33,38,42), roughly 33% have pits without clefts, 33% have pits with cleft lip-palate, and 33% have pits with cleft palate or submucous cleft palate. The combination of pits with cleft lip alone is very rare. Conversely, approximately 10% of those with the syndrome do not exhibit lip pits. Burdick (2) calculated that the risk of inheriting a cleft from an affected parent is approximately 20%; the risk of inheriting lip pits only or being nonpenetrant is approximately 25%.

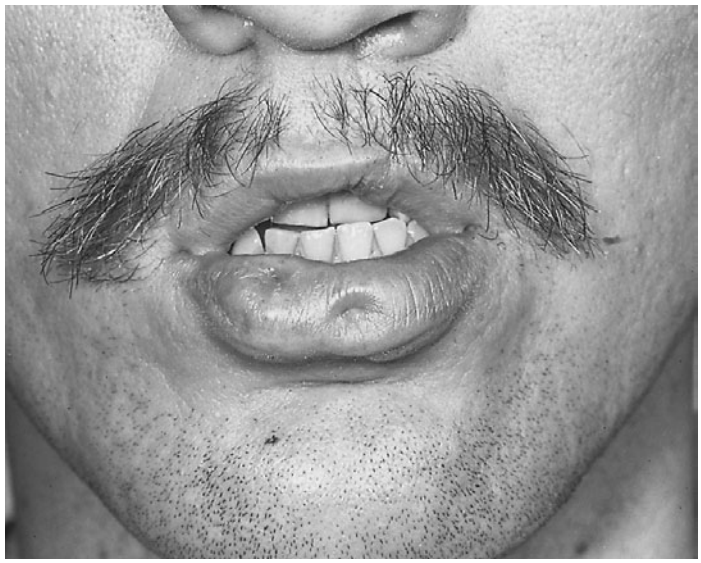
Adhesions between maxilla and mandible (syngnathia) have been noted (14,18). Absence of maxillary and mandibular second premolars has been described as part of the syndrome in 10%–20% of cases (23,28). Natal teeth have been found in monozygous twins (9).

Extremities. Talipes equinovarus (10,37) and 3–4 syndactyly of the fingers (16) have been reported

Other findings. Ankyloblepharon has been described in association with the condition (14,18). These patients, however, may have had mild expression of the *popliteal pterygium syndrome*. Accessory nipples, congenital heart defects (20), Hirschsprung disease (7,31), trichorrhexis nodosa (35), and amniotic band limb deficiency defects (12) have also been reported. These latter findings are likely due to chance.

Diagnosis. Because of variable expressivity, affected family members may exhibit clefts without pits. This may greatly complicate genetic counseling as the chances for transmitting cleft lip or palate vary depending on whether the anomaly is associated with lip pits (50%) or is an isolated phenomenon (2%–5%). Lip pits may also occur in *popliteal pterygium syndrome* and with *aganglionic megacolon and cleft lip and/or palate* and in *Kabuki syndrome*. The type of pits under discussion should not be confused with commissural lip pits at the corners of the mouth that are seen in 10%–20% of the population.

Prenatal diagnosis has been made using embryoscopy (6).



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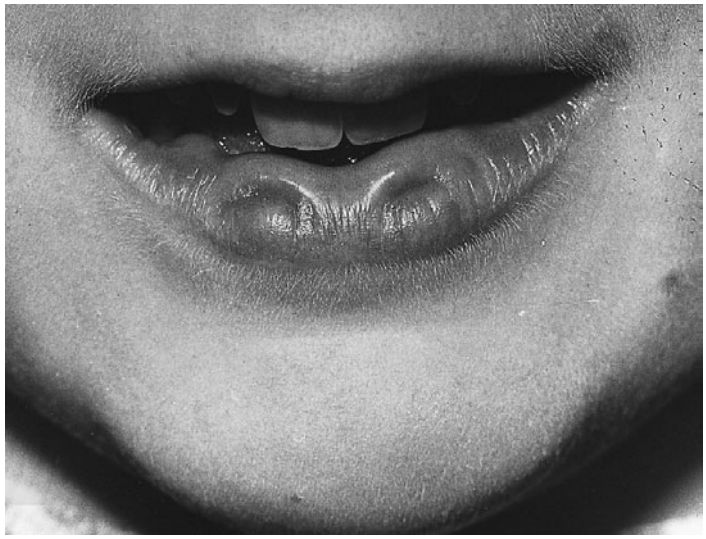

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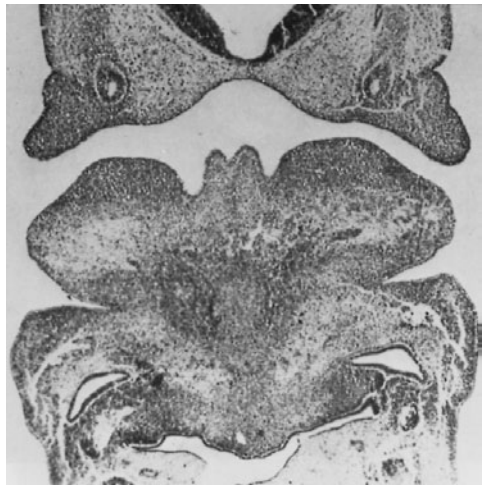

C

Fig. 21–37. *Van der Woude syndrome*. (A) Note repaired unilateral cleft lip, asymmetric sinuses of lower lip. (B) Symmetrical paramedian sinuses of lower lip. (C) Photomicrograph of 7.5 mm embryo demonstrating three invaginations in mandibular process. These disappear by the 14 mm stage. (From JG Warbrick et al, Br J Plast Surg 4:254, 1952.)

References [Van der Woude syndrome (cleft lip-palate and paramedian sinuses of the lower lip)]

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Velocardiofacial syndrome (Shprintzen syndrome, del22q11, Sedlacková syndrome)

In 1978, Shprintzen et al (66) reported a syndrome of typical facies, prominent nose, retruded mandible, cardiovascular anomalies, cleft palate, and learning disabilities subsequently known as *velocardiofacial (VCF) syndrome*. Since then, Shprintzen and colleagues have made numerous contributions to our understanding of this syndrome (1,2,6, 7,24,25,32,33,38,40,43,50,51,53,56,62,67,68,79,80,87). Stern et al (69), Strong (73), Kinouchi et al (35), Kimura et al (34), and Matsuoka et al (44) probably described the same entity, the Japanese preferring the term *conotruncal anomaly face*. Sedlacková and co-workers (16,64,78) included several examples of the syndrome under the title of *velofacial hypoplasia* as early as 1955. Some examples of *asymmetric crying facies (Cayler syndrome)* appear to be VCF syndrome (15,22,71). Velocardiofacial syndrome is not rare, comprising approximately 8% of patients seen in a cleft palate clinic, and appearing to be second only to *Stickler syndrome* as a cause (15%) of *Robin sequence* (67). Over 700 cases have been described (24,45).

Inheritance is autosomal dominant with variable expressivity (47, 67,79). A hemizygous microdeletion shared with *DiGeorge sequence* has been found with high resolution banding and FISH techniques at chromosome 22q11.2 in approximately 85% of the cases of velocardiofacial syndrome (6,7,14,33,37–39,44,51,62,81,82). Among patients with velopharyngeal insufficiency of unknown cause, Zori et al (88) noted that 37% had the deletion. The gene responsible for the cardiovascular aspects is *TBX1* (48). The phenotype in adults has been described (8). The deletion appears to be somewhat more frequently of maternal origin (10,51,63). Among 558 patients with interstitial deletion of 22q11, approximately 28% had inherited deletions predominantly (75%) from the female parent (4,5,60). The frequency of the deletion has been estimated to be 1/5000 live births. Imprinting plays no role in the etiology of VCF syndrome (51). No correlation has been found between the presence or size of the deletion and the phenotype (7). Phenotypic discordance has been reported in monozygous twins (27,86). An acronym for this combination called CATCH 22 (23,30) sounds denigratory and should be discouraged. Overlap with der(22) syndrome has been reported (20). Der(22) is rare, consisting of mental retardation, preauricular skin tags or pits, and conotruncal heart anomalies.

Facies. Approximately 40% are microcephalic. One patient had holoprosencephaly (84). Scalp hair is abundant in over 50%. The face is long with vertical maxillary excess (85%), malar flatness (70%), and mandibular retrusion (80%) (2,40,53). Approximately 15% exhibit *Robin sequence*. Conversely, approximately 15% of infants with Robin sequence have velocardiofacial syndrome. The nose is prominent with squared nasal root, hypoplastic alae nasi, and narrow nasal passages in 75% (2,40). The tip may be dimpled (29). The philtrum is long and the upper lip is thin. The mouth is often held open (Figs. 21–38 and 21–39). It is not rare for the face to be somewhat asymmetric. The adenoids are hypoplastic in almost 85% (80). There is resemblance to the Cycladic face depicted in Greek statues from about 3000 B.C.

Eyes. Narrow palpebral fissures with blue suborbital coloring or "allergic shiners" occur in 35%–50% (24). Tortuous retinal vessels, posterior embryotoxon, small optic discs or bilateral cataracts have been seen in possibly 70% (3,18,43,79). Ocular coloboma has been documented in a few cases (3,24). One of these patients (24) did not have a molecular deletion and perhaps did not have VCF syndrome.

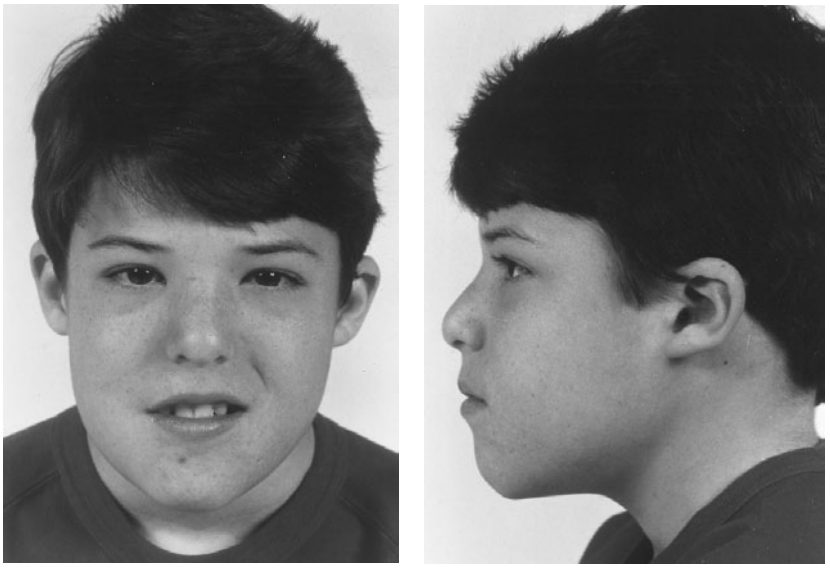
Fig. 21–38. *Velocardiofacial syndrome*. Two affected patients to the right contrasting sharply with their 6-year-old normal sister. Note narrow receding forehead, broad and prominent nasal bridge, upslanting short palpebral fissures, and epicanthal folds. (From P Meinecke et al, Eur J Pediatr 145:539, 1986.)

Ears. Small auricles and minor thickening of the helical rims have been seen in approximately 48% (Fig. 21–39B) (personal communication, Reyes and LeBlanc, 1997). Intermittent conductive hearing loss, noted in 75%, is probably secondary to frequent bouts of serous otitis media and cleft palate. Marked reduction in size of the nasopharyngeal lumen of the Eustachian tube has been noted. Sensorineural hearing loss has also been found in 8% (67, personal communication, Reyes and LeBlanc, 1997).

Cardiovascular aspects. Multiple, largely conotruncal, cardiac anomalies are present in 75%–80%, especially VSD (65%), right-sided aortic arch (35%), tetralogy of Fallot (20%), and aberrant left subclavian artery (20%) (31,40,65,84,87). McDonald-McGinn et al (45) found tetralogy of Fallot to be the most common finding in their series of 250 patients. Conversely, however, among patients with conotruncal anomalies, approximately 8% had 22q11 deletions (75). The combination of pulmonary atresia/VSD has been noted (63). Among patients with interrupted aortic arch type B (between left carotid and left subclavian arteries), 9 of 11 had the deletion (58). Aortic valve disease is not uncommonly found. Of interest and diagnostic significance, right-sided aortic arch was seen in 30% of patients with VSD, in 80% of those with tetralogy of Fallot, and in nearly 50% of patients with otherwise normal hearts. Approximately 10% die from congenital heart anomalies in early infancy (60). MacKenzie et al (42), Goldberg et al (24), Finkelstein et al (17), and D'Antonio and Marsh (9) noted enlargement, medial displacement, and tortuosity of the internal carotid arteries in the posterior pharyngeal wall in approximately 25% (Fig. 21–40). The carotids straighten out with age (30a). Goldmuntz et al (26) and Mehraein et al (46) found that approximately 20%–30% of "nonsyndromal" patients with conotruncal defects had the deletion. Takahashi et al (75) arrived at a figure of approximately 8% for a corresponding group. Transposition of the great arteries was associated with the deletion in 12% of 32 patients (47).

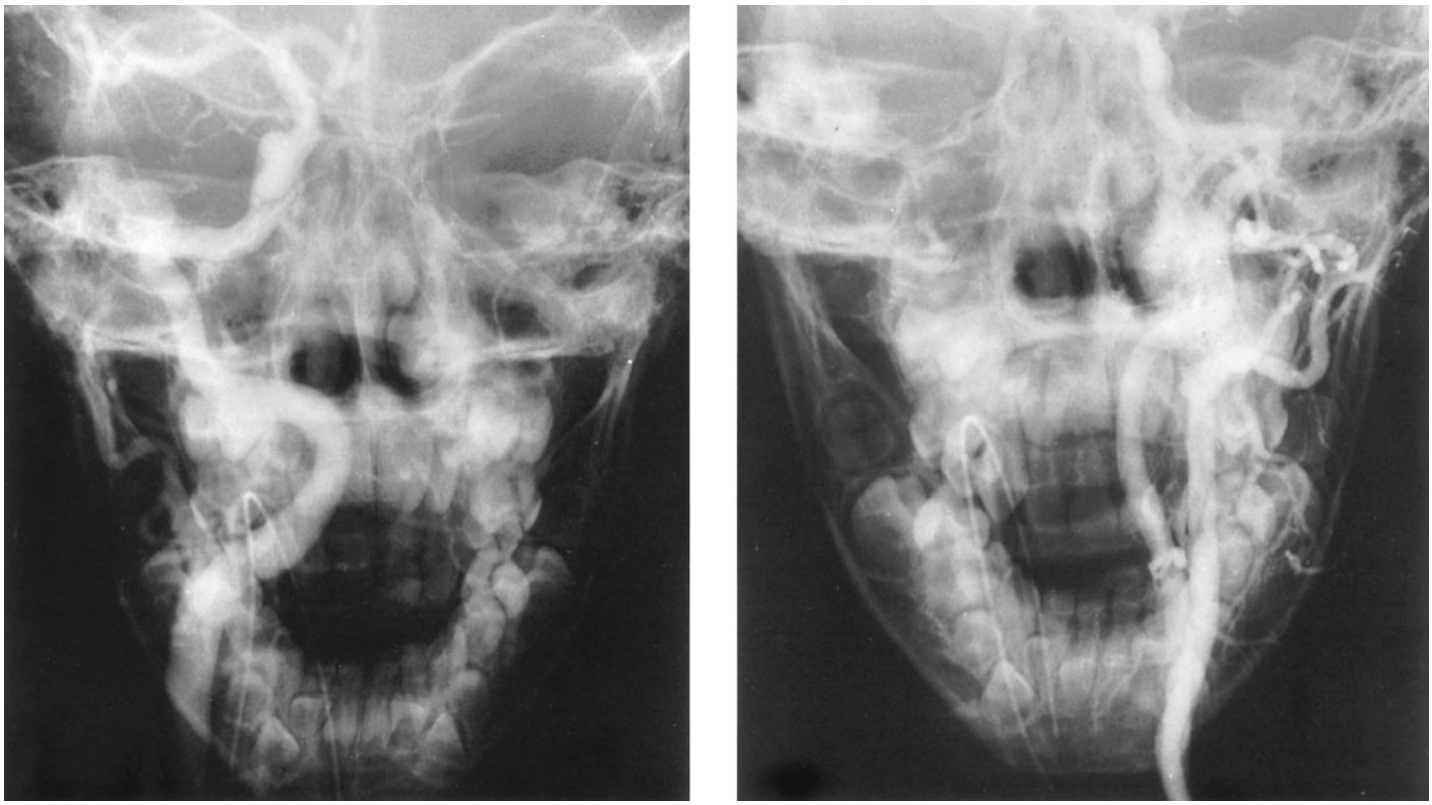
A number of patients have exhibited Raynaud's phenomenon.

Mental status. Learning disability to some degree is experienced by virtually all patients, although mild mental retardation is found in approximately 45% (36,74,74a,82). Severe retardation is rare in the syndrome. Language development is often slow (21). Speech is hypernasal, because of dysfunction of the velopharyngeal mechanism (Le Blanc, personal communication, 1997). The voice is hoarse and high-pitched. In secondary school age children, IQ scores ranged from 69 to 87 on verbal scale and 55 to 78 on performance scale (25,74). Mathematical concepts were poorly understood (52).



A B

Fig. 21–39. *Velocardiofacial syndrome*. (A,B) Note similar facies as well as small pinnae. (Courtesy of K MacKenzie, Toronto, Ontario, Canada.)



A B

Fig. 21–40. *Velocardiofacial syndrome*. (A,B) Carotid arteriograms showing tortuous right internal carotid artery and smaller than usual left internal carotid artery. (Courtesy of K MacKenzie, Toronto, Ontario, Canada.)

At all ages, the children tended to have bland affect (25). Social interaction was poor with respect to quality and quantity. The children were described as demonstrating extremes of behavior, being disinhibited, impulsive, and very affectionate or serious and shy. Reading comprehension, auditory processing deficit, mathematics, and comprehension of abstract concepts are especially poor (36). Most patients develop a spectrum of psychiatric disorders that include bipolar spectrum disorders and attention deficit disorder with hyperactivity. Those younger than 18 years old were affected with bipolar disorder. Older patients manifested paranoid and grandiose delusions (7). A suggestion has been made that a gene for schizophrenia at 22q11.2 may be deleted (26,32,56,68). Demyelination/gliosis, cerebellar atrophy, cerebellar hypoplasia, and cysts have been described (1,12,41,50). Neural tube defect is apparently increased (54,55).

Musculoskeletal findings. Hypotonia in infancy and childhood is frequent (40). Approximately 35%–50% are below the 3rd centile in height (24,40,79). Approximately 25% have umbilical or inguinal hernia and 15% have scoliosis (24,40,79). Talipes is found in 10% (40). The hands and fingers appear slender and tapered in approximately 60% (24). The digits may be hyperextensible. Radiographically, there is platybasia in 75%. Chiari I malformation is seen in 20%, occipitalization of the atlas in 15%, and velar paralysis in 25% (30b). Skeletal anomalies principally involving the extremities, ribs, and/or vertebrae have been noted in approximately 35% (49).

Anogenital and renal anomalies. Hypospadias has been noted in approximately 10% of males (24,40). Anal anomalies have also been reported (82,83). Silent renal anomalies have been found in 35% (60).

Immunologic and endocrine findings. Failure to thrive in infancy is seen in approximately 25%. Absent or small thymus (10%), tonsils (50%), and adenoids (85%), T-lymphocyte dysfunction, and hypocalcemia in infancy, noted in approximately 15%, indicate an association with the *DiGeorge sequence* (57,70,80). Ryan et al (60) found hypocalcemia in 60%. Autoimmune diseases (juvenile rheumatoid arthritis, Hashimoto thyroiditis) appear to be increased (13). Devriendt et al (12a) suggested that the annual incidence of velocardiofacial/DiGeorge syndrome was 1 per 4000.

Oral manifestations. In one study, cleft palate (35%), submucous cleft palate (33%), and occult submucous cleft palate or velar paresis (33%) resulting in hypernasal speech were found in nearly all patients, but this surely reflected ascertainment bias (24). In a more unbiased study, 10% had cleft palate whereas 35% had velopharyngeal insufficiency (60). McDonald-McGinn et al (45) found 27% with velopharyngeal incompetence. Lipson et al (40) and others (45) found that 2%–5% had cleft lip. Class I malocclusion is a common finding. The pharynx is hypotonic (Fig. 21–41). Obstructive sleep apnea has been found in approximately one-half of the neonates. Adenoidectomy and tonsillectomy must be avoided in these patients (17).

Diagnosis. *CHARGE association* must be excluded. Facial paresis may be in CHARGE association. Approximately 8% of patients with DiGeorge syndrome have unilateral facial nerve paralysis (82). There is some overlap with the *Ritscher-Schinzel (3C syndrome)* (12). The same deletion has been identified in some examples of *asymmetric crying facies* and anterior laryngeal webs (19,72) and *Kenny-Caffey syndrome* (61). The initial belief that the autosomal dominant form of *Opitz BBB/G syndrome* maps to the same area has been disputed (85). Bilateral cleft lip-palate with median facial dysplasia seems to have 22q11.2 deletion (62a), a group we have obviously missed because of phenotypic bias.

Prenatal diagnosis of 22q11 deletions has been made in fetuses with conotruncal anomalies (14,59).

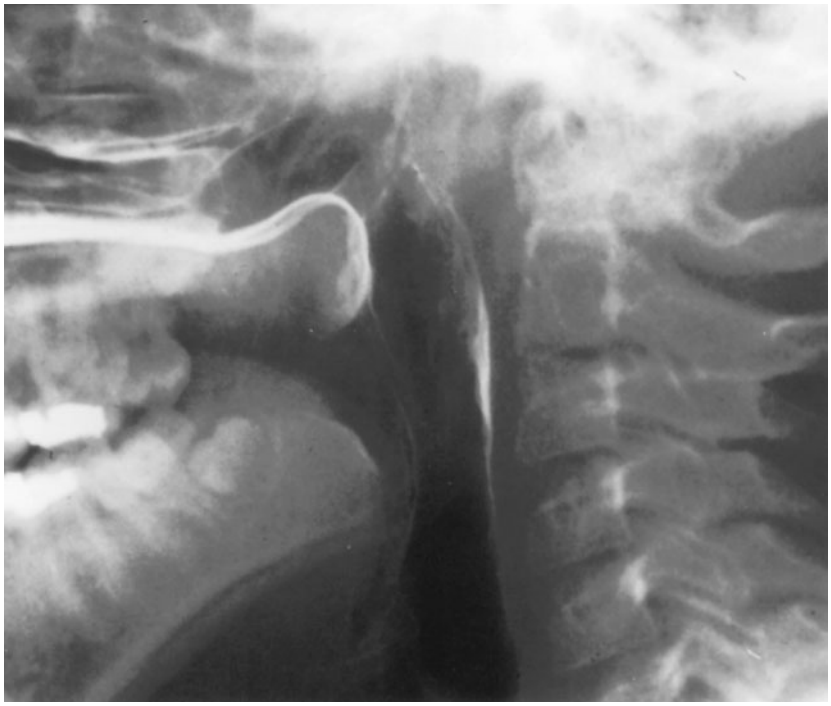


Fig. 21–41. *Velocardiofacial syndrome*. Videofluoroscopy showing inadequate velopharyngeal closure during speech. (Courtesy of K MacKenzie, Toronto, Ontario, Canada.)

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Velo-facio-skeletal syndrome

Teebi et al (1), in 1995, described a mother and daughter with short stature, unusual face, nasal speech, and skeletal anomalies.

The facies was characterized by elongated face, mild hypertelorism, broad high nasal bridge, and high arched palate. Both had nasal speech, but no mention was made of velopharyngeal insufficiency.

The hands and feet were short with prominent finger pads and hyperextensible finger joints. Mesomelic brachymelia was noted. Stature was small.

There was some facial resemblance to *velocardiofacial syndrome*, but no deletion at 22q11 was found on FISH study.

Reference (Velo-facio-skeletal syndrome)

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Chapter 22
Orofacial Clefting Syndromes: Other Syndromes

Aase-Smith syndrome I

Aase and Smith (1) in 1968 and Patton et al (3) in 1985 reported two generation inheritance of hydrocephalus, severe contractures of joints, dysmorphic pinnae, and cleft palate (Fig. 22–1). In each case, the parent was less severely affected (Fig. 22–2).

All extremities, including the fingers, were contracted (Fig. 22–3). There were thoracic scoliosis and dislocated hips (1). Talipes was seen in the other family (3).

The facies was normal, but the pinnae were dysmorphic in the patients of Aase and Smith (1). However, in those of Patton et al (3), there were broad forehead, short palpebral fissures, and broad nasal bridge. Cleft palate was found in most cases (1,3).

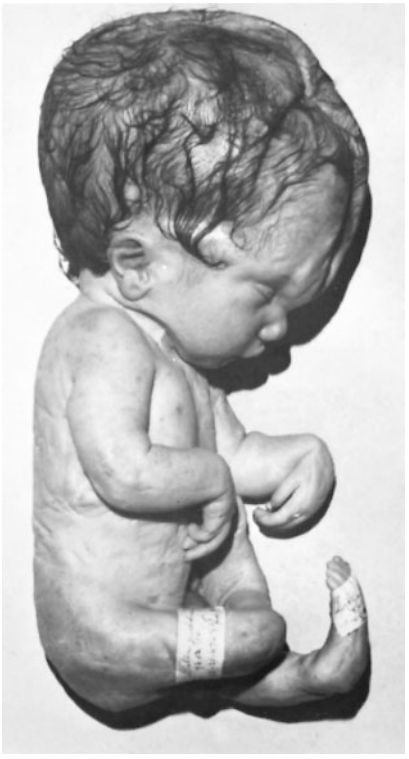
Dermal ridge patterning of palms and fingertips was hypoplastic.

Autopsy showed Dandy-Walker formation in the infants but not in the affected parent. A neuroblastoma was found in the adrenal in one case (1). A possible additional example is that of Potter and Parrish (4).

Dandy-Walker malformation may be an isolated finding or seen in combination with many disorders such as Joubert syndrome, *Walker-Warburg syndrome*, the *oral-facial-digital syndromes*, and, rarely, *Ellis-van Creveld syndrome*.

There is, at times, overlap with *Gordon syndrome*.

Fig. 22–1. *Aase-Smith syndrome I*. Hydrocephalus, cleft palate, malformed pinnae, joint contractures, hip dislocation. (From JM Aase and DW Smith, J Pediatr 73:606, 1968.)



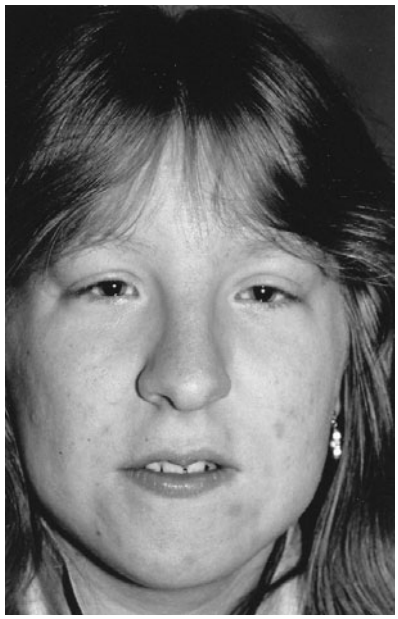


Fig. 22–2. *Aase-Smith syndrome I*. Mother of similarly affected child. Note broad forehead, broad nasal bridge, and short palpebral fissures. (From MA Patton et al, Clin Genet 28:521, 1985.)

References (Aase-Smith syndrome I)

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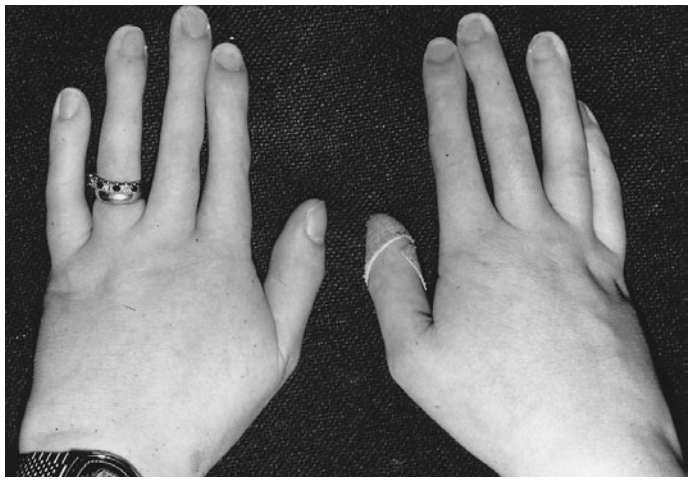
Fig. 22–3. *Aase-Smith syndrome I*. Long thin fingers. Note absence of finger creases. Patient was unable to make a fist. (From MA Patton et al, Clin Genet 28:521, 1985.)



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Aase-Smith syndrome II (Blackfan-Diamond syndrome)

Aase and Smith (1) reported male sibs with congenital hypoplastic anemia, triphalangeal thumbs, hypoplastic radii, and cleft lip (Fig. 22–4). One sib had narrow shoulders. Murphy and Lubin (11) described a male child with cleft lip-palate, congenital erythroid hypoplasia, and triphalangeal thumbs. Also noted were somatic and mental retardation, narrow shoulders, abnormal pigmentation of the skin, and short webbed neck. There was a family history of a similar thumb anomaly. Muis et al (10) reported a male infant with cleft lip-palate, congenital hypoplastic anemia, and triphalangeal thumbs. Others (9,12–16) have reported similar examples but without cleft lip and/or palate. RJ Gorlin has seen a child with cleft palate, strabismus, and Blackfan-Diamond syndrome. Approximately 10% of patients with Blackfan-Diamond syndrome have CL(P). K. Gripp et al (5a) noted microtia. Hasan and Inoue (7) described a child with cleft palate, microtia, and Blackfan-Diamond anemia. Cousins with cleft palate and microtia were noted by Gripp et al (5). Halal et al (6a) misdiagnosed a case as Nager syndrome.

We consider the combination of anomalies described by Aase and Smith to be Blackfan-Diamond syndrome (3,4). All of the anomalies reported by Aase and Smith have been described as part of the syndrome. These have been well tabulated by Alter (2) and Ball et al (3). Included are short stature, congenital hypoplastic anemia, triphalangeal or bifid or absent thumbs, hypoplastic thenar eminences, webbed neck, flat nasal bridge, narrow shoulders, cleft lip and/or palate, macrocytosis, elevated HbF, and erythrocytic adenosine deaminase. The gene has been mapped to 19q13 (6).

Although most examples are sporadic, some examples appear to autosomal dominant or recessive (8). Others present as a contiguous gene syndrome mapping to 19q13.2 (14).

References [Aase-Smith syndrome II (Blackfan-Diamond syndrome)]

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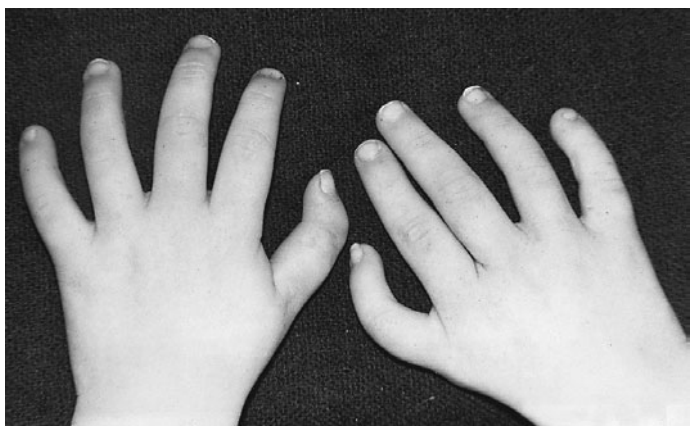
Fig. 22–4. *Aase-Smith syndrome II*. Digitalization of the thumbs. (Courtesy of JM Aase, Albuquerque, New Mexico.)



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Ablepharon-macrostomia syndrome

In 1977, McCarthy and West (7) reported a syndrome in two unrelated male children. Hornblass and Reifler (4) Price et al (9), Markouizos et at (6), and Stevens (personal communication, 2000) described the same condition. Common features were triangular facies, hypertelorism, late development of sparse thin hair, absence of upper and lower eyelids, eyebrows, and eyelashes, and internal strabismus. The pinnae were low-set and rudimentary in form with collapsed canals and associated hearing loss. The nose was small with some degree of coloboma formation of the mid-alae producing triangular nostrils. The zygomatic arches were flattened and the labial commissures were not adequately fused, producing macrostomia and thin vermilion (4) (Fig. 22–5A,B). The zygomatic arches may, in part, be missing (5).

The skin was dry and coarse with excess skin folds, especially over the hands and feet, buttocks, popliteal fossae, and neck. There was webbing between the proximal phalanges of the fingers and limitation of finger extension because of tight skin over the interphalangeal joints. The nipples were absent or hypoplastic (Fig. 22–5C).

Suggestion has been made that the gene maps to 18q (8). However, we suspect that the description better fits Barber-Say syndrome (vide infra). Affected sibs were described by Cruz et al (2,3) and Ferraz et al (3a). The father had a coloboma of his upper eyelid (3a).

The genitalia were ambiguous with posteriorly displaced micropenis, cryptorchidism, and absent scrotum (Fig. 22–5D). There was umbilical hernia or omphalocele in two of three cases.

The *Barber-Say syndrome* of hypertrichosis, atrophic skin, ectropion, and macrostomia has some resemblance to ablepharon-macrostomia. We suspect that the cases of Caesarino et al (1) and Pellegrino et al (8) have Barber-Say syndrome.

References (Ablepharon-macrostomia syndrome)

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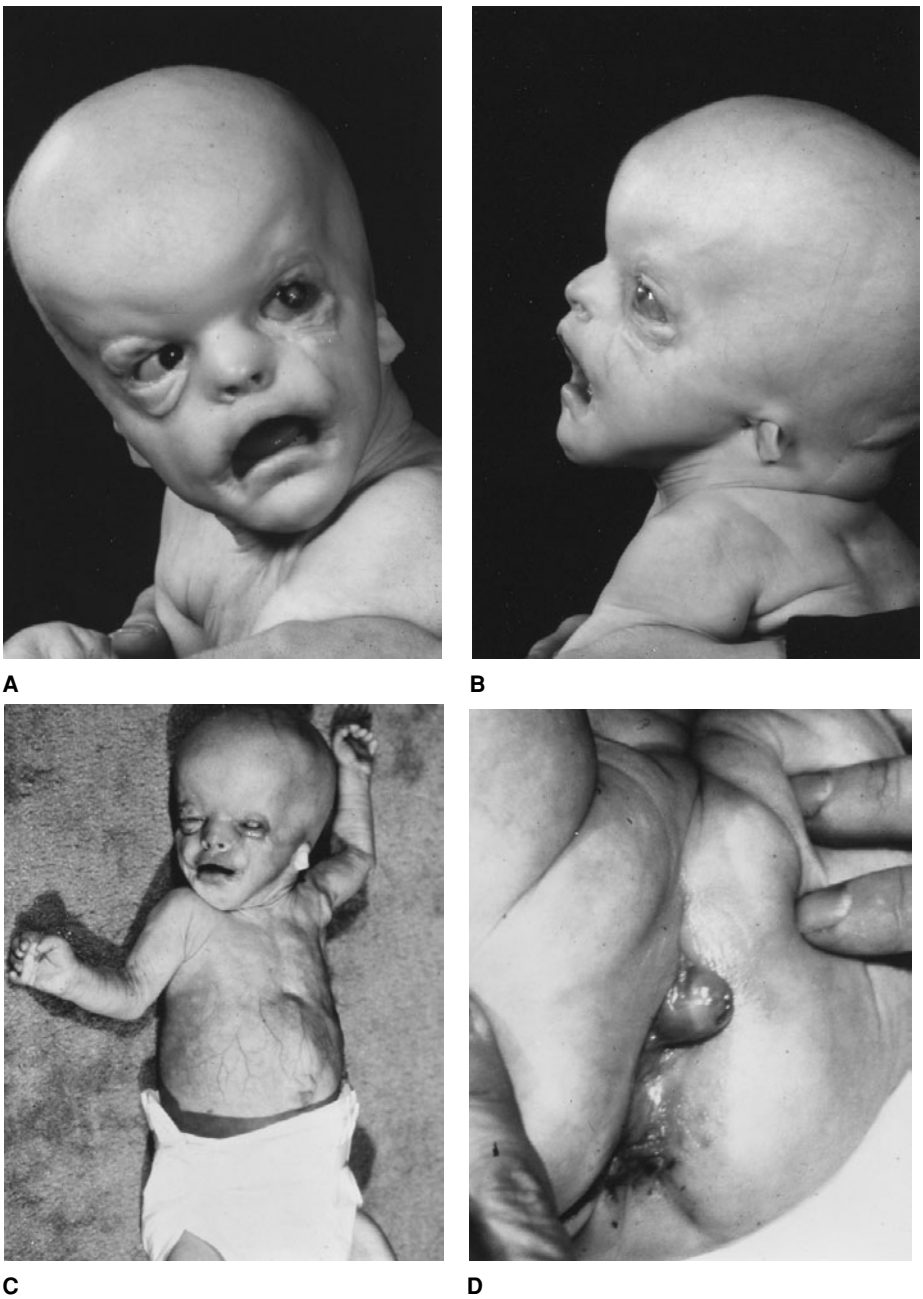

Fig. 22–5. *Ablepharon-macrostomia syndrome*. (A,B) Artificial eyelids made from nuchal skin. Note corneal opacity, macrostomia, indentation in malar arch, microtia and external auditory atresia. (C) Eyelids have been constructed. Note pronounced vascularity of skin of abdomen, dysplastic ears. (D) Ambiguous genitalia with posteriorly displaced micropenis, cryptorchidism, and absent scrotum. (A–D courtesy of S Sklower Brooks, Staten Island, New York.)

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Hirschsprung disease and cleft lip and/or palate (Goldberg-Shprintzen syndrome)

Goldberg and Shprintzen (5) described sibs with unusual facies, microcephaly, neonatal hypotonia, short stature, aganglionic megacolon of the short type, and submucous cleft palate. Sibs were also reported by Kumasaka and Clarren (9) and Yomo et al (16). One of the latter had cleft lip-palate, the other cleft palate. At least 20 patients have been described (1–7,9,11,17,18). A less likely example is that of Brunoni et al (3). Consanguinity was documented by Hurst et al (7) and Brooks et al (2), and autosomal recessive inheritance is possible. Possible localization to 2q22–q23 has been suggested.

The facies was characterized by microcephaly, fine scalp hair, hypertelorism, narrow palpebral fissures, synophrys, thick eyebrows, thick curly eye lashes, prominent nose with broad nasal bridge, large ears with indented lobes, maxillary hypoplasia, microstomia, and pointed chin (Fig. 22–6). Ptosis was noted in a few patients (7,16). Iris coloboma has been reported in 30% (7). Submucous cleft palate was noted by Goldberg and Shprintzen (5).

All have been mentally retarded (IQ 25–60). Abnormal cranial computed tomography (CT) scan has been noted in most patients (agenesis of corpus callosum, atrophy of white matter, enlarged ventricles), abnormal electroencephalographic findings in a few patients (7,11,17), agenesis of the corpus callosum, and congenital heart disease (ASD, VSD, PDA) in 30% (6,11,17).

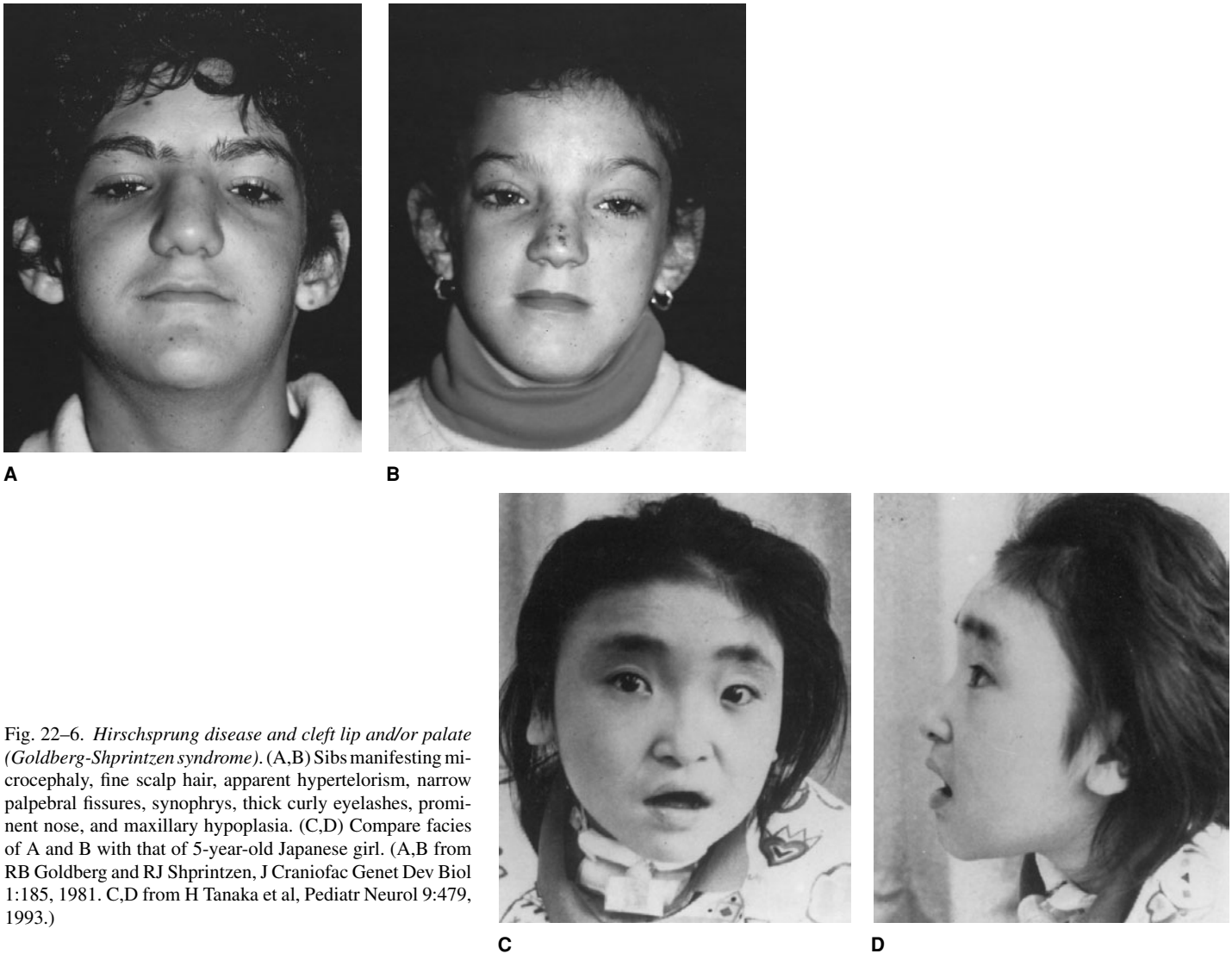

Fig. 22–6. *Hirschsprung disease and cleft lip and/or palate (Goldberg-Shprintzen syndrome).* (A,B) Sibs manifesting microcephaly, fine scalp hair, apparent hypertelorism, narrow palpebral fissures, synophrys, thick curly eyelashes, prominent nose, and maxillary hypoplasia. (C,D) Compare facies of A and B with that of 5-year-old Japanese girl. (A,B from RB Goldberg and RJ Shprintzen, J Craniofac Genet Dev Biol 1:185, 1981. C,D from H Tanaka et al, Pediatr Neurol 9:479, 1993.)

Aganglionic megacolon has also been seen with submucous *cleft palate and paramedian pits of the lower lip* (16), with bilateral cleft lip-palate (15), with cleft palate and hearing loss (1), *Aarskog syndrome*, and *Waardenburg syndrome*. The report of Hirschsprung anomaly with bicolored irides is probably Waardenburg syndrome (10). It is also seen in approximately 6% of those with trisomy 21. There is increased frequency in severe *Smith-Lemli-Opitz syndrome, Nager syndrome*, *Bardet-Biedl syndrome, cartilage-hair hypoplasia, multiple endocrine neoplasia, types 2A and 2B, Aarskog syndrome, rubella embryopathy*, Kaufman-McKusick syndrome, and primary hypoventilation syndrome.

Hirschsprung disease is heterogeneous. At least four genes have been mapped, one at 10q11.2 and the others at 13q22, 19p13.3, and 5p13.1 (12,14).

References [Hirschsprung disease and cleft lip and/or palate (Goldberg-Shprintzen syndrome)]

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Baraitser syndrome and cleft lip-palate

Baraitser syndrome is a presumed autosomal recessive pattern of anomalies defined on the basis of a 5 1/2-year old female of normal karyotype and an 18-week-old male fetus (1). There was one normal sib. Both parents were normal and consanguinity was denied.

The 5 1/2-year old proband manifested craniosynostosis involving the coronal suture, mental retardation, seizures, choroidal colobomas, mild hypertelorism, beaked nose, cleft lip-palate, protuberant ears, mild mesomelic shortening of the upper and lower extremities, short broad fingers, and cystic dysplastic kidneys.

A second case was diagnosed prenatally by fetoscopy at 16 weeks. The presence of cleft lip was indicative with high probability of the full syndrome. The pregnancy was terminated and postmortem examination at 18 weeks showed cleft lip-palate, small posterior fontanel, and findings consistent with choroidal coloboma.

Reference (Baraitser syndrome and cleft lip-palate)

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Bencze syndrome (facial asymmetry, strabismus, and submucous cleft palate)

The Bencze syndrome (1,2) consists of mild facial asymmetry, esotropia, amblyopia, and submucous cleft palate. The syndrome has autosomal dominant inheritance with variable expression. On the hypoplastic side, the palpebral fissure is usually upslanting (Fig. 22–7). Other body proportions are symmetric.

References [Bencze syndrome (facial asymmetry, strabismus, and submucous cleft palate)]

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Blepharo-cheilo-dontic (BCD) syndrome

Blepharo-cheilo-dontic (BCD) syndrome was first brought to our attention by Piper (14) in 1957. From reading his publication one can tell relatively little about the child he illustrated. However, one can see euryblepharon, ectropion of lower eyelids and bilaterally cleft lip-palate. Gorlin et al (7), in a 1996 review, suggested the term "blepharo-cheilo-dontic syndrome."

Allanson and McGillivray (1) were probably the first to report a large, four-generation family with euryblepharon, ectropion of lower eyelids, bilateral cleft lip-palate, and conically-shaped anterior teeth. Eyebrows, eyelashes and scalp hair were sparse. Among the 20 affected members, approximately 25% had cleft lip and/or palate, 40% had ectropion and approximately 50% had teeth with conical crown form. Several other large kindreds and numerous isolated examples have been published (6–8,10,11).

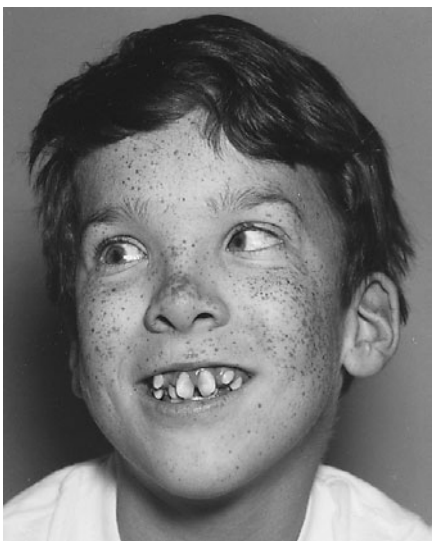
Inheritance is autosomal dominant with full penetrance and variable expressivity (1,6,7,10,11).

Ophthalmologic findings. The upper eyelid may be the site of a double row of eyelashes (distichiasis); the lower eyelid exhibits ectropion (Fig. 22–8A). The palpebral fissures are wider than normal (euryblepharon). As a result, the eyes often cannot be closed (lagophthalmia). Ankyloblepharon has also been noted (8).

Euryblepharon is bilaterally symmetrical and is often accompanied by epiphora and conjunctivitis. It has been present in approximately 70% of the patients. Approximately 60% manifest distichiasis, an accessory row of lashes that may consist of only a few cilia running along the inner part of the intermarginal strip, occupying the site of the orifices of the Meibomian glands. The lashes are usually small, soft, and fine. Ectropion, an outward turning of the lower eyelid, was seen in approximately 40%. Lagophthalmia, a condition in which the eye cannot be entirely closed, has been described in association with euryblepharon (16,19) and has been documented in approximately 25%.

Cutaneous findings. Some patients have sparse scalp hair, eyebrows, and eyelashes (1,8). The nails have been hypoplastic in a few patients (10).

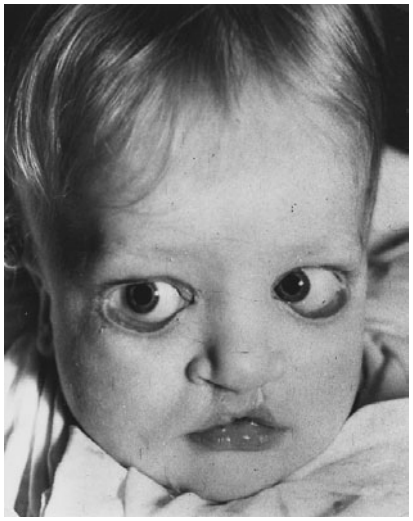
Oral findings. The oral changes consist of cleft lip-palate, usually bilateral (Fig. 22–8A). Although most patients have come to attention because of this, not all have this anomaly. Falace and Hall (6) found only 15% with cleft lip or palate, whereas Anderson and McGillivray (1) noted 25% with clefts. All the patients of Korula et al (10) had bilateral cleft lip-palate whereas one of our 8 patients did not have a cleft (7).



A

B

Fig. 22–7. *Bencze syndrome*. (A) Primary telecanthus, strabismus, malocclusion. (B) Aunt of proband showing facial asymmetry and upslanting palpebral fissure on hypoplastic side. (From D Kurnit et al, Clin Genet 16:301, 1979.)



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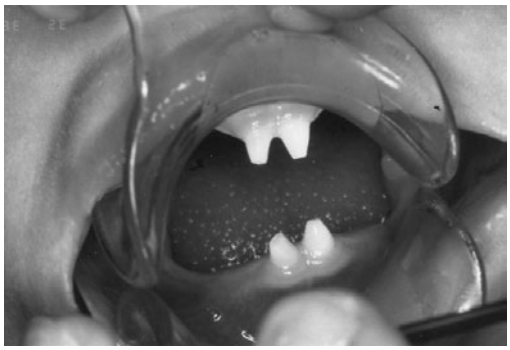

B

Fig. 22–8. *Blepharo-cheilo-dontic (BCD) syndrome*. (A) Ectropion of lower eyelids, bilateral cleft lip-palate, lagophthalmia, euryblepharon. (B) Oligodontia. Note reduced crown form. (From RJ Gorlin et al, Am J Med Genet 65:109, 1996.)

Reduction in the number of teeth and anterior teeth with conical crown form is a common finding (Fig. 22–8B). Falace and Hall (6), noting these changes in 75%, Anderson and McGillivray (1) in 50%, Korula et al (10) in 12%, and Gorlin et al (7) in over 80%.

Other findings. A miscellaneous group of findings include: umbilical hernia (8), sinus of frontotemporal area (8), small head circumference (8), imperforate anus (1,8), nasolacrimal obstruction (8), syndactyly of first two fingers (11), pili torti (11), and dermoid of lateral eyelids (10).

Differential diagnosis. Several of the changes described here have been reported as isolated findings or in other combinations. Hence, we cannot judge in many cases whether one is dealing with the syndrome. For example, Becker (3) and Weve (20) reported severe euryblepharon with ectropion of lower eyelids. Duke-Elder (5) noted a combination of euryblepharon, ectropion of lower eyelids, and lagophthalmia. Ectropion of the lower eyelid may be a solitary finding or it may be seen in *postaxial acrofacial dysostosis*. Distichiasis, often inherited as an isolated autosomal dominant trait (4,12), may be associated with ectropion, and can be found with lymphedema and/or spinal extradural cysts (15,17,18). Picó (13) found 13 of 20 affected in 3 generations with distichiasis and/or ectropion.

Patients with CL(P) exhibit agenesis of teeth more often than do normal individuals. The differential diagnosis of syndromes having oligodontia and/or microdontia is legion and does not warrant discussion here. Distichiasis has been reported in combination with cleft palate in a child with Robin sequence, but there is no evidence that this child had blepharo-cheilo-dontic syndrome (2). Neither did the patient described by Jester (9) with lymphedema, distichiasis and cleft palate. A male patient with some overlapping findings was seen in Gentofte Hospital, Gentofte, Denmark in 1973 by M. Warburg. Findings included repaired bilateral cleft lip-palate, euryblepharon, lagophthalmia, and ectropion of lower eyelids. However, his other findings have not been noted in any other patient with blepharo-cheilo-dontic syndrome. These include colobomas of choroid and optic nerve, mild microphthalmia, atrial septal defect, sensorineural hearing loss, short stature, and hypogonadism (micropenis). His appearance was illustrated in the 1976 edition of *Syndromes of the Head and Neck*.

References [Blepharo-cheilo-dontic (BCD) syndrome]

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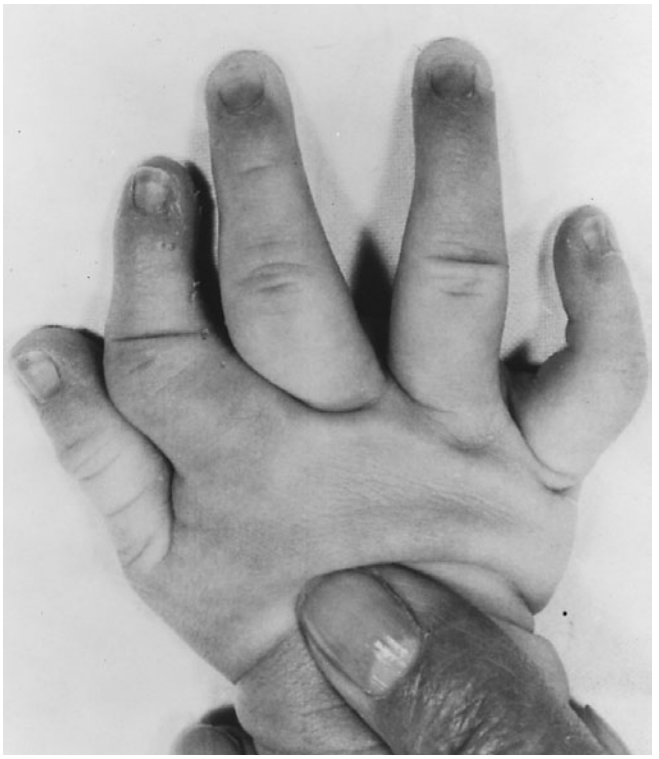
Catel-Manzke syndrome (palatodigital syndrome)

Catel (3), in 1961, and Manzke (13), in 1966, reported the same patient with cleft palate, micrognathia, and bilateral clinodactyly (radial angulation) of the index finger (Fig. 22–9). Approximately 25 cases (1-19,21) have been documented to date, all but five (5,9,12) in males. RJ Gorlin and MM Cohen, Jr. have each seen a case of the syndrome in a female patient. Although there has been some familial aggregation (2,8,17), in our view X-linked recessive inheritance is not tenable and recurrence risk is low. We cannot accept the case of Petit et al (14) as an example of the syndrome.



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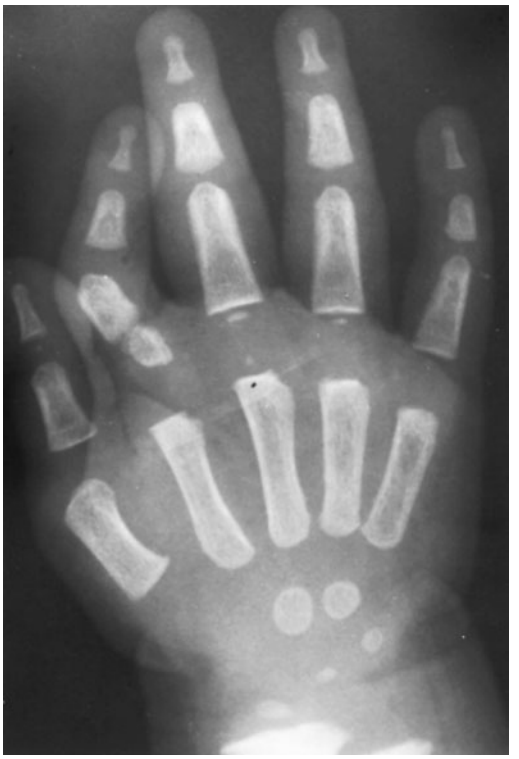

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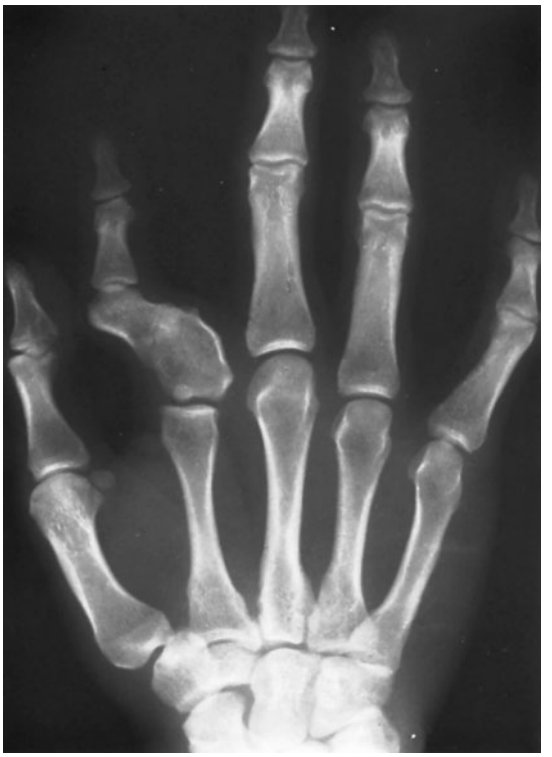


C

Fig. 22–9. *Catel-Manzke syndrome*. (A) Note marked clinodactyly of index finger. (B) Note separate bone at base of proximal phalanx of index finger. (C) Same anomaly in older patient, but fusion has taken place. (A courtesy of E Brude, Eur J Pediatr 142:222, 1984. B,C from W Holthusen, Ann Radiol 15:253, 1972.)

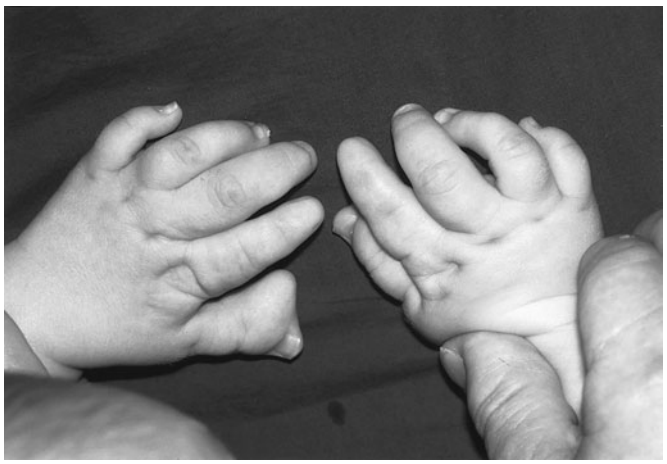
The cranium may be globular in shape with shallow orbits. Dysmorphic ears have been noted in 35%. Approximately 90% have cleft palate and small mandible and have been classified as examples of Robin sequence. One child had cleft lip-palate (16). The neck has been noted to be short in approximately 40%.

Postnatal growth delay has been found in at least 65% (20).

In addition to hyperphalangy of the index finger, other anomalies of the extremities have included short fingers and toes (50%), clinodactyly of 5th fingers (35%), single palmar creases (40%), and talipes equinovarus (15%). Other skeletal defects have been pectus excavatum (20%), joint laxity (25%), and vertebral/rib anomalies (20%) (7,10,19).

Cardiac septal defects (ASD, VSD), overriding aorta, aortic coarctation and dextrocardia have been found in 50% (7,8,15,17,18).

Radiographically, the clinodactyly is seen to result from an accessory bone, irregular in form, located between the shortened second metacarpal and the corresponding shortened proximal phalanx of the index finger.



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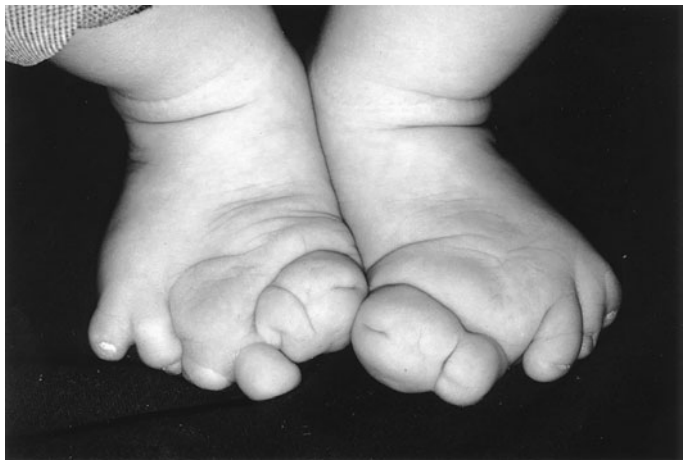

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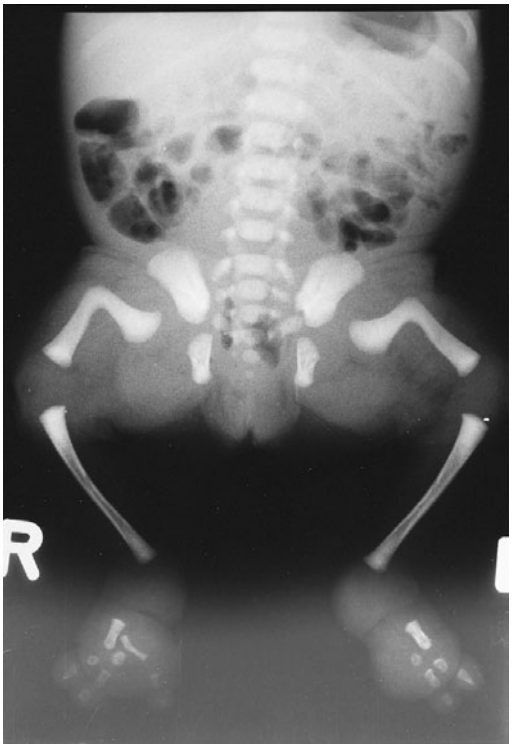

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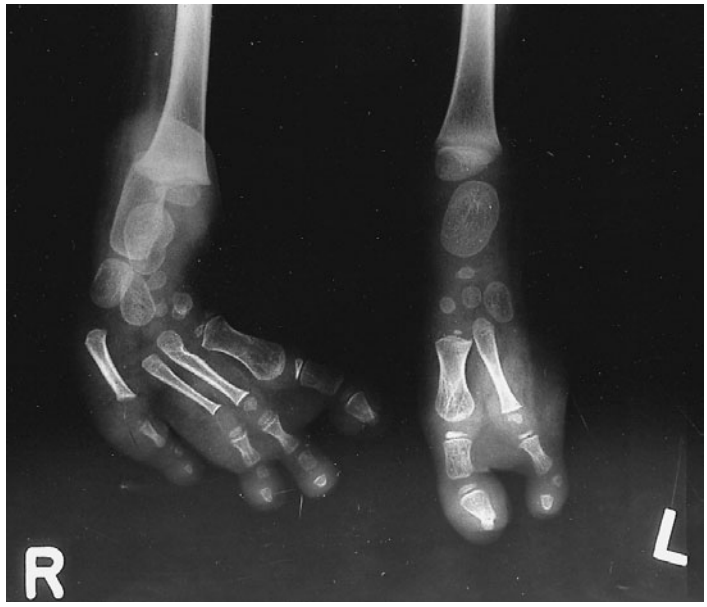

D

Fig. 22–10. *Cleft lip-palate, agenesis of fibula and ulna, bowing of femora, and contractures (Fuhrmann syndrome).* (A,B) Dysplastic digits with nail aplasia. (C) Bent femora, unusual shape of ilia, absence of femora, oligodactyly. (D) Talipes, asymmetric oligodactyly. (From W Fuhrmann et al, Eur J Pediatr 133:123, 1980.)

With time, the supernumerary bone fuses with both the radially deviated proximal phalanx and the metacarpal (10) (Fig. 22–9A,B). Miscellaneous bony anomalies have included bifurcated first metacarpal (10) and multiple vertebral anomalies (17).

Having the same digital anomalies but a different phenotype (bushy eyebrows, prominent eyes, hallux valgus, bronchomalacia, and no cleft palate) is a child reported by Chitayat et al (4). Several other disorders having hyperphalangy of the index fingers (of a different kind) clearly represent other conditions. Devriendt et al (4a) described severe short stature, severe mental retardation, unusual facies, and an additional phalanx in the index fingers with short second metacarpal. Hyperphalangism may occur as an isolated finding (21) and as part of *Desbuquois syndrome*. The patient described by Wilson et al (20) was short, retarded and had iris coloboma. Two other patients are worthy of mention: Camera and Costa (2a) noted unilateral index finger involvement, VSD, and hearing loss while Temtamy et al (18a) found hyperphalangism of digits I–III, preaxial polydactyly, deafness, and talon cusps of the maxillary central incisors.

References [Catel-Manzke syndrome (palatodigital syndrome)]

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Cleft lip-palate, agenesis of fibula and ulna, bowing of femora, and contractures (Fuhrmann syndrome)

Pfeiffer et al (3), in 1998, described two sibs of Turkish origin. The parents were consanguineous. They cited the report of Fuhrmann et al (1) of three somewhat similarly affected sibs. Lipson et al (2) also described affected sibs. Inheritance is autosomal recessive.

Cleft lip and palate were noted only in the sibs reported by Pfeiffer et al (3). The cranium bulged. The neck was short. Communicating hydrocephalus, absence of cerebellar vermis, and Arnold-Chiari anomaly were reported (3).

Radiographically, the fibula was aplastic in all cases and the ulna was aplastic or hypoplastic. The radius was present. There was oligodactyly in one set of sibs (3), polydactyly in another set (1), and aplasia of nails. The humerus and tibia were normal, but the femur was markedly bowed and the pelvis abnormally shaped. All joints were somewhat contracted (Fig. 22–10).

References [Cleft lip-palate, agenesis of fibula and ulna, bowing of femora, and contractures (Fuhrmann syndrome)]

1. Fuhrmann W et al: Poly-, syn- and oligodactyly, aplasia or hypoplasia of fibula, hypoplasia of pelvis and bowing of femora in three sibs—a new autosomal recessive syndrome. Eur J Pediatr 133;123–129, 1980.

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Cleft lip-palate, pili torti, malformed ears, partial syndactyly of fingers and toes, and mental retardation (Zlotogora-Oğur syndrome)

In 1987, Zlotogora et al (12) and, in 1988, Oğur and Yüksul (5) reported sibs with a syndrome of cleft lip-palate, sparse hair with pili torti, partial syndactyly of fingers and toes, and mental retardation. Subsequently, approximately a dozen additional examples have been reported (1,2,6,7,9–11) (Fig. 22–11).

Inheritance is autosomal recessive. Mutations of PVRL1 which encodes a cell-cell adhesion molecule are responsible (8a). The gene maps to 11q23 and is allelic to *Margarita Island ectodermal dysplasia*.

The hair is sparse and abnormal in quality (kinky hair, pili torti). Hair loss occurs as the patient ages (1). The eyebrows are sparse, especially laterally. The skin of the palms and soles becomes hyperkeratotic. The nails may be dysplastic. Hypohidrosis is mild. Nipples may be hypoplastic (5,7,10).

Various tooth anomalies have been described: hypodontia, microdontia, and delayed eruption.

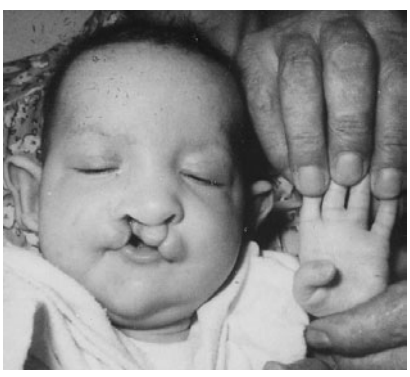
Cleft lip-palate has been present in most of the affected. The pinnae may be outstanding and/or dysmorphic. Hearing loss has been described in a few patients (5,7).

Mental retardation has been variable.

Partial syndactyly of fingers 2-3-4 and toes 2–3 is frequent. Rarely toes 4–5 are fused (9).

Various genitourinary anomalies have been reported (5,7,11).

There is some overlap with *AEC, EEC, Rapp-Hodgkin* and *Bowen-Armstrong syndromes*. The female child reported by Freihofer et al (3)



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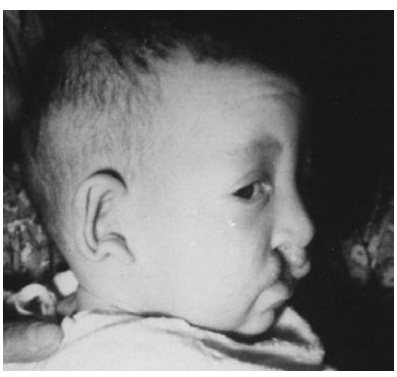

B

Fig. 22–11. *Cleft lip and palate, pili torti, malformed ears, partial syndactyly of fingers and toes, and mental retardation (Zlotogora-Oğur syndrome).* (A,B) Note high forehead, sparse hair, dysmorphic pinnae, bilateral cleft lip, partial soft tissue syndactyly of fingers 3–4, and transverse palmar crease. (From J Zlotogora et al, J Med Genet 24:291, 1987.)

was much more severely affected than those with Zlotogora-Oğur syndrome. We view cases 2 and 3 of Rosselli and Gulienetti (8) as a unique entity.

The girl described by Martinez et al (4) had cleft lip-palate, anodontia of deciduous dentition, oligodontia of permanent dentition, pili torti, long eyelashes, hypertelorism, prominent eyes, lagophthalmos, midface hypoplasia, syndactyly, and other findings. This is *BCD syndrome*.

References [Cleft lip-palate, pili torti, malformed ears, partial syndactyly of fingers and toes, and mental retardation (Zlotogora-Oğur syndrome)]

1. Bustos T et al: Autosomal recessive ectodermal dysplasia. An undescribed dysplasia/malformation syndrome. Am J Med Genet 41:398–404, 1991.
2. Falace PB, Hall BD: A new ectodermal dysplasia syndrome with syndactyly, cleft lip/palate and short stature. Proc Greenwood Genet Ctr 7:214–215, 1988.
3. Freihofer HP et al: Ectodermal dysplasia, cleft lip/palate, and severe cutaneous and osseous syndactyly in a mentally retarded girl: A new multiple malformation syndrome. Am J Med Genet 70:211–215, 1997.
4. Martinez RB et al: Cleft lip/palate-oligodontia-syndactyly-hair alterations, a new syndrome: Review of conditions combining ectodermal dysplasia and cleft lip/palate. Am J Med Genet 27:23–31, 1987.
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8. Rosselli D, Gulienetti R: Ectodermal dysplasia. Br J Plast Surg 14:190–204, 1961 (Cases 2,3).
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10. Zlotogora J: Syndactyly, ectodermal dysplasia and cleft lip/palate. J Med Genet 31:957–959, 1994.
11. Zlotogora J, Oğur G: Syndactyly, ectodermal dysplasia, and cleft lip and palate. J Med Genet 25:503, 1988.
12. Zlotogora J et al: Cleft lip and palate, pili torti, malformed ears, partial syndactyly of fingers and toes and mental retardation. J Med Genet 24:291–293, 1987.

Cleft lip-palate, ectodermal dysplasia, marked syndactyly, and mental retardation

Freihofer et al (1) reported a mentally retarded female with cleft lip-palate, severe cutaneous and osseous syndactyly, and ectodermal dysplasia.

The parents were consanguineous.

Short stature, head circumference below the 10th centile, and mental retardation were noted. The child was subsequently found to be congenitally hypothyroid. Eyebrows and eyelashes were ample. The scalp hair was thin and barely pigmented. Frontal bossing, high hairline, lagophthalmos, broad nasal base, hypoplastic maxilla, marked oligodontia, and bilateral cleft lip-palate were evident.

Marked cutaneous and osseous syndactyly with fused nails of fingers 2–4, broad metacarpals 3–5, and syndactyly of hypoplastic toes and absent distal phalanges were noted. The first metatarsals were broad.

There is considerable overlap with the autosomal recessive Zlotogora-Oğur syndrome (*cleft lip and palate, pili torti, malformed ears, partial syndactyly of fingers and toes, and mental retardation*) and the somewhat similar disorder reported by Martinez (2), which we have diagnosed as having *blepharo-cheilo-dontic syndrome*. However, the degree of syndactyly was much more severe.

The syndrome also has overlap with *cleft palate, congenital hypothyroidism, curly hair, and choanal atresia*.

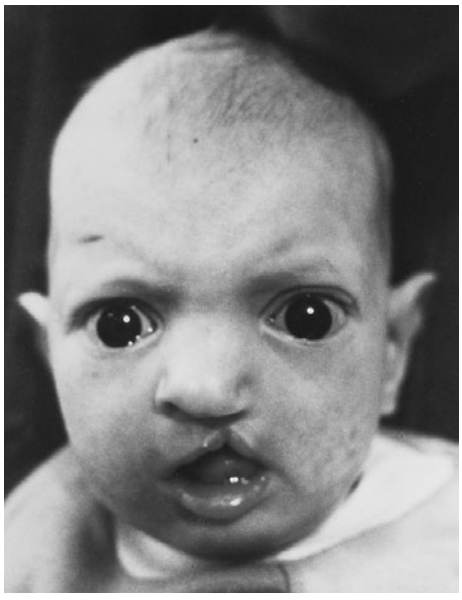
References (Cleft lip-palate, ectodermal dysplasia, marked syndactyly, and mental retardation)

1. Freihofer HPM et al: Ectodermal dysplasia, cleft lip/palate, and severe cutaneous and osseous syndactyly in a mentally retarded girl: A new multiple malformation syndrome. Am J Med Genet 70:211–215, 1997.
2. Martinez RB et al: Cleft lip/palate-oligodontia-syndactyly-hair alterations, a new syndrome: Review of the conditions combining ectodermal dysplasia and cleft lip/palate. Am J Med Genet 27:23–31, 1987.

Cleft lip-palate, prominent eyes, and congenital heart disease

Dinno (1), in 1987, described three generations with cleft lip-palate, large ears, prominent eyes, high forehead, hypertelorism, and a beak-shaped nose with a short philtrum (Fig. 22–12).

Possibly the same condition was described by Kumar et al (2).



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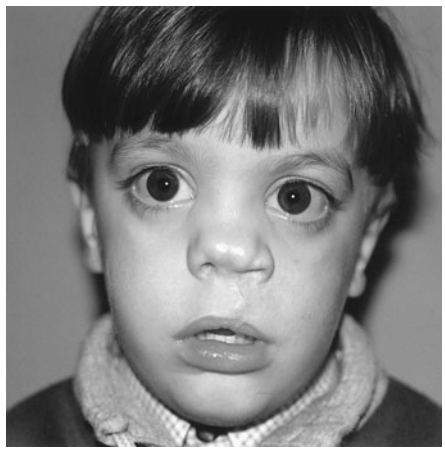
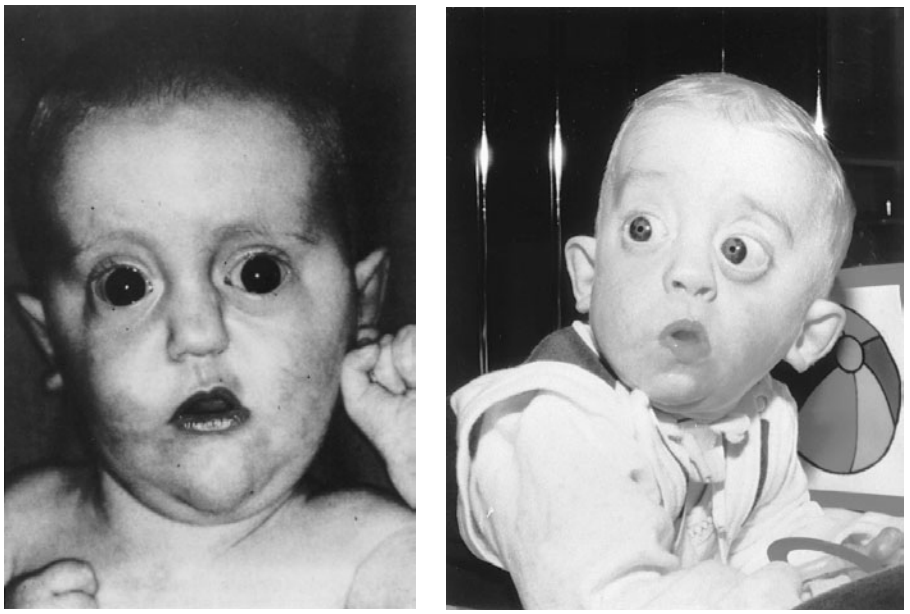


B

Fig. 22–12. *Cleft lip-palate, prominent eyes, and congenital heart disease*. (A) Note cleft lip, very prominent eyes, hypertelorism, short philtrum. (B) One of nonidentical twins whose mother was similarly affected. Note mild hypertelorism, wide flat nasal bridge, and repaired cleft lip. (A courtesy of ND Dinno, Seattle, Washington. B courtesy of D Kumar, Sheffield, England.)



A B

Fig. 22–13. *Prominent eyes, deglutition function, choanal stenosis, and cleft palate*. Female with prominent eyes, deviated nose, cleft palate, exophthalmos, interalveolar synechiae, severe deglutition dysfunction, and thoracolumbar kyphoscoliosis. (A from KH Ørstavik et al, Am J Med Genet 78:260, 1998. B courtesy of KH Ørstavik, Oslo, Norway.)

References (Cleft lip-palate, prominent eyes, and congenital heart disease)

1. Dinno ND: Cleft lip and cleft palate, high forehead, abnormal ears, prominent eyes and congenital heart disease in three generations: A new syndrome. March of Dimes Clinical Genetics Conference, Minneapolis, July, 1987.
2. Kumar D et al: A distinct syndrome of familial cleft lip and palate with prominent eyes and characteristic facies in two unrelated families. Clin Dysmorphol 5:295–301, 1996.

Prominent eyes, deglutition dysfunction, choanal stenosis, and cleft palate

Ørstavik et al (1), in 1998, reported a brother and sister with unusual facies and deglutition dysfunction. The unusual appearance was because of exophthalmos secondary to shallow orbits. There was nasal deviation and choanal stenosis. The ear lobules were prominent. The male sib had interjaw alveolar synechiae, ankylosis of the temporomandibular joint, and hypoplastic malar area. A sister had cleft palate (Fig. 22–13).

Both had severe deglutition dysfunction. The girl developed thoracolumbar kyphoscoliosis. Intelligence was normal.

Inheritance may be autosomal recessive or, less likely, an example of parental gonadal mosaicism.

One must exclude *cleft lip-palate, prominent eyes, and congenital heart anomalies* and *Cole-Carpenter syndrome*.

Reference (Prominent eyes, deglutition dysfunction, choanal stenosis, and cleft palate)

1. Ørstavik KH et al: Severe craniofacial malformations and deglutition dysfunction in a brother and sister: New syndrome? Am J Med Genet 78:260–262, 1998.

Cleft lip-palate, abnormal ears, congenital heart defect, and skeletal anomalies

The sibs described by Verloove-Vanhorick et al (1) had bilateral short femur and humerus, absence of one metacarpal and one metatarsal with partial soft syndactyly of fingers and toes, four lumbar vertebrae, tapering of proximal femur with absence of femoral head, and absence of calcaneus.

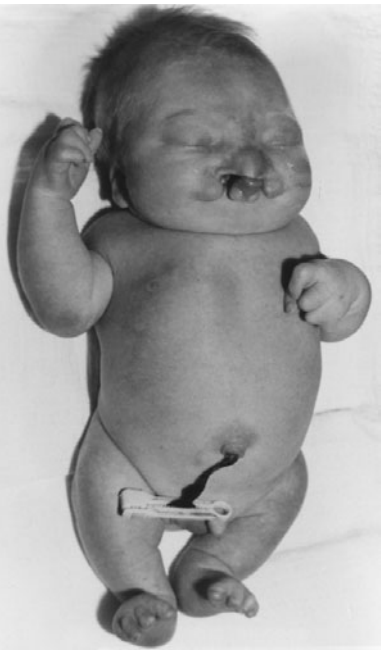
There were bilateral cleft lip-palate, micrognathia, and malformed pinnae with absent external meatus (Fig. 22–14). Internal anomalies included cryptorchidism, persistent truncus arteriosus, bilobed lungs, and parathyroid aplasia.

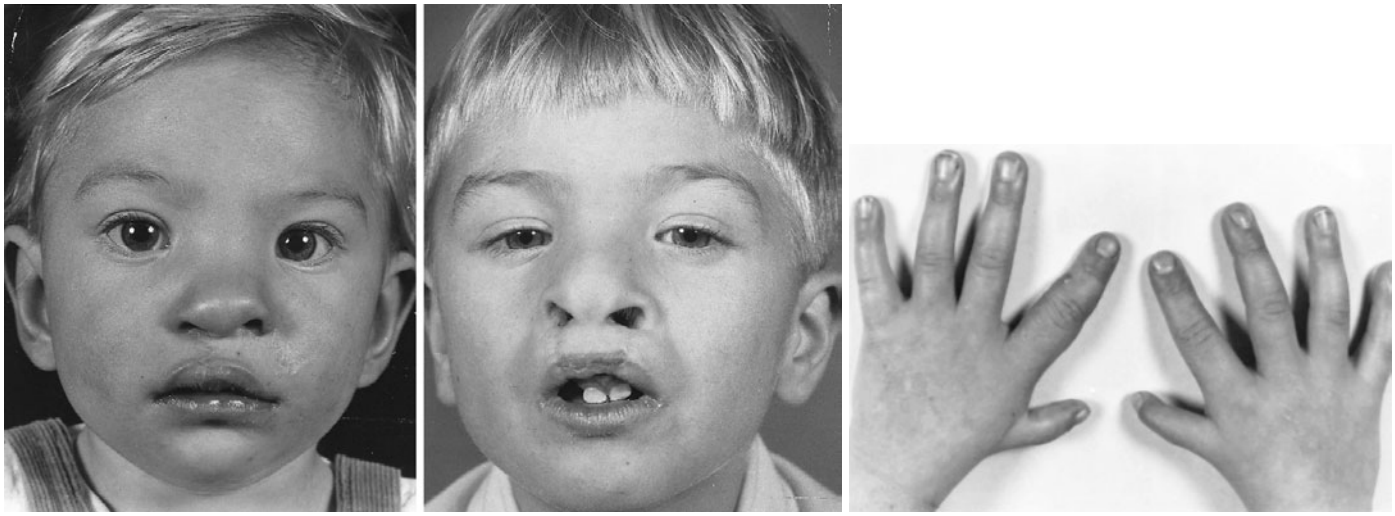
This lethal condition possibly had autosomal recessive inheritance.

Reference (Cleft lip-palate, abnormal ears, congenital heart defect, and skeletal anomalies)

1. Verloove-Vanhorick SP et al: Extensive congenital malformations in two siblings. Acta Paediatr Scand 70:767–769, 1981.

Fig. 22–14. *Cleft lip-palate, abnormal ears, congenital heart defect, and skeletal anomalies*. One of two sibs with bilateral cleft lip-palate and short extremities. (From SP Verloove-Vanhorick et al, Acta Paediatr Scand 70:767, 1981.)





A B C

Fig. 22–15. *Cleft lip-palate, microcephaly, and hypoplasia of radius and thumb (Juberg-Hayward syndrome).* (A,B) Sibs with cleft lip, hypertelorism, epicanthal folds, broad nasal bridge, and hypoplastic columella. (C) Severe hypoplasia of thumbs. (From RC Juberg and JR Hayward, J Pediatr 74:755, 1969.)

Cleft lip-palate, microcephaly, and hypoplasia of radius and thumb (Juberg-Hayward syndrome, orocraniodigital syndrome)

Juberg and Hayward (1), in 1969, reported three of six sibs with cleft lip-palate, mild microcephaly, hypertelorism, hypoplastic and distally positioned thumbs, limited extensions of the elbows because of anterior displacement of the radial head, and short stature (Fig. 22–15). Birthweight was low. Nevin et al (5), Kingston et al (4), and Kantaputra and Mongkolchaisup (2) described isolated examples. The child reported by Nevin et al (5) was found to have absence of the pituitary fossa and flattened vertebral bodies. There were no hormone deficiencies. Kingston et al (4) noted isolated growth hormone deficiency, micropenis, and bilateral thumb aplasia in their patient. Kato (3) tabulated several case reports, some of which may represent the condition. Verloes et al (9) described three isolated examples. Cleft lip-palate, upslanting eyebrows, hypertelorism, and anomalies of the extremities (luxation of radial head, hypoplasia/aplasia of the thumb), and horseshoe kidneys were noted as well as ptosis, anterior anal displacement, and mental retardation. Perçin et al (6) described a family with microcephaly, cleft lip-palate, digital anomalies, and congenital heart anomalies. The authors made comparison to Juberg-Hayward syndrome, but we cannot see the similarity. Silengo and Tornetta (8) described additional vertebral anomalies. The reader is referred to a recent survey (3). Overlap with *Malpuech syndrome* is discussed (7).

References [Cleft lip-palate, microcephaly, and hypoplasia of radius and thumb (Juberg-Hayward syndrome, orocraniodigital syndrome)]

1. Juberg RC, Hayward JR: A new familial syndrome of oral, cranial and digital anomalies. J Pediatr 74:755–762, 1969.
2. Kantaputra PN, Mongkolchaisup S: Juberg-Hayward syndrome: A new case report and clinical delineation of the syndrome. Clin Dysmorphol 8:123–128, 1999.
3. Kato K: Congenital absence of the radius with review of literature and report of three cases. J Bone Joint Surg Br 6:589–626, 1924.
4. Kingston HM et al: Orocraniodigital (Juberg-Hayward) syndrome with growth hormone deficiency. Arch Dis Child 57:790–792, 1981.
5. Nevin NC et al: A case of the orocraniodigital (Juberg-Hayward) syndrome. J Med Genet 18:478–480, 1981.
6. Perçin EF et al: A new syndrome with cardiac malformation, cleft lip-palate, microcephaly, and digital anomalies. Clin Genet 48:264–267, 1995.
7. Reardon W et al: An atypical case suggesting the possibility of overlap between Malpuech and Juberg-Hayward syndromes. Clin Dysmorphol 10: 123–128, 2001.
8. Silengo M, Tornetta L: Juberg-Hayward syndrome—report of a case with cleft palate, distally displaced thumbs and vertebral anomalies. Clin Dysmorphol 9:127–130, 2000.
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Cleft lip-palate, microcephaly, mental retardation, and holoprosencephaly

Martin et al (3) reported three generations of a large kindred in which there was variable expression of cleft lip and/or cleft palate, microcephaly, mental retardation, hypotelorism, downslanting palpebral fissures, large pinnae, skeletal anomalies including scoliosis and talipes, and chronic constipation. One of the affected clearly had the premaxillary agenesis form of holoprosencephaly. Two others had agenesis of maxillary central and lateral incisors. Three affected males lived past 20 years of age whereas three affected females died early in infancy.

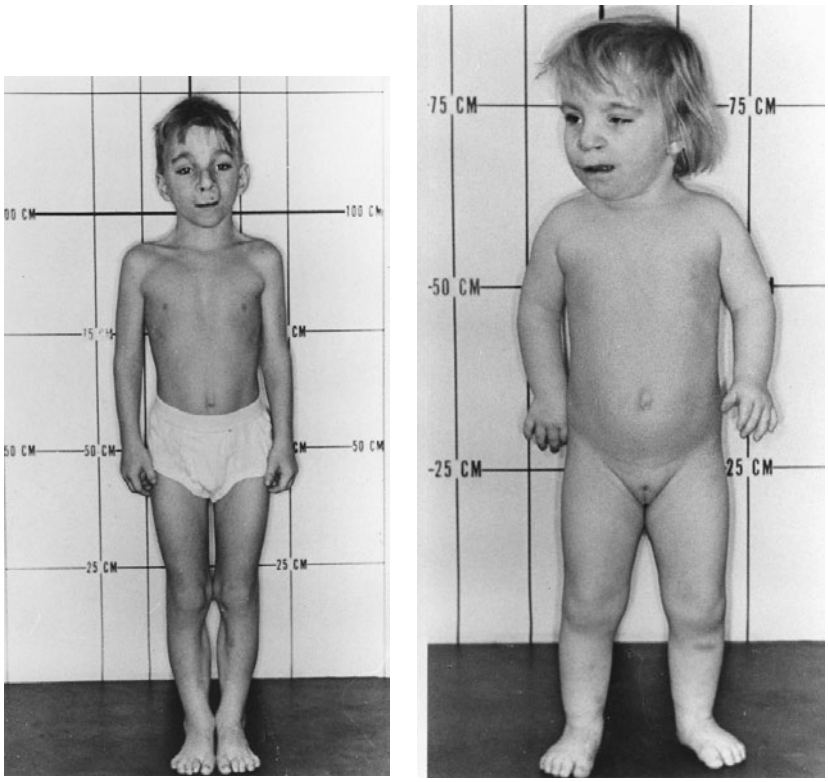
Martin et al (4) separated this disorder from familial isolated holoprosencephaly (1,2) because of the skeletal anomalies found in this family. See *holoprosencephaly* for more extensive discussion.

References (Cleft lip-palate, microcephaly, mental retardation, and holoprosencephaly)

1. Benke PJ, Cohen MM Jr: Recurrence of holoprosencephaly in families with a positive history. Clin Genet 24:324–328, 1983.
2. Cantú JM et al: Dominant inheritance of holoprosencephaly. Birth Defects 14(6B):215–220, 1978.
3. Martin AO et al: An autosomal dominant midline cleft syndrome resembling familial holoprosencephaly. Clin Genet 12:65–72, 1977.

Cleft lip-palate, posterior keratoconus, short stature, mental retardation, and genitourinary anomalies

Young et al (8) described two sibs with keratoconus posticus circumscriptus, retinal colobomas, short stature, moderate mental retardation, vertebral segmentation and fusion anomalies, tight heel cords, and cleft lip-palate. The nose was prominent. The neck was mildly webbed with low posterior hairline (Figs. 22–16 and 22–17). Extension at the elbows



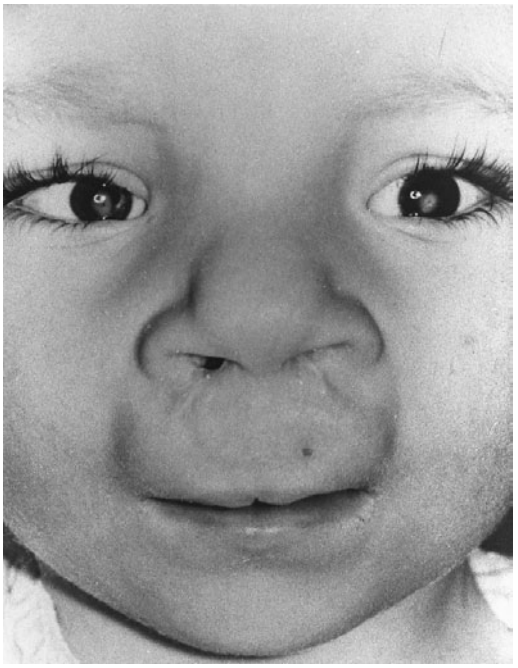
A B

Fig. 22–16. *Cleft lip-palate, posterior keratoconus, short stature, mental retardation, and genitourinary anomalies*. (A,B) Mentally retarded brother and sister with cleft lip-palate, short stature, mild neck webbing, small hands and feet. (Courtesy of ID Young, Leicester, England.)

was mildly limited. Haney and Falls (3) and Streeten et al (6) described somewhat similarly affected sibs.

It may be argued that posterior keratoconus is a mild form of the Peters anomaly (developmental defect of Descemet membrane and deep stromal layers of the cornea with or without iris-cornea adhesions) that has also been reported with cleft lip-palate (1,2,4,5,7). (See sections on *coloboma, hearing loss, hematuria, and cleft lip-palate* and *Peters plus syndrome* for overlap.)

Fig. 22–17. *Cleft lip-palate, posterior keratoconus, short stature, mental retardation, and genitourinary anomalies*. Boy with central corneal opacities (Peters-like anomaly). (Courtesy of ID Young, Leicester, England.)



References (Cleft lip-palate, posterior keratoconus, short stature, mental retardation, and genitourinary anomalies)

1. Anyane-Yeboa K et al: Cleft lip and palate, corneal opacities and profound psychomotor retardation: A newly recognized genetic syndrome. Cleft Palate J 20:246–250, 1983.
2. Bettini F et al: La Sindrome di Peters. Pathologica 72:699–705, 1980.
3. Haney WP, Falls HF: The occurrence of congenital keratoconus posticus circumscriptus in two siblings presenting a previously unrecognized syndrome. Am J Ophthalmol 7:841–842, 1975.
4. Harcount B: Anterior chamber cleavage syndrome associated with Weill-Marchesani syndrome and craniofacial dysplasias. J Pediatr Ophthalmol Strabismus 7:24–29, 1970.
5. Ide CH et al: Dysgenesis mesodermalis of the cornea (Peters anomaly) associated with cleft lip and palate. Ann Ophthalmol 7:841–842, 1975.
6. Streeten BW et al: Posterior keratoconus associated with systemic abnormalities. Arch Ophthalmol 101:616–622, 1983.
7. Van Schoonveld MJ et al: Peters'-plus: A new syndrome. Ophthalmol Paediatr Genet 4:141–146, 1984.
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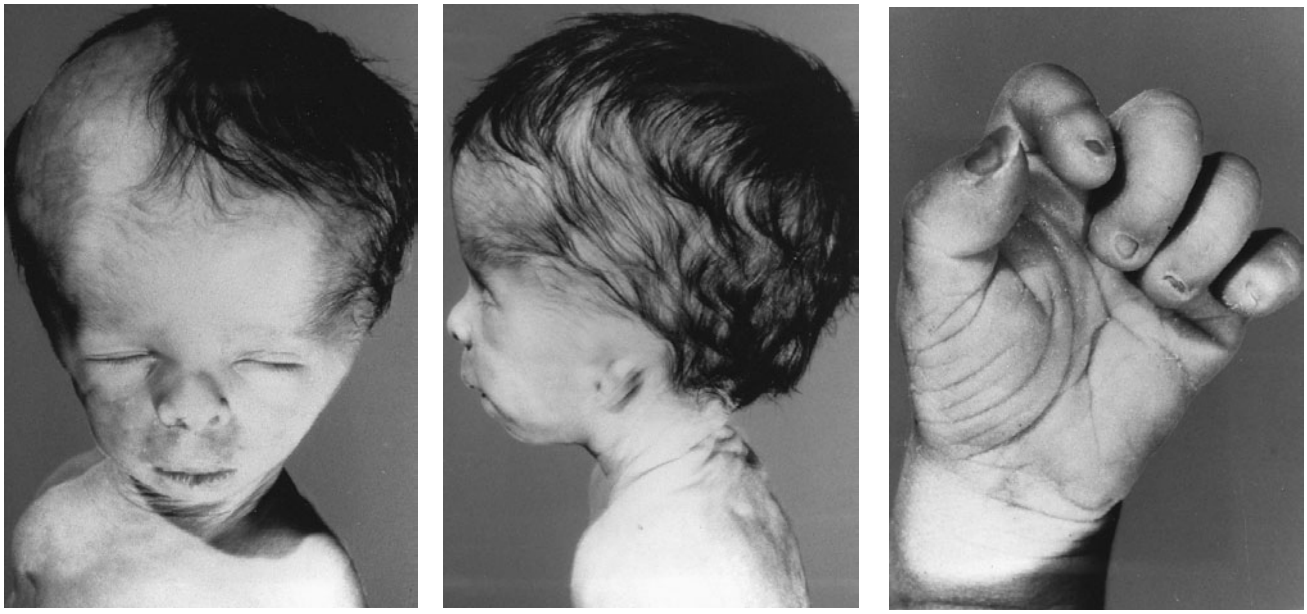
Toriello-Carey syndrome

In 1988, Toriello and Carey (10) noted four children, three of whom were sibs, with postnatal growth retardation, agenesis of corpus callosum, hypotonia, short palpebral fissures, micrognathia, and congenital heart anomalies. Subsequently, others (1–9) confirmed the syndrome, approximately 15 examples having been documented.

About 70% died within 3 months of birth. All exhibited hypotonia and 30% had seizures.

Craniofacial findings include hypertelorism (100%), small palpebral fissures (90%), small nose (100%), depressed nasal root (100%), low-set malformed pinnae (85%), and micrognathia (100%). Cleft palate or submucous cleft palate was noted in 70%. Laryngeal hypoplasia was seen in all that survived early infancy. Excess skin was seen at the nape in 70% (Fig. 22–18A,B).

Congenital heart anomalies were noted in 90% (4).



A B C

Fig. 22–18. *Toriello-Carey syndrome*. (A,B) Macrocephaly, short nose, telecanthus, micrognathia, microtia, excess nuchal skin. (C) Hypoplastic nails. (From P Czarnecki et al, Am J Med Genet 65:291, 1996.)

Various other anomalies have included: cryptorchidism (60%), Hirschsprung anomaly (25%), abnormal number of ribs (50%), and esophageal reflux (35%) and digital anomalies (Fig. 22–18C). Anteriorly-placed anus and talipes were noted in one case (1).

Autosomal recessive inheritance was originally suggested because of occurrence in two pairs of sibs and parental consanguinity (8). However, there have been twelve males and two females affected and the question of X-linked recessive inheritance has been raised (1,3,4,8,11). The females are less severely affected and are still alive whereas the males have all died.

References (Toriello-Carey syndrome)

1. Aftimos S, McGaughran J: Toriello-Carey syndrome: Case report and additional findings. Am J Med Genet 98:273–276, 2001.

1a. Camera G et al: Toriello-Carey syndrome: Report of a new case. Clin Dysmorphol 2:260–263, 1993.

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6. Mueller RF, Young ID: The Toriello-Carey syndrome: 3 further cases and review. 7th Manchester Birth Defects Conference, Manchester, England, 1996.

7. Ohta H et al: Toriello-Carey syndrome with endocardial fibroelastosis. Am J Med Genet 87:271–272, 1999.

8. Supovitz KR, Wulfsberg EA: Three year follow-up of a patient with Toriello-Carey syndrome. Am J Hum Genet 57A:104, 1995.

9. Till M et al: Toriello-Carey syndrome. Am J Med Genet 70:332, 1997.

10. Toriello HV, Carey JC: Corpus callosum agenesis, facial anomalies, Robin sequence, and other anomalies. A new autosomal recessive syndrome? Am J Med Genet 31:17–23, 1988.

11. Wegner KJ, Hersh JA: Toriello-Carey syndrome. Clin Dysmorphol 10: 145–148, 2001.

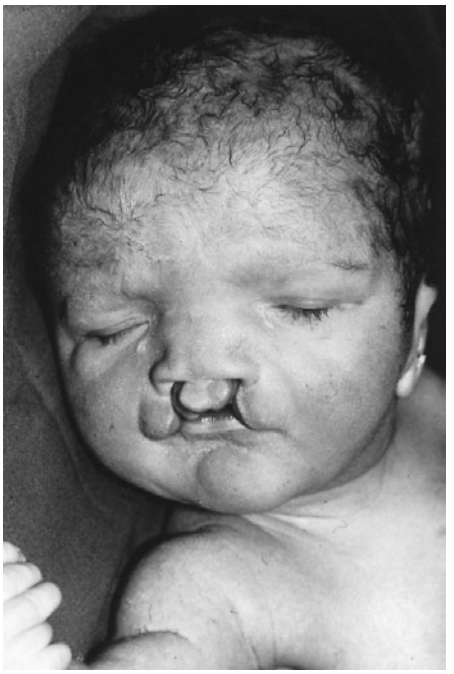
Cleft lip-palate, preaxial and postaxial polydactyly of hands and feet, congenital heart defect, and genitourinary anomalies

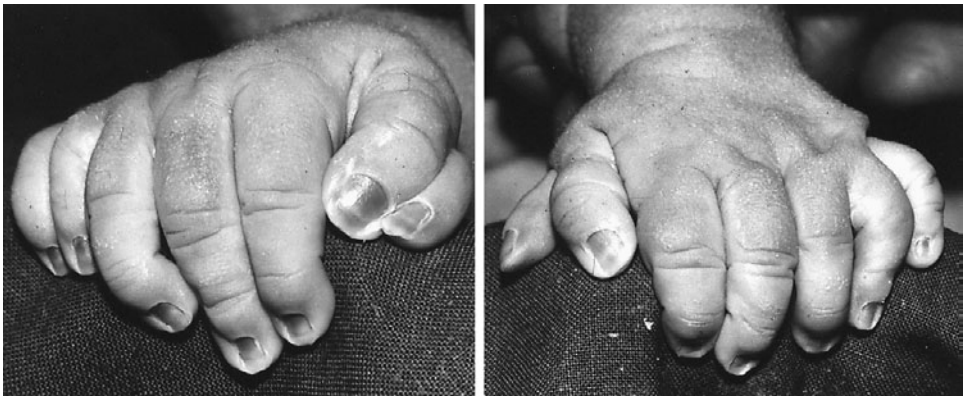
Töllner et al (1), in 1981, reported a child with bilateral cleft lip-palate, preaxial and postaxial polydactyly of the hands and feet, internal hydrocephalus, ependymal cysts of the lateral ventricle, complex malformations of the heart and great vessels, horseshoe kidney, and micropenis (Figs. 22–19 to 22–22). The karyotype was normal.

Reference (Cleft lip-palate, preaxial and postaxial polydactyly of hands and feet, congenital heart defect, and genitourinary anomalies)

1. Töllner J et al: Heptocarpo-octatarso-dactyly combined with multiple malformations. Eur J Pediatr 136:207–210, 1981.

Fig. 22–19. *Cleft lip-palate, preaxial and postaxial polydactyly of hands and feet, congenital heart defect, and genitourinary anomalies*. Cleft lip-palate and hypertelorism. (From U Töllner et al, Eur J Pediatr 136:207, 1981.)





A B

Fig. 22–20. *Cleft lip-palate, preaxial and postaxial polydactyly of hands and feet, congenital heart defect, and genitourinary anomalies*. (A,B) Heptadactyly of hands. (From U Töllner et al, Eur J Pediatr 136:207, 1981.)

Cleft lip-palate, urogenital anomalies, caudal appendage, somatic and mental retardation (Malpuech syndrome)

Malpuech et al (4) reported six sibs in a highly inbred Gypsy family with cleft lip-palate, somatic retardation (−3 to −5 SD), moderate mental retardation, and various urogenital anomalies. There was marked hypertelorism (Fig. 22–23). The urogenital abnormalities consisted of unilateral aplasia or bilateral hypoplasia of the kidney, ectopia or malrotation of the kidney, vesicoureteral reflex, bladder diverticulosis, micropenis, shawl scrotum, penoscrotal hypospadias, and ectopic testes. Three of the sibs were stillborn. Their cousin and seven other second or third degree relatives were similarly affected. Additional examples appear to be those of Chinen and Naritomi (1), Guion-Almeida (3), and Crisponi et al (2). Overlap with *Juberg-Hayward syndrome* is noted (5).

The patient of Chinen and Naritomi (1) had congenital heart anomaly (VSD), cryptorchidism, hypoplastic scrotum, and periarticular skin dimples. Wormian bones were noted. The three patients of Guion-Almeida (3) also had pre- and postnatal growth failures, omphalocele, mixed hearing loss, aniridia, corneal leukoma, and caudal appendage. The sibs noted by Crisponi et al (2) had micropenis, shawl scrotum, caudal appendage, umbilical hernia, and sensorineural hearing loss.

Inheritance is autosomal recessive. Resemblance to *del4p* has been suggested (6). It is possible that the patient reported by van Langen and Hennekam (7) actually had Malpuech syndrome.

References [Cleft lip-palate, urogenital anomalies, caudal appendage, somatic and mental retardation (Malpuech syndrome)]

1. Chinen Y, Naritomi K: Malpuech found clefting syndrome in a Japanese boy with cardiac defects. Jpn J Hum Genet 40:335–338, 1995.
2. Crisponi G et al: Two sibs with Malpuech syndrome. Am J Med Genet 86:294–299, 1999.
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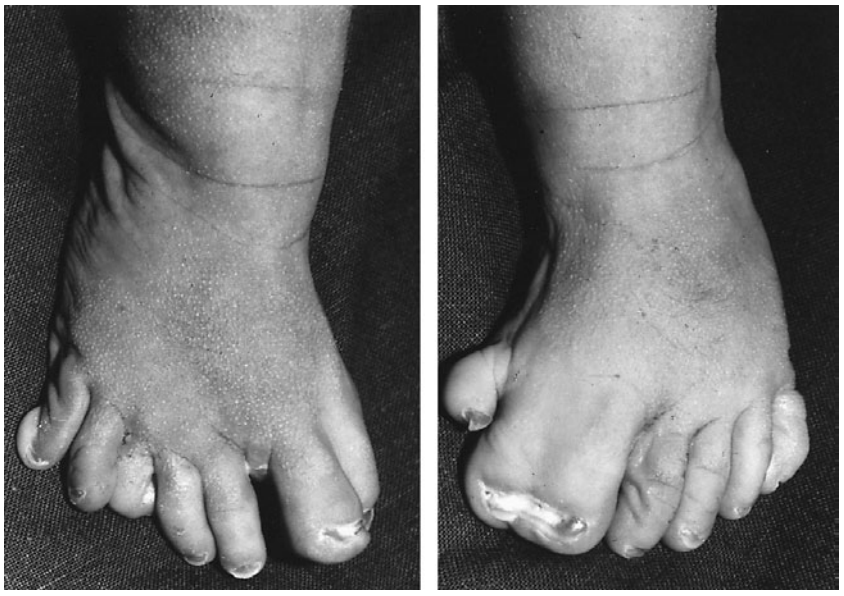
4. Malpuech G et al: A previously undescribed autosomal recessive multiple congenital anomalies/mental retardation (MCA/MR) syndrome with growth failure, lip/palate cleft(s) and urogenital anomalies. Am J Med Genet 16:475–480, 1983.
5. Reardon W et al: An atypical case suggesting the possibility of overlap between Malpuech and Juberg-Hayward syndromes. Clin Dysmorphol 10: 123–128, 2001.
6. Selicorni A, Faravelli F: Malpuech syndrome: A possible relationship with Wolf-Hirschhorn/Pitt-Rogers-Danks phenotype. Am J Med Genet 95:291, 2000.
7. Van Langen I, Hennekam RCM: Another example of the human homolog of the mouse mutant *disorganization*? Clin Dysmorphol 3:361–362, 1994.

Cleft palate, absent tibiae, preaxial polydactyly of the feet, and congenital heart defect

Ho et al (1) reported a child with lower legs symmetrically curved so that the feet were oriented cranially with the plantar surfaces facing dorsally.



A B

Fig. 22–21. *Cleft lip-palate, preaxial and postaxial polydactyly of hands and feet, congenital heart defect, and genitourinary anomalies*. (A,B) Octodactyly of feet. (From U Töllner et al, Eur J Pediatr 136:207, 1981.)

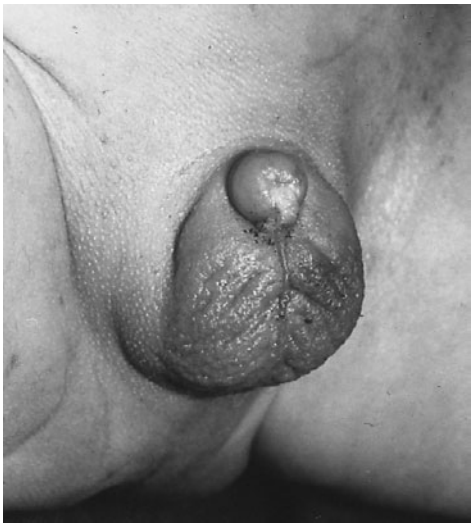
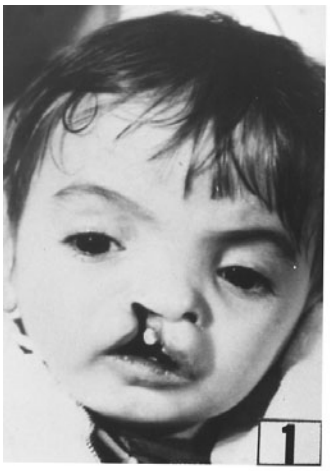


Fig. 22–22. *Cleft lip-palate, preaxial and postaxial polydactyly of hands and feet, congenital heart defect, and genitourinary anomalies*. Micropenis and penis palmatus. (From U Töllner et al, Eur J Pediatr 136:207, 1981.)

Fig. 22–23. *Cleft lip-palate, urogenital anomalies, caudal appendage, somatic and mental retardation (Malpuech syndrome)*. (A–D) Four of six sibs exhibiting cleft lip-palate, somatic retardation, moderate mental retardation, and various urogenital anomalies (unilateral aplasia or bilateral hypoplasia of kidney, reflux, bladder diverticulosis, micropenis, hypospadias). (From G Malpuech et al, Am J Med Genet 16:475, 1983.)



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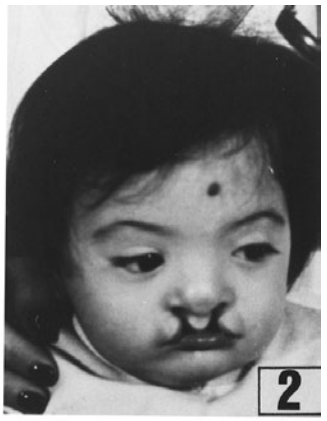

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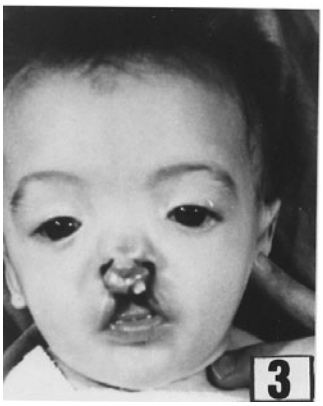

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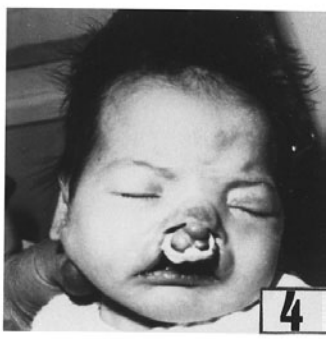

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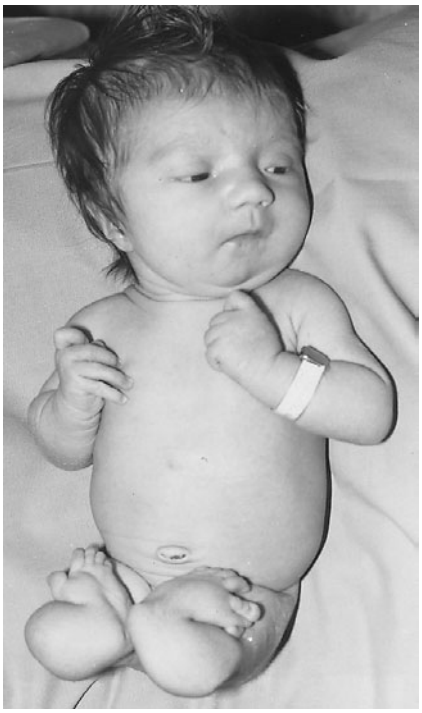


Fig. 22–24. *Cleft palate, absent tibiae, preaxial polydactyly of the feet, and congenital heart defect*. Small mandible, ulnar deviation of fingers, bowing of lower extremities, polydactyly. (From CK Ho et al, Am J Dis Child 129:714, 1975.)

There was preaxial polydactyly of the halluces. The fingers were long with ulnar deviation. The child also had cleft palate, micrognathia, VSD, and bilateral single palmar creases (Fig. 22–24). Radiographically, wormian bones, absent tibias, and fibulas curved at midshaft were evident (Fig. 22–25). The authors cited several reports of agenesis of the tibia with preaxial polydactyly but indicated that none was truly similar to their case.

There are several autosomal dominant tibial hemimelia syndromes: Werner 2 syndrome, tibial hemimelia-ectrodactyly syndrome, tibial hemimelia-diplopodia syndrome, and tibial hemimelia-micromelia-trigonomacrocephaly syndrome, among others (2). There are also several autosomal recessive tibial hemimelia syndromes: tibial hemimelia with normal upper limbs, tibial hemimelia and ectrodactyly, and tibial hemimelia with sensorineural hearing loss (2). Richieri-Costa (2) described a child with tibial hemimelia and cleft lip-palate.

References (Cleft palate, absent tibiae, preaxial polydactyly of the feet, and congenital heart defect)

1. Ho CK et al: Cleft palate, congenital heart disease, absent tibiae and polydactyly. Am J Dis Child 129:714–716, 1975.
2. Richieri-Costa A: Tibial hemimelia-cleft lip/palate in a Brazilian child born to consanguineous parents. Am J Med Genet 28:325–329, 1987.

Cleft palate, craniofacial sclerosis, and musculoskeletal abnormalities

Currarino and Friedman (1) reported a family having variable expression of a syndrome of abnormal facies, cleft palate, and various musculoskeletal abnormalities.

The facies in the boy was characterized by large calvaria with biparietal bossing, thick arched eyebrows, synophrys, long upper lip with Cupid's bow form, cleft palate, and thick dental arches. There was delayed shedding of deciduous teeth. A speech defect and conductive hearing loss were noted.

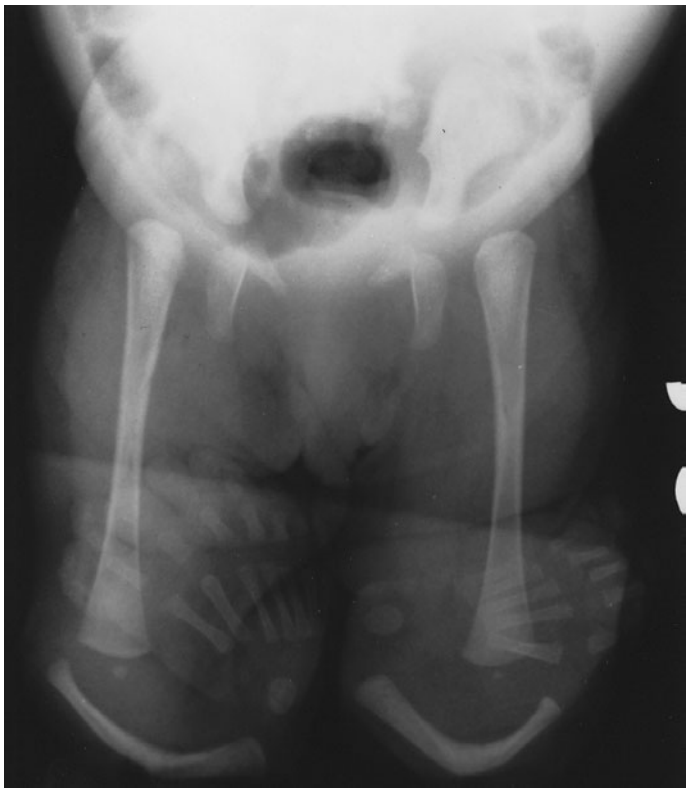


Fig. 22–25. *Cleft palate, absent tibiae, preaxial polydactyly of the feet, and congenital heart defect*. Absent tibiae, dislocated and bowed fibulae, dislocated hips, polydactyly. (From CK Ho et al, Am J Dis Child 129:714, 1975.)

Musculoskeletal changes include short stature, inguinal hernia, digital anomalies, progressive lumbar lordosis, dislocation of radial heads, and hallux valgus (Fig. 22–26).

Radiographically, enlarged calvaria, vertical clivus, cervical kyphosis, severe lumbar lordosis, and delta phalanx of middle phalanges of the index fingers and proximal phalanges of halluces were found.

The mother exhibited osteopathia striata, enlarged head, highly arched eyebrows, and Cupid's bow mouth. Another child who died during infancy had enlarged head, cleft palate, large soft pinnae, omphalocele, and hypospadias.

Although the mother has findings compatible with *cleft palate, osteopathia striata, cranial sclerosis, and hearing loss*, the findings in her children are too severe for that diagnosis to be considered.

Reference (Cleft palate, craniofacial sclerosis, and musculoskeletal abnormalities)

1. Currarino G, Friedman JM: Severe craniofacial sclerosis with multiple anomalies in a boy and his mother. Pediatr Radiol 16:441–447, 1986.

Cleft palate, dwarfism, trichodysplasia, and unusual facies

Jorgenson and Bick (1) described two brothers with an apparently new malformation syndrome. At birth, both were below the third centile for length, weight, and head circumference. The elder was still dwarfed when examined at age three. Both had sparse, coarse, and brittle hair. Light and scanning electron microscopy of the hair showed fractures, thin shafts, and a decreased number of cuticles. The palpebral fissures were narrow (below the third centile by measurement), and the elder had bilateral entropion of the lashes. Both had prominent pinnae, micrognathia, and cleft palate. The older had telecanthus, abnormally shaped incisors, bilateral inguinal herniae, and bilateral clinodactyly of the fifth fingers. The younger had bilateral single palmar flexion creases. Sensory, motor, and cerebellar functions appeared normal in each, although the older used only 10 words at age three. Skeletal radiographs were unremarkable.

Parental consanguinity was denied, although both parents were from a small village near Sabinas, Mexico. Autosomal recessive inheritance is likely. The possibility of this being a trichothiodystrophy exists because cleft lip-palate has been reported (2).

References (Cleft palate, dwarfism, trichodysplasia, and unusual facies)

1. Jorgenson RJ, Bick D: A new syndrome of dwarfism, trichodysplasia, cleft palate and unusual facies. March of Dimes Clinical Genetics Conference. Baltimore, Maryland, 1988.

2. Schepis C et al: A new case of trichothiodystrophy associated with autism, seizures and mental retardation. Pediatr Dermatol 14:125–128, 1997.

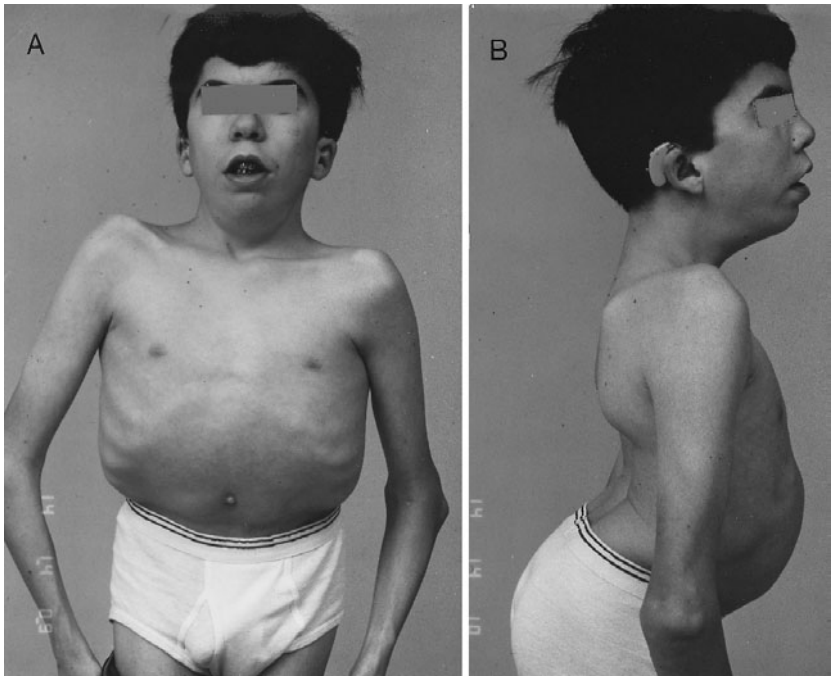


Fig. 22–26. *Cleft palate, craniofacial sclerosis, and musculoskeletal abnormalities*. (A,B) Note large calvaria, biparietal bossing, thick arched eyebrows, long upper lip with cupid's bow form, conductive hearing loss, short stature, progressive lumbar lordosis, dislocation of radial heads. (From G Currarino and JM Friedman, Pediatr Radiol 16:441, 1986.)

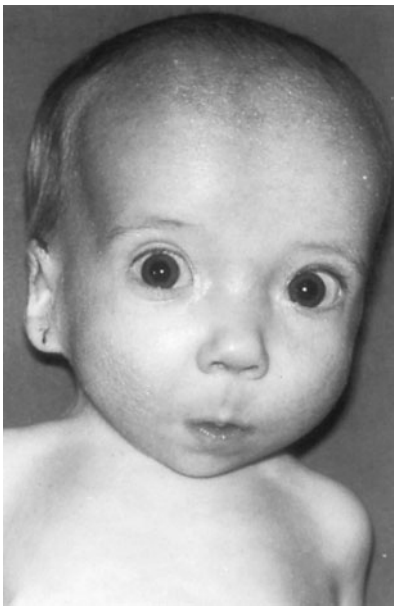


Fig. 22–27. *Cleft palate, dysmorphic facies, and digital defects*. Child has cleft palate, micrognathia, and rhizomelic dwarfism. [From J Martsolf et al, Syndrome Ident 5(1):14, 1977.]

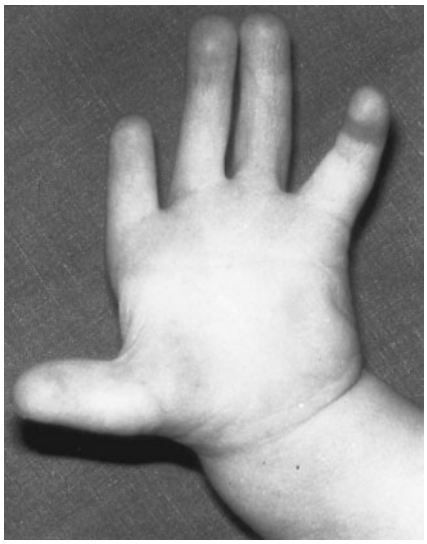
Cleft palate, dysmorphic facies, and digital defects

Martsolf et al (1), in 1977, reported a male infant with a rhizomelic dwarfism, polydactyly, and Robin sequence. Length at birth was below the third centile.

At 18 months, he had a prominent, square forehead, the anterior fontanel was still widely patent with apparent hypertelorism and marked micrognathia (Fig. 22–27).

The thumbs were broad with varus deflexion, and there was hypoplasia of the third and fifth middle phalanges and absence of the middle phalanx of the index fingers (Fig. 22–28). The halluces were broad with valgus deflexion and there was bilateral postaxial hexadactyly of the feet (Fig. 22–29). Radiographic studies showed reversal of normal curvature of the spine, increased sacral angle, abnormal acetabula, short tubular bones, and tibial bowing.

Fig. 22–28. *Cleft palate, dysmorphic facies, and digital defects*. Broad thumb with varus deflection. Index finger is short because of agenesis of middle phalanx. Note single palmar flexion crease. [From J Martsolf et al, Syndrome Ident 5(1):14, 1977.]



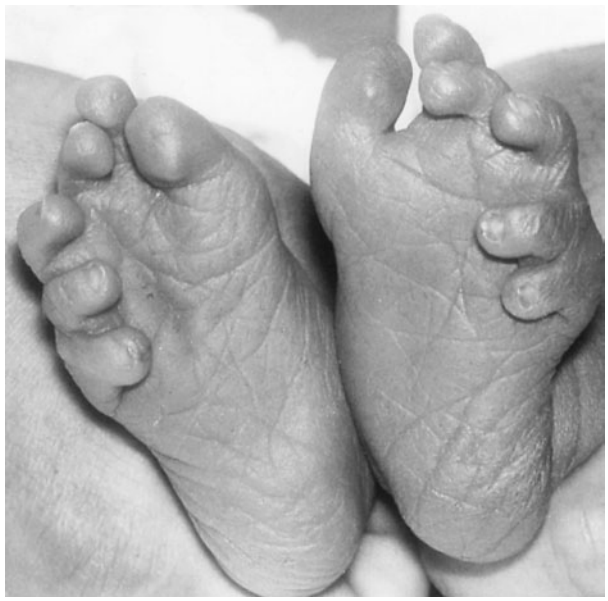


Fig. 22–29. *Cleft palate, dysmorphic facies, and digital defects*. Postaxial hexadactyly. [From J Martsolf et al, Syndrome Ident 5(1):14, 1977.]

We were not able to place this in any of the *oral-facial-digital syndromes*.

Reference (Cleft palate, dysmorphic facies, and digital defects)

1. Martsolf JT et al: Case report 56: Skeletal dysplasia, Robin anomalad, and polydactyly. Syndrome Ident 5(1):14–18, 1977.

Cleft palate, ectodermal dysplasia, growth failure, and apparent pancreatic insufficiency

Donlan (1) described a brother and sister with V-shaped cleft palate, relative micrognathia, growth failure, eczema, and apparent pancreatic insufficiency (Fig. 22–30). There was diarrhea with absence of stool trypsin. The skin appeared thin and there was a deficiency of teeth and enamel hypoplasia. Inheritance is probably autosomal recessive. In spite of overlap of signs and symptoms, there was no facial resemblance to *Johanson-Blizzard syndrome*.

Reference (Cleft palate, ectodermal dysplasia, growth failure, and apparent pancreatic insufficiency)

1. Donlan MA: Growth failure, cleft palate, ectodermal dysplasia and apparent pancreatic insufficiency—a new syndrome. Birth Defects 13(3B):230–231, 1977.

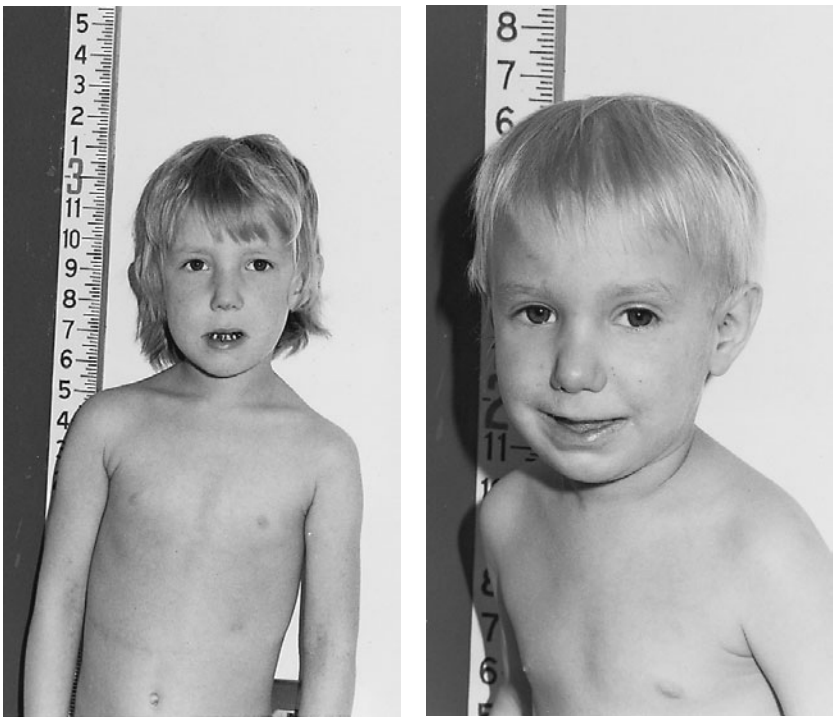
Cleft palate, eye coloboma, short stature, hypospadias, and mixed hearing loss (Abruzzo-Erickson syndrome)

In 1977, Abruzzo and Erickson (1) described a syndrome of cleft palate, coloboma of the eye, hypospadias, short stature, radial synostosis, and mixed hearing loss in two male sibs and their mother's brother.

Three affected males with minor stigmata in carrier females suggests X-linked inheritance.

Stature was below the 3rd centile in all three. Adult height in the maternal uncle was 5 feet.

The face tended to be flat with the pinnae long and soft. Cleft palate was present in both sibs and a submucous cleft palate was evident in the uncle. Sensorineural hearing loss was noted at 20 years in the uncle. It was progressive and severe at 34 years. Both sibs had 10–25 dB sensorineural loss and a greater conductive loss attributed to many middle ear infections



A B

Fig. 22–30. *Cleft palate, ectodermal dysplasia, growth failure, and apparent pancreatic insufficiency*. (A,B) Sibs affected with cleft palate, short stature, mild micrognathia, diarrhea with absence of stool trypsin. Teeth were deficient in number and enamel. [From MA Donlan, Birth Defects 13(3B):230, 1977.]

secondary to cleft palate. Colobomas of the iris, choroid, and retina were found in both sibs.

Radial synostosis was noted in the uncle and in one sib. There was wide spacing between the second and third metacarpals and some ulnar deviation of index fingers.

Hypospadias of varying degree was present in all three affected individuals. Cryptorchidism was noted in the uncle. A horseshoe kidney was found in one sib.

Several of the stigmata are found in *CHARGE association* (3–5). Abruzzo and Erickson (2) have argued convincingly that because their patients did not have choanal atresia, retarded development, or genital hypoplasia, they did not have familial CHARGE association.

References [Cleft palate, eye coloboma, short stature, hypospadias, and mixed hearing loss (Abruzzo-Erickson syndrome)]

1. Abruzzo MA, Erickson RP: A new syndrome of cleft palate associated with coloboma, hypospadias, deafness, short stature and radial synostosis. J Med Genet 14:76–80, 1977.

2. Abruzzo MA, Erickson RP: Re-evaluation of new X-linked syndrome for evidence of CHARGE syndrome or association. Am J Med Genet 34:397–400, 1989.

3. Davenport SLH et al: The spectrum of clinical features on CHARGE syndrome. Clin Genet 29:298–310, 1986.

4. Metlay LA et al: Familial CHARGE syndrome: Clinical report with autopsy findings. Am J Med Genet 26:577–581, 1987.

5. Mitchell JA et al: Dominant CHARGE association. Ophthalmol Paediatr Genet 6:31–36, 1985.

Cleft palate, hypotonia, and mental retardation

Davis and Lafer (1) reported a brother and sister with cleft palate, mental retardation, hypotonia, failure to thrive, frontal bossing, and epicanthal folds. The male sib had hypospadias, cryptorchidism, and inguinal hernias.

Reference (Cleft palate, hypotonia, and mental retardation)

1. Davis JG, Lafer C: A possible new mental retardation syndrome. Birth Defects 12(5):235–238, 1976.

Cleft palate, poikiloderma, alopecia, and micrognathia

Verloes et al (1), using the term PARC as an acronym for *P*oikiloderma, *A*lopecia, *R*etrognathia, and *C*left palate, reported a father and son with a syndrome that vaguely resembled *Rothmund-Thompson syndrome*.

Reference (Cleft palate, poikiloderma, alopecia, and micrognathia)

1. Verloes A et al: Poikiloderma, alopecia, retrognathia, and cleft palate: The PARC syndrome. Is this an undescribed dominantly inherited syndrome? Dermatologica 181:142–144, 1990.

Cleft palate, microcephaly, large ears, and short stature (Say syndrome)

Say et al (5) reported a dominantly inherited syndrome of cleft palate associated with microcephaly, large pinnae, and short stature affecting four members of a family (Fig. 22–31). The mother and her sister had distally tapering fingers with hypoplastic distal phalanges of the second and fourth digits bilaterally, ulnar deviation of the middle fingers, low-set thumbs, and bilateral acromial dimples.

The proband also had ptosis, hypospadias, delayed bone age, and developmental delay. A patient seen by Abu-Libdeh et al (1) had sparse scalp hair, delayed bone age, and proximal renal tubular acidosis with cystic dysplasia of the kidneys in addition to the cardinal features. Ashton-Prolla and Félix (2), Guion-Almeida et al (3), and Pagnan et al (4) have reported similar findings. In all, approximately eight cases have been tabulated to date.

References [Cleft palate, microcephaly, large ears, and short stature (Say syndrome)]

1. Abu-Libdeh B et al: Syndrome of cleft palate, microcephaly, large ears, and short stature (Say syndrome). Am J Med Genet 45:358–360, 1993.

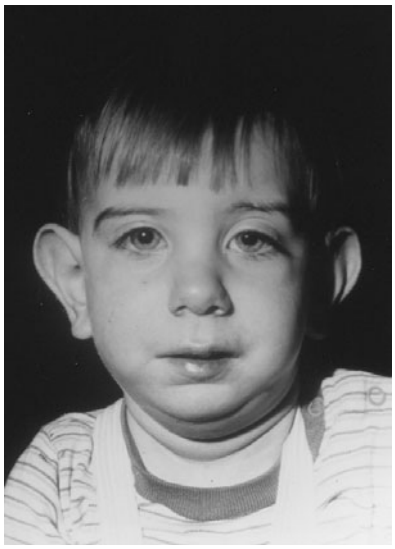


Fig. 22–31. *Cleft palate, microcephaly, large ears, and short stature*. Child with microcephaly, outstanding pinnae, and cleft palate. Mother, mother's sister, and maternal grandfather had similar findings but also had hypoplastic second and fourth digits. (From B Say et al, Humangenetik 26:267, 1975.)

2. Ashton-Prolla P, Felix TM: Say syndrome: A new case with cystic renal dysplasia in discordant monozygotic twins. Am J Med Genet 70:353–356, 1997.

3. Guion-Almeida ML et al: Say syndrome—a new Brazilian case. Genet Molec Biol 21:449–451, 1998.

4. Pagnan NAB et al: Say syndrome: Report of a familial case. Am J Med Genet 86:165–167, 1999.

5. Say B et al: A new dominantly inherited syndrome of cleft palate. Humangenetik 26:267–269, 1975.

Cleft palate, microcephaly, mental retardation, and musculoskeletal mass deficiency (Weaver-Williams syndrome)

Weaver and Williams (1) described male and female sibs with mental retardation, microcephaly, unusual facies, and cleft palate. Autosomal recessive inheritance is possible.

There was marked deficiency in muscle mass (Fig. 22–32A,B). Weight was −4 SD. Height was less significantly reduced. Head circumference was −5 SD, but because the facial bones were small, it did not appear severe. There was midface hypoplasia and the mouth was small and downturned. The neck was long and was held in an extended position (Fig. 22–32C,D). The incisors had a somewhat conical crown form.

Both sibs manifested moderate to severe mental retardation with incomprehensible speech.

The limbs were extremely thin. The fingers exhibited clinodactyly.

Radiographically, there was generalized bone hypoplasia with increased tubulation, tall narrow vertebral bones, downward sloping ribs, short ulnas and fibulas, and delayed bone age (Fig. 22–33).

Reference [Cleft palate, microcephaly, mental retardation, and musculoskeletal mass deficiency (Weaver-Williams syndrome)]

1. Weaver DD, Williams CPS: A syndrome of microcephaly, mental retardation, unusual facies, cleft palate and weight deficiency. Birth Defects 13(3B):69–84, 1977.

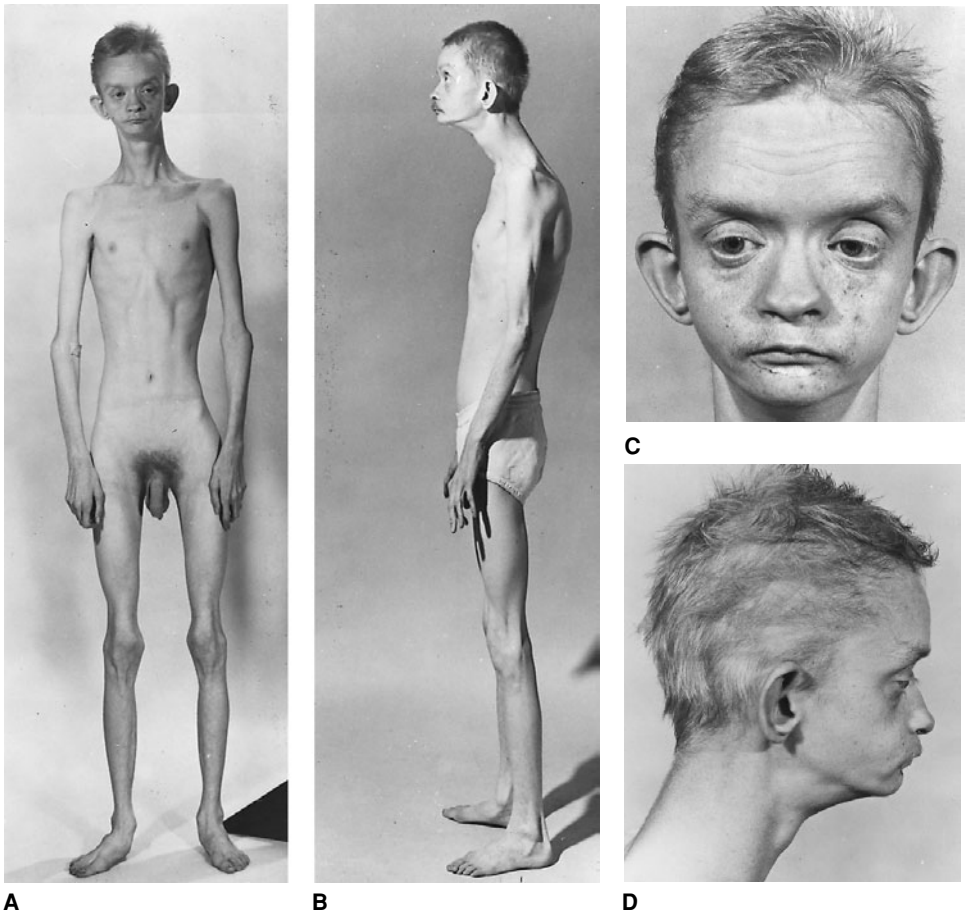


Fig. 22–32. *Cleft palate, microcephaly, mental retardation, and musculoskeletal mass deficiency*. (A,B) Very thin limbs with normal leg and trunk proportions. Long neck. (C,D) Microcephaly, cupped pinnae, broad nose, midfacial hypoplasia, small mouth with downturned corners, micrognathia, and long thin neck. [From DD Weaver and CPS Williams, Birth Defects 13(3B):69, 1977.]

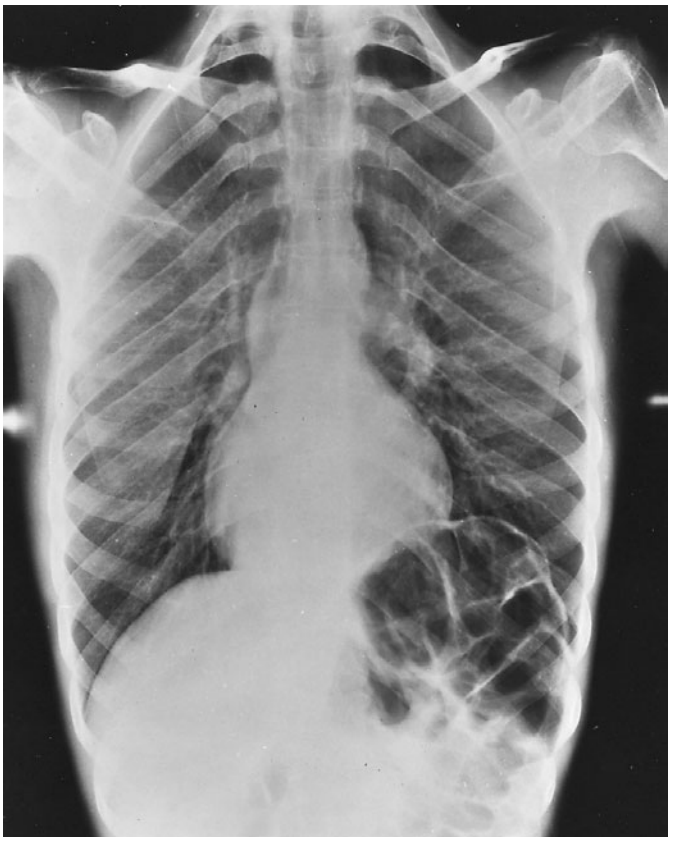


Fig. 22–33. *Cleft palate, microcephaly, mental retardation, and musculoskeletal mass deficiency*. Markedly down-sloping ribs with diminished muscles of chest and shoulders. Note elevated left hemidiaphragm. [From DD Weaver and CPS Williams, Birth Defects 13(3B):69, 1977.]

Cleft lip-palate, hypospadias, and inguinal hernia

RJ Gorlin has seen two male siblings with the following findings: large anterior fontanel, patent posterior fontanel, superficial capillary angioma of forehead, mild hypertelorism, absent eyebrows, small palpebral fissures, cleft lip and palate in one sib, cleft palate in the second, broad nasal base, hypospadias, large inguinal hernia, and atrial septal defect in both. One sib died at the age of 4 months and the other at 2 weeks from infection. Only one of the sibs had the following: two-vessel cord, metatarsus adductus, digitalized thumbs, proximally placed thumbs, bilateral coloboma of iris, unilateral ear tags, and double urinary collecting system. We were unable to find any additional examples of this syndrome in the literature.

Cleft palate, stapes fixation, and oligodontia

Gorlin et al (1) described two sisters, the offspring of a consanguineous marriage, who had stapes fixation, cleft palate, and oligodontia (1). Neither girl had ever had more than three or four deciduous teeth, and those had conical crown form. No permanent teeth were ever present, and alveolar ridges were absent.

There was coalition of all cuneiform bones, as well as coalition of the navicular and talus, the talus and calcaneus, and the first cuneiform with the first metatarsal. The talus was malformed, having a superior and medial hump. The carpal navicular was sharply wedge-shaped, lacking its normal convexity (Fig. 22–34).

Reference (Cleft palate, stapes fixation, and oligodontia)

1. Gorlin RJ et al: Stapes fixation and oligodontia—a new autosomal recessively inherited syndrome. Birth Defects 7(7):87–88, 1971.

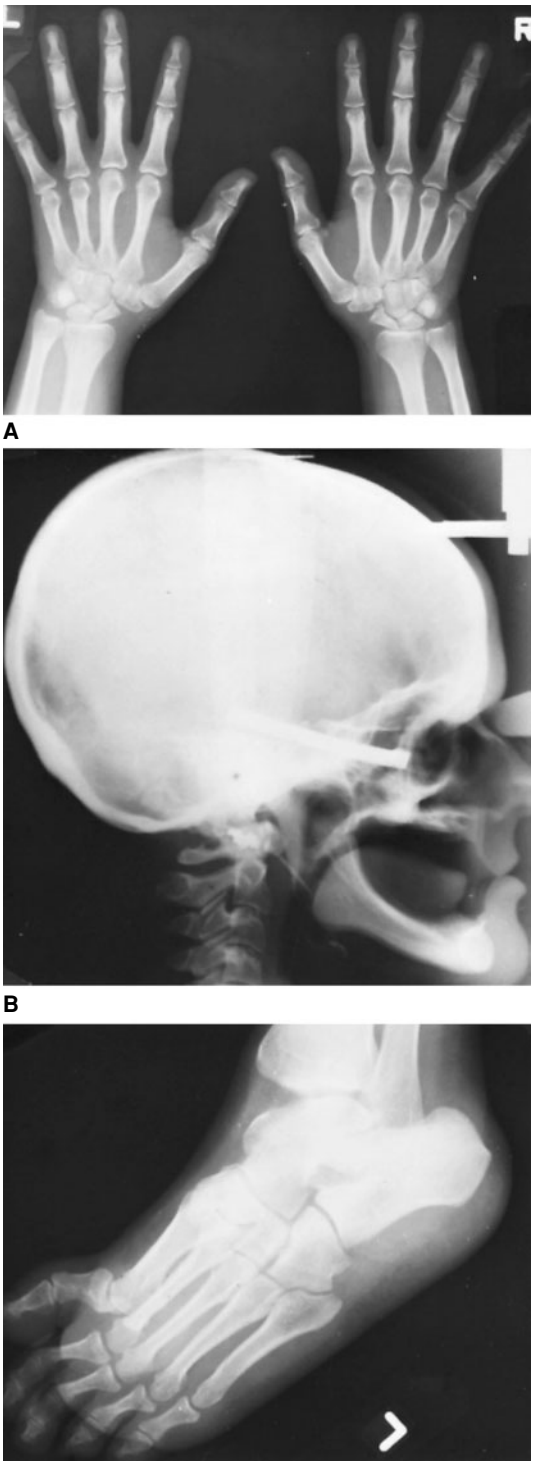


Fig. 22–34. *Cleft palate, stapes fixation, and oligodontia*. (A) Hypoplasia of navicular bones. (B) Absence of alveolar processes because of severe oligodontia. (C) Talocalcaneal fusion with unusual tibiotalar articulation and talar hump. [From RJ Gorlin et al, Birth Defects 7(7):87, 1971.]

Cleft palate, unusual facies, conductive hearing loss, and male pseudohermaphroditism

Ieshima et al (1) described male and female sibs with cleft of the soft palate, intrauterine growth retardation and failure to thrive, severe mental retardation, microcephaly, hypotonia, repeated respiratory infections, conductive hearing loss, and pulmonary hypertension with PDA.

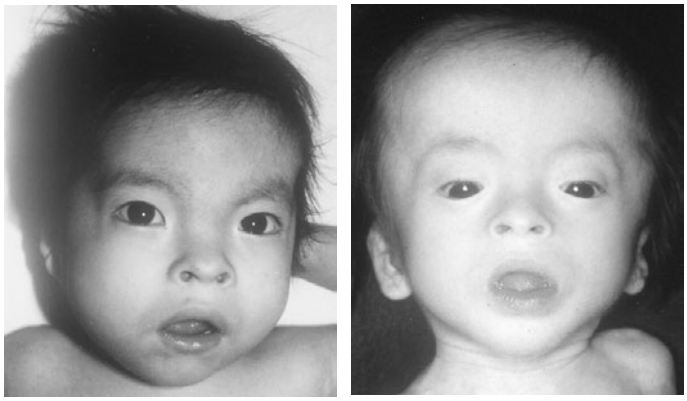


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Fig. 22–35. *Cleft palate, unusual facies, conduction hearing loss, and male pseudohermaphroditism.* (A,B). One of two sibs having hypertelorism, arched eyebrows, broad flat nasal bridge, profound hearing loss, severe psychomotor retardation, cleft palate, and short neck. (From A Ieshima et al, Clin Genet 30:136, 1986.)

The facies was characterized by asymmetry, arched eyebrows, hypertelorism, broad nasal bridge, small nose, anteverted nostrils, microtia, and micrognathia (Fig. 22–35).

The male had hypospadias, micropenis, cryptorchidism, and shawl scrotum (Fig. 22–36).

Inheritance is probably autosomal recessive.

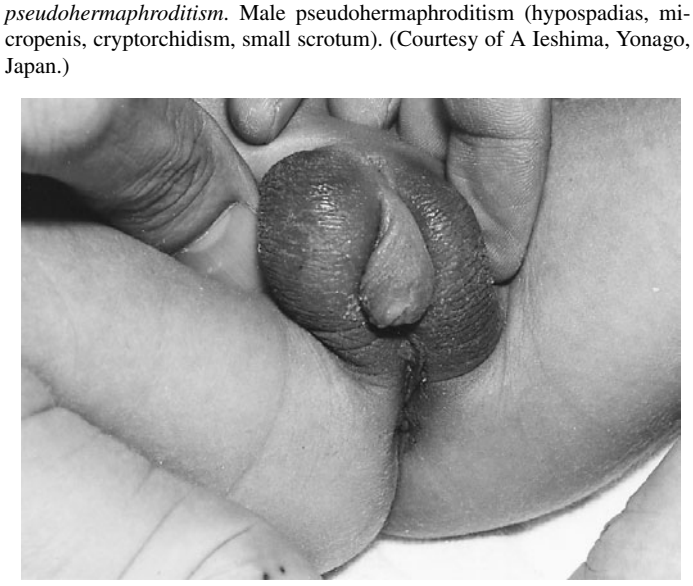
Reference (Cleft palate, unusual facies, conductive hearing loss, and male pseudohermaphroditism)

1. Ieshima A et al: Peculiar facies, deafness, cleft palate, male pseudohermaphroditism, and growth and psychomotor retardation: A new autosomal recessive syndrome? Clin Genet 30:136–141, 1986.

Cleft palate, unusual facies, mental retardation, and limb abnormalities

Palant et al (1) described two sisters with mild microcephaly, short stature, severe mental retardation, almond-shaped upslanting deep-set eyes, bulbous nasal tip, cleft palate, clinodactyly of toes, and firm nonbony prominence of the anteromedial aspect of the wrists. The syndrome possibly has autosomal recessive inheritance (Fig. 22–37).

Fig. 22–36. *Cleft palate, unusual facies, conduction hearing loss, and male pseudohermaphroditism.* Male pseudohermaphroditism (hypospadias, micropenis, cryptorchidism, small scrotum). (Courtesy of A Ieshima, Yonago, Japan.)



Reference (Cleft palate, unusual facies, mental retardation, and limb abnormalities)

1. Palant Dl et al: Unusual facies, cleft palate, mental retardation and limb abnormalities in siblings—a new syndrome. J Pediatr 78:686–689, 1971.

Cleft palate, ventricular septal defect, persistent truncus arteriosus, and intrauterine death

Lowry and Miller (1) noted sibs with cleft palate, persistent truncus arteriosus, and abnormal right pulmonary artery. The left pulmonary artery came off the truncus. Presumably the syndrome has autosomal recessive inheritance.

Reference (Cleft palate, ventricular septal defect, persistent truncus arteriosus, and intrauterine death)

1. Lowry RB, Miller JR: Cleft palate and congenital heart disease. Lancet 1:1302–1303, 1971.

Cleft uvula, conductive hearing loss, nephrosis, congenital urinary tract, and digital anomalies

The syndrome was found by Braun and Bayer (2) in five of seven boys and in none of five girls in a sibship. Inheritance appears to be X-linked or, less likely, autosomal recessive.

The hearing defect proved to be a conductive deficit in all but one child who had mixed hearing loss. The digital anomaly consisted of shortening and broadening of the distal portion of the thumbs and great toes. Radiographic examination revealed that the distal phalanges were rudimentary with bifid ends. The urinary tract anomalies present in two children were bandlike constrictions of the ureter and duplication of the renal pelvis and ureter. The nephrosis appeared in infancy.

The uvula was bifid in two of five affected males. This appears to be statistically significant, since the prevalence of bifid uvula in whites is approximately 1 in 100.

Four male sibs were reported by Bakarat et al (1) with nephrosis, sensorineural hearing loss, and hypoparathyroidism. However, this appears to be a different disorder.

References (Cleft uvula, conductive hearing loss, nephrosis, congenital urinary tract, and digital anomalies)

1. Bakarat AY et al: Familial nephrosis, nerve deafness, and hypoparathyroidism. J Pediatr 91:61–64, 1977.

2. Braun FC Jr, Bayer JF: Familial nephrosis associated with deafness and congenital urinary tract anomalies in siblings. J Pediatr 60:33–41, 1962.

Cleft uvula, preaxial and postaxial polysyndactyly, and somatic and motor retardation

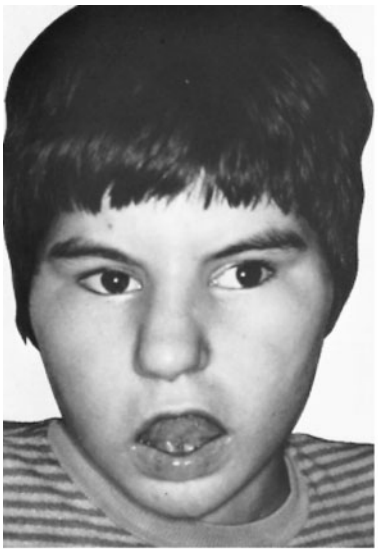
Engelhard and Yatziv (1) reported a male with short stature, microcephaly, psychomotor retardation, eyelid ptosis, stenosis of lacrimal points, asymmetric manual preaxial and postaxial polysyndactyly, brachyphalangy, and kyphosis (Fig. 22–38). The uvula was bifid. The mandibular incisors were fused.

The parents were cousins. The authors considered acropectorovertebral (F) syndrome (2) in differential diagnosis.

References (Cleft uvula, preaxial and postaxial polysyndactyly, and somatic and motor retardation)

1. Engelhard D, Yatziv S: Pre- and postaxial polysyndactyly, microcephaly and ptosis. Eur J Pediatr 130:47–51, 1979.

2. Grosse FR et al: The F-form of acro-pectorovertebral dysplasia: The F syndrome. Birth Defects 5(3):48–63, 1969.



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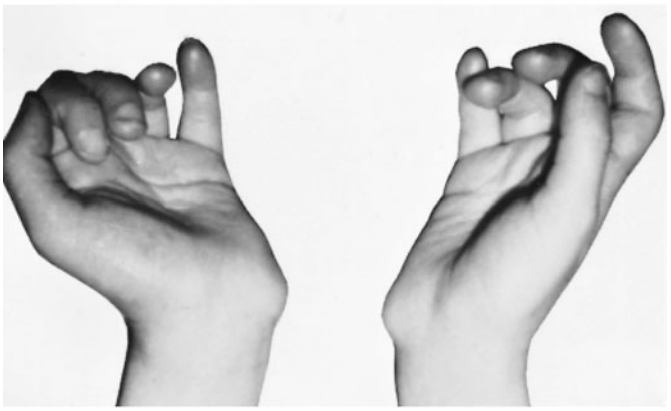

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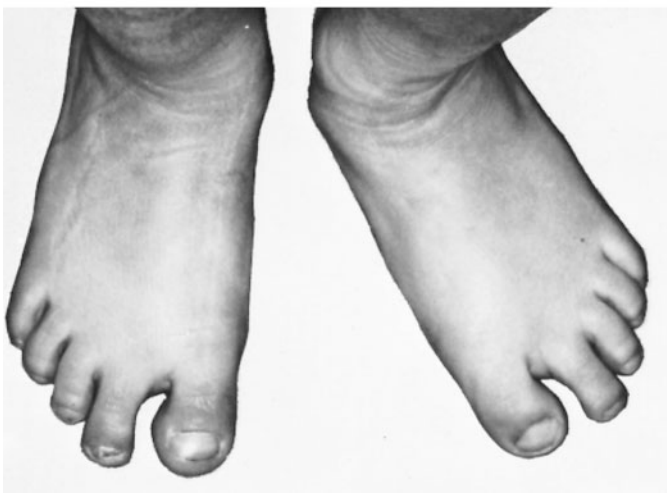
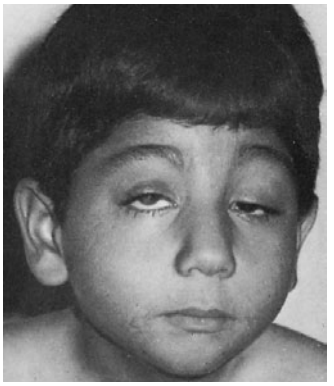


C

Fig. 22–37. *Cleft palate, unusual facies, mental retardation, and limb abnormalities*. (A) One of the two female sibs with cleft palate, short stature, bulbous nasal type. (B) Firm nonbony prominences of anteromedial aspects of wrists. (C) Short halluces with space between hallux and second toe. (From DI Palant et al, J Pediatr 78:686, 1971.)



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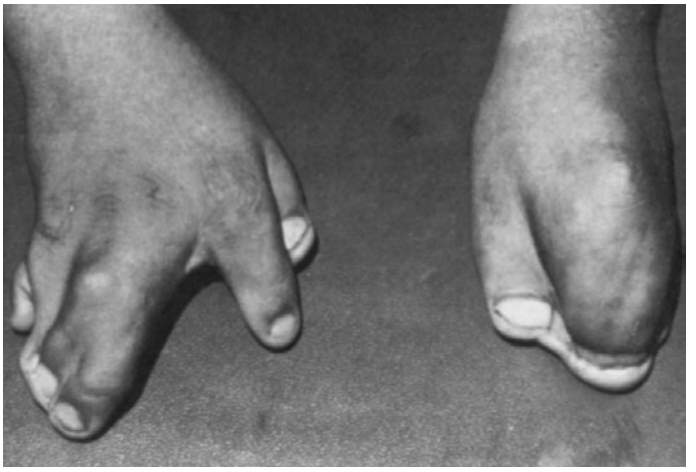

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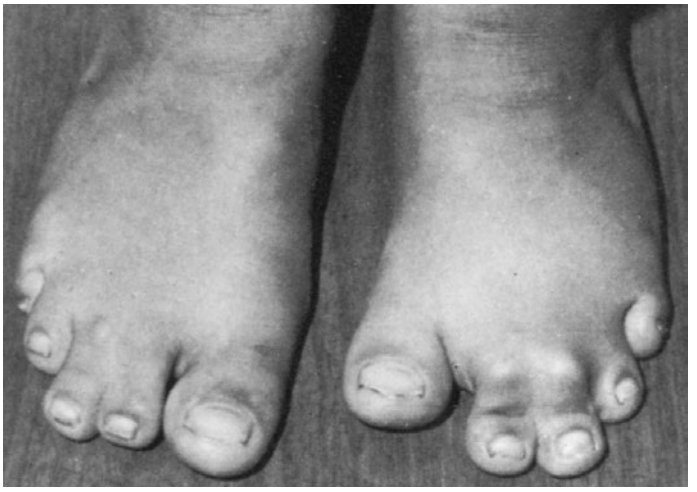
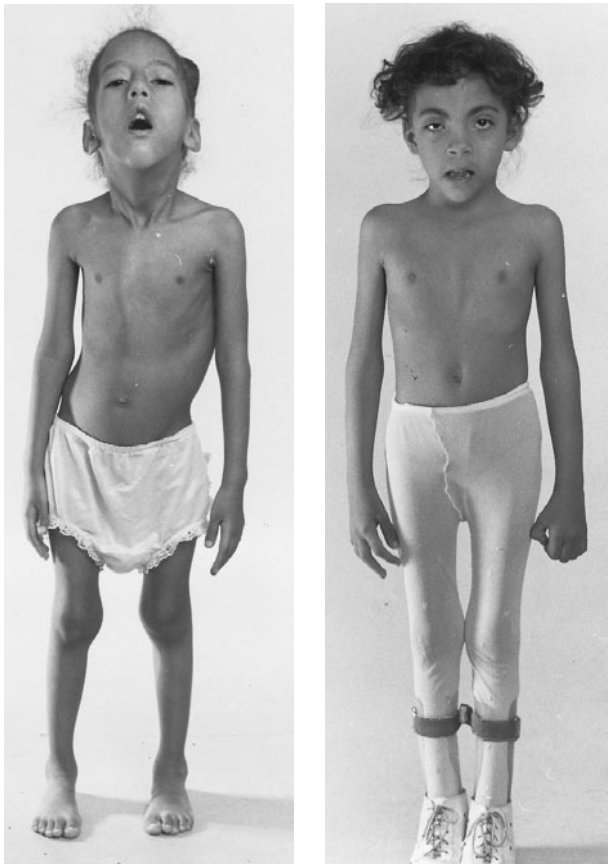


C

Fig. 22–38. *Cleft uvula, preaxial and postaxial polysyndactyly, and somatic and motor retardation*. (A) Five-year-old male with bilateral ptosis, congenital bilateral dacryostenosis, and bilateral leukoma. (B) Asymmetric cutaneous syndactyly of fingers. (C) Bilateral syndactyly of toes 2–3 with widened space between hallux and second toes. (From D Engelhard and S Yatziv, Eur J Pediatr 130:47, 1979.)



A B

Fig. 22–39. *Congenital myopathy, malignant hyperthermia, and cleft palate*. (A,B) Two children of Lumbee Indian extraction exhibiting congenital myopathy, malignant hyperthermia, scoliosis, and cleft palate. Note eyelid ptosis and facial resemblance of child shown in B to that of Noonan syndrome. (From CR Stewart et al: Pediatr Neurol 4:371, 1988.)

Congenital myopathy, malignant hyperthermia, and cleft palate

Stewart et al (8) reported six children of similar ethnic origin (Lumbee Indians of south central North Carolina) with congenital myopathy, malignant hyperthermia, skeletal anomalies, and cleft palate (Fig. 22–39). Affected sibs suggest autosomal recessive inheritance.

The facies was characterized by myotonia and eyelid ptosis. The mouth appeared small.

Musculoskeletal anomalies consisted of short stature, generalized weakness, myotonia, congenital kyphoscoliosis, and talipes. Tendon reflexes were hypoactive to absent. Plantar responses were flexor. The hyperthermia makes anesthesia hazardous.

This disorder has marked overlap with King syndrome (short stature, motor delay, slowly progressive myopathy, downslanting palpebral fissures, posteriorly rotated pinnae, mandibular hypoplasia, scoliosis, pectus carinatum, cryptorchidism, and susceptibility to malignant hyperthermia), a sporadic disorder (3,4,6,7). Cleft palate is not a frequent component of King syndrome. King syndrome, in turn, has been alleged to be a subset of *Noonan syndrome* (1), but we remain skeptical of creating a separate nosologic status although we recognize the hazard that hyperthermia creates for anesthesia.

Malignant hyperthermia appears to be a genetic heterogeneity, one gene was mapped to 19q13, another to 17q and a third to neither (2,5).

References (Congenital myopathy, malignant hyperthermia, and cleft palate)

1. Allanson JE et al: Noonan syndrome: The changing phenotype. Am J Med Genet 21:507–514, 1985.
2. Ball SP, Johnson KJ: The genetics of malignant hyperthermia. J Med Genet 30:89–93, 1993.
3. Heiman-Paterson T et al: King-Denborough syndrome: Contracture testing and literature review. Pediatr Neurol 2:175–177, 1986.
4. King JO, Denborough MA: Anesthetic-induced malignant hyperthermia in children. J Pediatr 83:37–40, 1973.
5. Levitt RC et al: Evidence for genetic heterogeneity in malignant hyperthermia susceptibility. Genomics 11:543–547, 1991.
6. McPherson EW, Taylor CA: The King syndrome: Malignant hyperthermia, myopathy, and multiple anomalies. Am J Med Genet 8:159–165, 1981.
7. Steenson AJ, Torkelson RD: King syndrome with malignant hyperthermia. Am J Dis Child 141:271–273, 1987.
8. Stewart CR et al: Congenital myopathy with cleft palate and increased susceptibility to malignant hyperthermia: King syndrome? Pediatr Neurol 4:371–374, 1988.

Crane-Heise syndrome (cleft lip-palate, agenesis of clavicles and cervical vertebrae, and talipes equinovarus)

Crane and Heise (2) described three sibs having disproportionately large head, small face, hypertelorism, low-set dysmorphic pinnae, depressed nasal bridge with upturned nares, micrognathia, cleft lip and/or cleft palate, and short neck (Fig. 22–40).

In addition, they had intrauterine growth retardation, partial soft tissue syndactyly of the second to fourth fingers and toes, talipes equinovarus, short penis, and cryptorchidism. Radiographic studies revealed poorly mineralized calvaria, apparently absent cervical vertebrae and clavicles, small scapulae, and dislocated radial heads (Fig. 22–41).

Agenesis of the corpus callosum was noted in one sib and single palmar creases in two sibs. This apparently lethal syndrome probably has autosomal recessive inheritance.

Several other patients have been described as resembling Crane-Heise syndrome. Barnicoat et al (1) described a male fetus, the product of consanguineous parents. The child had all of the anomalies save that of cranial bone defects. Another is a male, reported by Weaver and Johnson (3), currently approximately 18 years of age. His parents are not consanguineous. Findings included deficient mineralization, disproportionately large head, hypoplastic clavicles, cleft lip-palate, downslanting palpebral fissures, hypertelorism, unusual pinnae, talipes equinovarus, radial head dislocation, genital hypoplasia, cryptorchidism, and severe growth retardation. Intelligence is almost normal.

We do not see any resemblance to *aminopterin embryopathy*.

References [Crane-Heise syndrome (cleft lip-palate, agenesis of clavicles and cervical vertebrae, and talipes equinovarus)]

1. Barnicoat AJ et al: Fetus with features of Crane-Heise syndrome and aminopterin syndrome sine aminopterin (ASSAS). Clin Dysmorphol 3:353–357, 1994.
2. Crane JP, Heise RL: New syndrome in three affected siblings. Pediatrics 68:235–237, 1981.
3. Weaver DD, Johnson JA: Cranial bone deficiency, craniosynostosis, and facial and limb defects. Dysmorphol Clin Genet 1:67–70, 1987.

Genito-palato-cardiac syndrome (Gardner-Silengo-Wachtel syndrome)

Greenberg et al (5) coined the term genito-palato-cardiac syndrome to describe a disorder of cleft palate, male pseudohermaphroditism (46,XY gonadal dysgenesis), and conotruncal anomalies. They cited a number of earlier cases (1,3,4,6–9) as examples of the disorder. Inheritance is probably autosomal recessive (1).

There has been debate as to whether this is a disorder separate from severe *Smith-Lemli-Opitz* syndrome, (3). Opitz and Lowry (6) have reserved judgment. Determination of 7-dehydrocholesterol levels should settle the debate.

Most of the infants succumbed during the neonatal period.

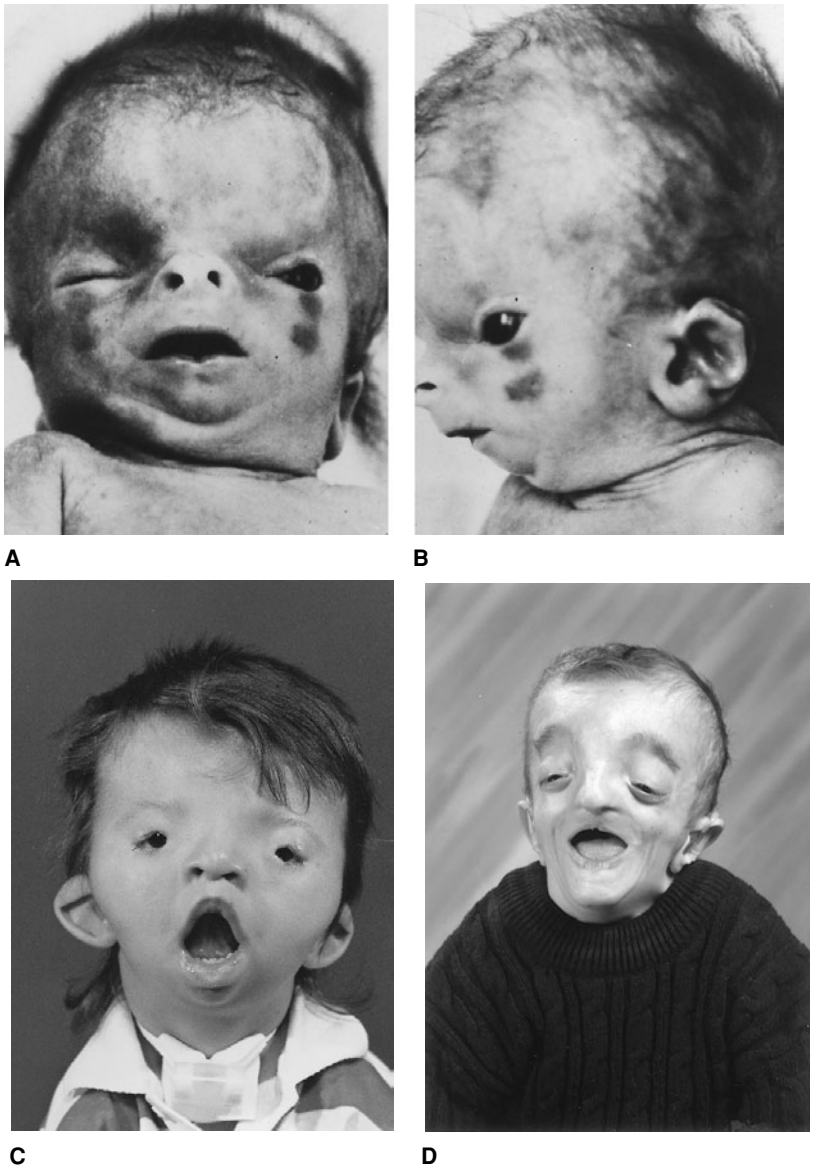


Fig. 22–40. *Crane-Heise syndrome*. (A,B) Postmortem view of one of three sibs showing large head, depressed nasal bridge with anteverted nares, apparent hypertelorism, hypoplastic helices, and short neck. (C) Five-year-old. (D) Fourteen-year-old. Note similarity in facial phenotype. (A,B from JP Crane and RL Heise, Pediatrics 68:235, 1981. C courtesy of M Lubinsky and A Denny, Milwaukee, Wisconsin. D courtesy of B Guzzo, Evansville, Indiana.)

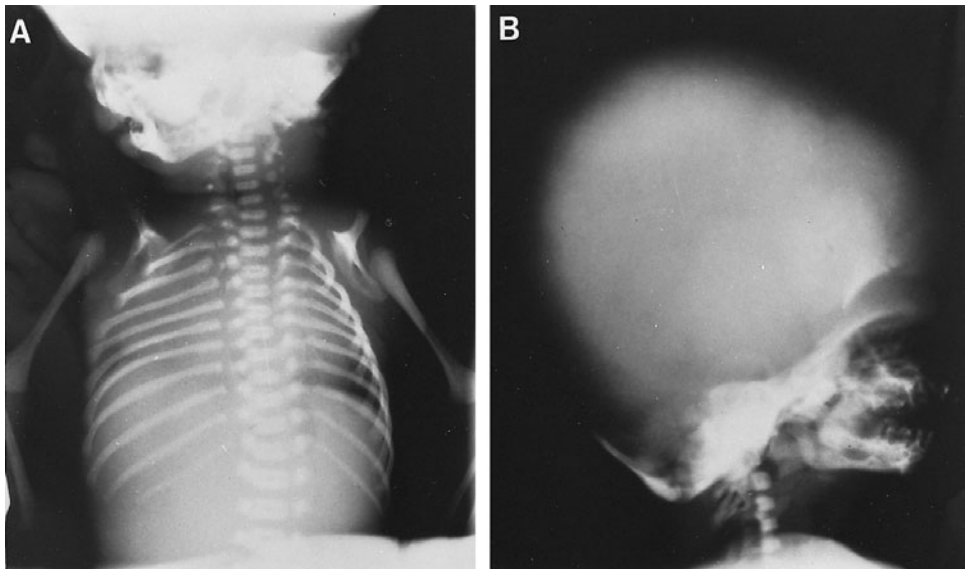


Fig. 22–41. *Crane-Heise syndrome*. (A,B) Note hypoplasia of cervical vertebrae, absent clavicles, small scapulae, markedly deficient mineralization of calvaria. (From JP Crane and RL Heise, Pediatrics 68:235, 1981.)

Hydrocephalus was found in two cases (5,9). A few manifest downslanting palpebral fissures. The pinnae were low set in nearly all cases. Cleft palate (1,2,4,5,8,9) or cleft lip (5) and micrognathia were virtually constant findings.

Musculoskeletal defects included flexion deformities of thumb and great toes (5), camptodactyly (7), dysplastic ribs (7), postaxial polydactyly (2), prominent heels (2), and clubfeet (7,9). Congenital heart defects such as double outlet right ventricle and/or VSD, right aortic arch, transposition of great vessels, and tetralogy of Fallot were documented (1,2,5).

Although the phenotypic sex is nearly always female, the chromosomal sex is 46,XY. Thus, there is sex reversal. Hypospadias was found in one infant with a male phenotype (5). The genitalia have usually been normal female with rare exception, when gonadal dysgenesis has been found (2,8). Miscellaneous abnormalities have included cystic kidneys (5), dysgenesis of urinary bladder (5), agenesis of gall bladder (5), and intestinal malrotation (5).

References [Genito-palato-cardiac syndrome (Gardner-Silengo-Wachtel syndrome)]

1. Beemer FA, Ertbruggen IV: Peculiar facial appearance, hydrocephalus, double-outlet right ventricle, genital anomalies, and dense bones with lethal outcome. Am J Med Genet 19:391–394, 1984.

2. Bernstein R et al: Female phenotype and multiple abnormalities in sibs with a Y chromosome and partial X chromosome duplication: H-Y antigen and Xg blood group findings. J Med Genet 17:291–300, 1980.

3. Curry CJR et al: Smith-Lemli-Opitz syndrome type II: Multiple congenital anomalies with male pseudohermaphroditism and frequent early lethality. Am J Med Genet 26:45–57, 1987.

4. Gardner LI et al: 46,XY female: Anti-androgenic effects of oral contraceptive? Lancet 2:667–668, 1970.

5. Greenberg F et al: The Gardner-Silengo-Wachtel or genito-palato-cardiac syndrome: Male pseudohermaphroditism with micrognathia, cleft palate, and conotruncal cardiac defect. Am J Med Genet 26:59–64, 1987.

6. Opitz JM, Lowry RB: Lincoln vs. Douglas again; comments on the papers by Curry et al, Greenberg et al, and Belmont et al. Am J Med Genet 26:69–72, 1987.

7. Robbing M et al: Case report 118: Coastal dysgenesis in male pseudohermaphroditism: A new syndrome? J Clin Dysmorphol 2(2):23–26, 1984.

8. Silengo M et al: A 46,XY infant with uterus, dysgenetic gonads and multiple anomalies. Hum Genet 25:65–68, 1974.

9. Wolman SR et al: Aberrant testicular differentiation in 46,XY gonadal dysgenesis: Morphology, endocrinology, serology. Hum Genet 55:321–325, 1980.

Cleft palate, camptodactyly, and clubfoot (distal arthrogryposis, type 3; Gordon syndrome)

Gordon et al (6) first recognized the syndrome of camptodactyly, talipes, and cleft palate. Several additional families have been described (8,10,11,13,14,16). The classification of the distal arthrogryposes by Hall et al (9) was updated by Bamshad et al (2) in 1996, and Gordon syndrome was classified as type 3. The patient reported by Bijlsma (3) also had spasticity and mental retardation and cannot be accepted as a valid example of this disorder. The patients reported by McCormack et al (12), Sack (15), Gripp et al (7), Bocian et al (4), Boles (5), and Sweet and Seaver (17) probably have Gordon syndrome, and perhaps even the patient described by Al-Chamdi et al (1).

There is autosomal dominant inheritance with variable expressivity and incomplete penetrance, possibly being more reduced in females.

The camptodactyly affects only the PIP joints, sparing the thumbs. Cleft palate occurs in approximately 20%. Other patients have exhibited submucous cleft palate or bifid uvula.

Additional components of the syndrome appear to be short stature, hip dislocation, various vertebral abnormalities (lumbar lordosis, kyphoscoliosis), and short neck with mild pterygia. Some patients have ptosis of eyelids, epicanthal folds, and nevus flammeus of the face (9,13,14,16). Cryptorchidism may be part of the syndrome (5,14).

One must exclude Tel Hashomer syndrome (11).

References [Cleft palate, camptodactyly, and clubfoot (distal arthrogryposis, type 3; Gordon syndrome)]

1. Al-Ghamdi M et al: Arthrogryposis multiplex congenita, craniofacial abnormalities, and normal intelligence: A new syndrome? Am J Med Genet 71:401–405, 1997.

2. Bamshad M et al: A revised and extended classification of the distal arthrogryposes. Am J Med Genet 65:277–281, 1996.

3. Bijlsma JB: Cleft palate, flexion contracture, aqueductal stenosis and mental retardation. Syndrome Ident 6(1):4–5, 1980.

4. Bocian M et al: Distal arthrogryposis with cleft palate, restricted extraocular movements, ptosis, scoliosis, and short stature: DA-5, new syndrome, or classification buster? 19th Annual David W. Smith Workshop on Malformations and Morphogenesis, Whistler, BC, Canada, 1998.

5. Boles RG: Cleft palate, ptosis, digital anomalies, and mental retardation: A new syndrome or a distal arthrogryposis variant? Clin Dysmorphol 8:63–66, 1999.

6. Gordon H et al: Camptodactyly, cleft palate and club foot: Syndrome showing the autosomal dominant pattern of inheritance. J Med Genet 6:266–274, 1969.

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9. Hall JG et al: The distal arthrogryposes: Delineation of new entities-review and nosologic discussion. Am J Med Genet 11:185–239, 1982.

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13. Moldenhauer E: Klinik des Nielson-Syndroms. Dermatol Wochenschr 150:599–601, 1964.

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15. Sack GF Jr: A dominantly inherited form of arthrogryposis multiplex congenita with unusual dermatoglyphics. Clin Genet 14:317–323, 1978.

16. Say B et al: The Gordon syndrome. J Med Genet 17:405, 1980.

17. Sweet K, Seaver L: Family with autosomal dominant distal arthrogryposis, ophthalmoplegia, and elbow dislocation: Extending the spectrum. Proc Greenwood Genet Ctr 17:13–19, 1998.

Distal arthrogryposis, unusual facies, cleft lip with/without cleft palate, short stature, hydronephrosis, and normal intelligence

Sonoda and Kouno (1) reported two brothers with joint contractures of the distal limbs, an unusual facies characterized by marked hypertelorism, and blepharophimosis, one with cleft lip, the other with cleft lip and palate, short stature, hydronephrosis, undescended testes, and normal intelligence. Although the authors suggested that they represented a form of *oto-palato-digital syndrome*, we disagree, and further suggest that it represents a new entity.

Reference (Distal arthrogryposis, unusual facies, cleft lip with/without cleft palate, short stature, hydronephrosis, and normal intelligence)

1. Sonoda T, Kouno K: Two brothers with distal arthrogryposis, peculiar facial appearance, cleft palate, short stature, hydronephrosis, retentio testis, and normal intelligence: A new type of distal arthrogryposis? Am J Med Genet 91:280–285, 2000.

Cleft palate, micrognathia, talipes equinovarus, atrial septal defect, and persistence of left superior vena cava

Gorlin et al (1,2) presented a kindred exhibiting cleft palate, micrognathia, talipes equinovarus, atrial septal defect, persistence of the left superior vena cava, a cardiac conduction anomaly, and death in infancy. The occurrence of the syndrome in several male children of sisters suggests X-linked recessive inheritance.

It is possible that other examples have been reported. Smith and Stowe (4), in their survey of 39 patients with Robin sequence, noted that 5 died of congenital heart anomaly and that 3 had clubfeet. No mention was made of the sex of the affected. Sachtleben (3) described a male infant with ASD of the primum type, cleft palate, inguinal hernia, and talipes equinovarus. He further noted two brothers with this combination.

References (Cleft palate, micrognathia, talipes equinovarus, atrial septal defect, and persistence of left superior vena cava)

1. Gorlin RJ et al: Robin's syndrome: A probably X-linked subvariety exhibiting persistence of left superior vena cava and atrial septal defect. Am J Dis Child 119:176–178, 1970.
2. Gorlin RJ et al: Facial clefting and its syndromes. Birth Defects 7(7):3–49, 1971.
3. Sachtleben P: Zur Pathogenese and Therapie des Pierre Robin-Syndroms. Arch Kinderheilkd 171:55–63, 1964.
4. Smith JL, Stowe FR: The Pierre Robin syndrome: A review of 39 cases with emphases on ocular lesions. Pediatrics 27:128–133, 1961.

Kabuki (Niikawa-Kuroki) syndrome

In 1981, Niikawa et al (34) and Kuroki et al (24) independently reported a syndrome characterized by mild to moderate mental retardation, postnatal progressive growth retardation, and strikingly unusual facies reminiscent of the make-up used in Kabuki theatre (15). An estimate of frequency is 1 per 32,000–50,000 liveborn (11,35). Approximately 200 examples have been reported, approximately one-third in non-Japanese (1,48). There is currently favor for the term "Kabuki syndrome."

Almost all cases reported to date have been isolated examples. However, it has been described in two generations (6a,14,18,21,43,45). The majority of reported patients have been Japanese. There is no sex predilection (42). We suspect that the condition is just more difficult to diagnose in non-Japanese (2,4,13,14,19,21,23,31,33,37,39,42,48).

Craniofacial findings. Perhaps 30% have some degree of microcephaly (15,39). The palpebral fissures are long (100%) with eversion of the lateral third of the lower eyelid (90%). (Fig. 22–42A–C). Ptosis has been noted in 35%. The eyebrows are arched (80%) and tend to be diminished laterally. The lashes are heavy and long. The sclerae are blue in 30%. Strabismus and epicanthal folds are present in 50%–60% (20a). Nocturnal lagophthalmos is noted in 50% (H. Toriello, personal communication, 2000). The pinnae are large, outstanding, and poorly folded in 80%. The nose is broad with a depressed tip (80%) and/or short septum (90%) (Fig. 22–42A,B). The teeth are widely spaced in 65%. Cleft lip and/or cleft palate or submucous cleft palate have been found in 40% (3,26,48). The philtrum is prominent and broad. The occipital hairline is often low. One-third have retrognathia. There is often an exaggerated depression below the midpoint of the lower lip. Lower paramedian lip pits have been reported (7,9,22,29) but were shown to be unrelated to the van der Woude mutation (29). Hypodontia, missing mandibular incisors, and incisors with conical crown form or screw-driver shape have been noted in a patient (27,30a,32).

The ears are large and outstanding with prominent lobules in 85%. The anthelix tends to be hypoplastic. Approximately 25% have a pretragal pit. Otitis media is extremely frequent during childhood (60%), and there is hearing loss in 40% (20,35,41–44). The ossicles may rarely be severely malformed (37), and Mondini dysplasia of the cochlea has been found in at least 30% (16a,39).

Skeletal system. Frequent anomalies include short stature (80%), short fifth fingers (80%), scoliosis (30%), congenital sagitally-cleft vertebrae (35%), dislocation of hip (20%), various rib anomalies (20%), and spina bifida occulta (15%) (11,34). Hypermobile joints (75%) may be more common in non-Japanese (13,17,31,38,39). Hypoplastic clavicles have been noted (10).

Neurologic findings. Microcephaly is documented in 25%. Mental retardation has been found in over 90% (26,48). Approximately 30% exhibit hypotonia, 75% have joint laxity, and 75% have feeding problems (6a,42). Seizures are seen in 50% (20,48). Mirror image movements of the extremities may be seen (46). A subarachnoid cyst has been noted (6). Poor feeding in infancy is noted in 40% (20,48).

Cardiovascular system. Congenital heart abnormalities have been reported in approximately 55%: ASD, VSD, single ventricle with common atrium, PDA, and juxtaductal coarctation of the aorta (6b,7,16, 20,24,36).

Integumentary system. There is persistence of fetal fingertip pads in approximately 80% (2,4,48) (Fig. 22–42D). Dermatological findings include increased ulnar loops and hypothenar loop patterns (70%) and absent digital triradius *c* and/or *d* (11,21). Trichorrhexis nodosa and hypoplastic nails have been reported (6a,27).

Anogenital and endocrine findings. Early breast development in females and/or elevated gonadotropin levels have been described in 35% (3,9,25,45) (Fig. 22–42E). Approximately 15% have imperforate anus, anal stenosis, or anovestibular fistulae (3,22,30,35). Turner syndrome or ovarian dysfunction has been noted in two cases (37,47), male pseudohermaphroditism in another (12). The mother of a patient was a Turner mosaic (46). Hypospadias has also been reported (13) in 15%. Neonatal hypoglycemia has been described in 40% (1,3,35,48). Growth hormone deficiency has also been described (10a,40).

Immunodeficiency. There have been isolated reports of immunodeficiency (1,5,8). Approximately 60% have increased infections in childhood (48).

Miscellaneous. Extrahepatic biliary atresia has been found in two patients (7,30b,42a,45a). Neonatal sclerosing cholangitis and dysplastic kidneys have also been described (8). Diaphragmatic defects apparently are more frequent in non-Asians (6c,39,43,45a).

Diagnosis. A Kabuki-like syndrome has been found in association with pseudodicentric chromosome 13(28).

References [Kabuki (Niikawa-Kuroki) syndrome]

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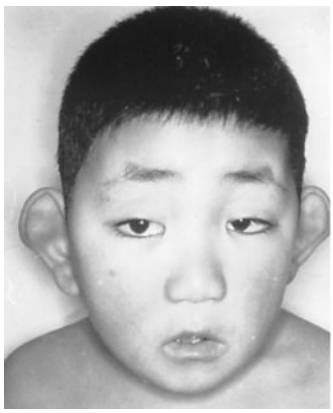

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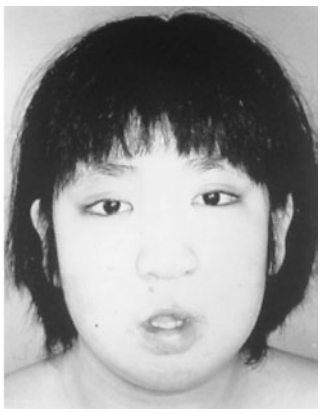

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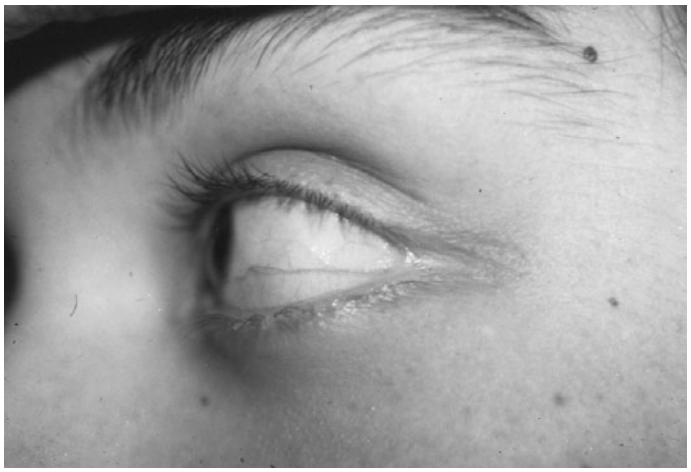

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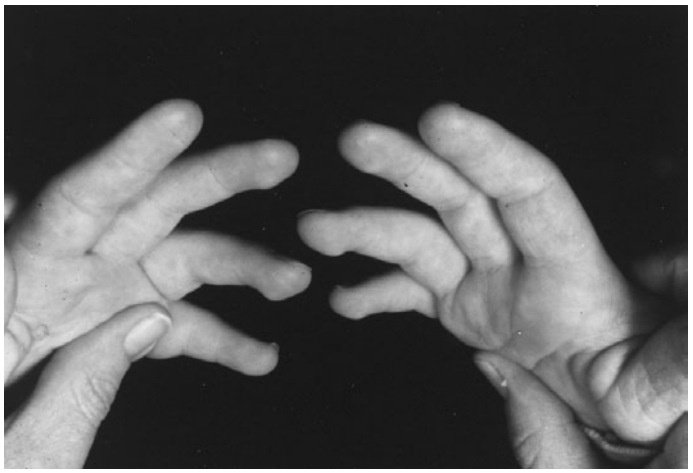

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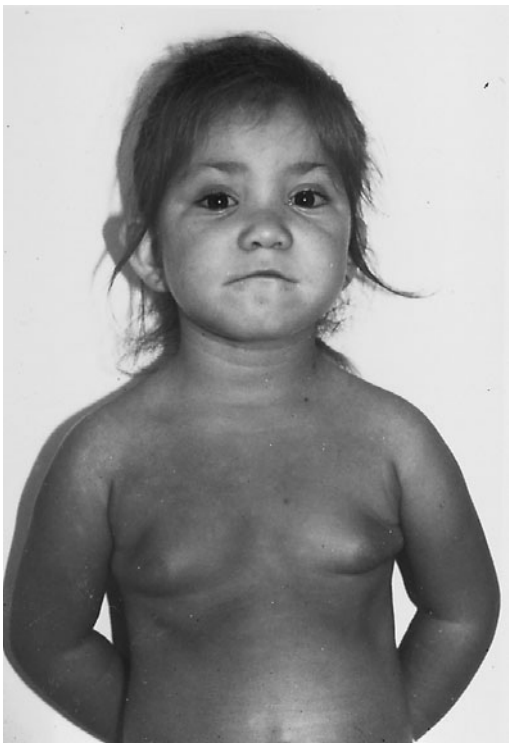

E

Fig. 22–42. *Kabuki (Niikawa-Kuroki syndrome)*. (A,B) Note long palpebral fissures, highly arched abnormal eyebrows, large pinnae, depressed nasal tip, and repaired cleft lip. (C) Hyperextension of outer canthus. (D) Fetal finger pads. (E) Premature thelarche. (A,B courtesy of Y Kuroki, Yokahama, Japan.)

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Cleft palate-lateral synechiae syndrome

Unilateral or bilateral bands may extend from the edges of a palatal cleft to the lateral margins of the tongue or oral floor (Fig. 22–43). Several authors have reported autosomal dominant inheritance with variable expressivity for this syndrome (1–5). RJ Gorlin has seen the disorder in two generations. Also see *syngnathia and cleft palate*.

Preus et al (7) emphasized the variable expression of the disorder. Nakata et al (6) reported three cases, two being sibs whose parents were normal and nonconsanguineous. In addition to the usual findings, they noted short stature, microcephaly, long upslanting palpebral fissures, and prominent pinnae. Mild mental retardation was documented in two patients (3,6). L Sadler (personal communication, 1999) found that VSD was an associated finding. Fernandez et al (2a) noted recto-vaginal fistula. Although the sibs described by Nakata et al (6) may represent a new syndrome, the variable expressivity of the syndrome and the possibility of gonadal mosaicism do not make this likely. Dinardo et al (2) used the term "cleft palate lateral synechia syndrome," but they referred to a child with *syngnathia and cleft palate*.

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Posterior palatal synechiae and cleft palate

The buccopharyngeal membrane is an evanescent structure that undergoes dissolution in the 4th embryonal week. It separates the primitive mouth from the oral pharynx. In a few cases, there has been membranous extension of the cleft palate to the base of the tongue (1,2,3,5–9,11) (Fig. 22–44). All examples have been isolated. It has been suggested that this represents persistence of the buccopharyngeal membrane. We are skeptical, given that the tongue develops behind the buccopharyngeal membrane. Cases of subglossopalatal membrane and cleft palate (8,10–13) appear to be more legitimate examples of persistence of the membrane. Associated anomalies included ankylosis of the distal interphalangeal joints of the fifth fingers, absence of the distal phalanx of the fifth toes (10), toenail hypoplasia, umbilical hernia, and hypospadias (13). Seghers (11), Flannery (6), and RJ Gorlin have seen associated rib and vertebral changes similar to those in *cerebro-costo-mandibular syndrome*. Complete failure of development of the mandible has been associated with cleft palate and persistence of the buccopharyngeal membrane (4). We do not know how to classify the patient described by Wassermann (12).

One must exclude *Holzgreve-Wagner-Rehder* syndrome (bilateral renal agenesis, buccopharyngeal membrane, cleft palate, congenital heart anomalies, mesoaxial hexadactyly, and bifid metacarpal) as a single entity. Several examples have been reported (2, 8,10).

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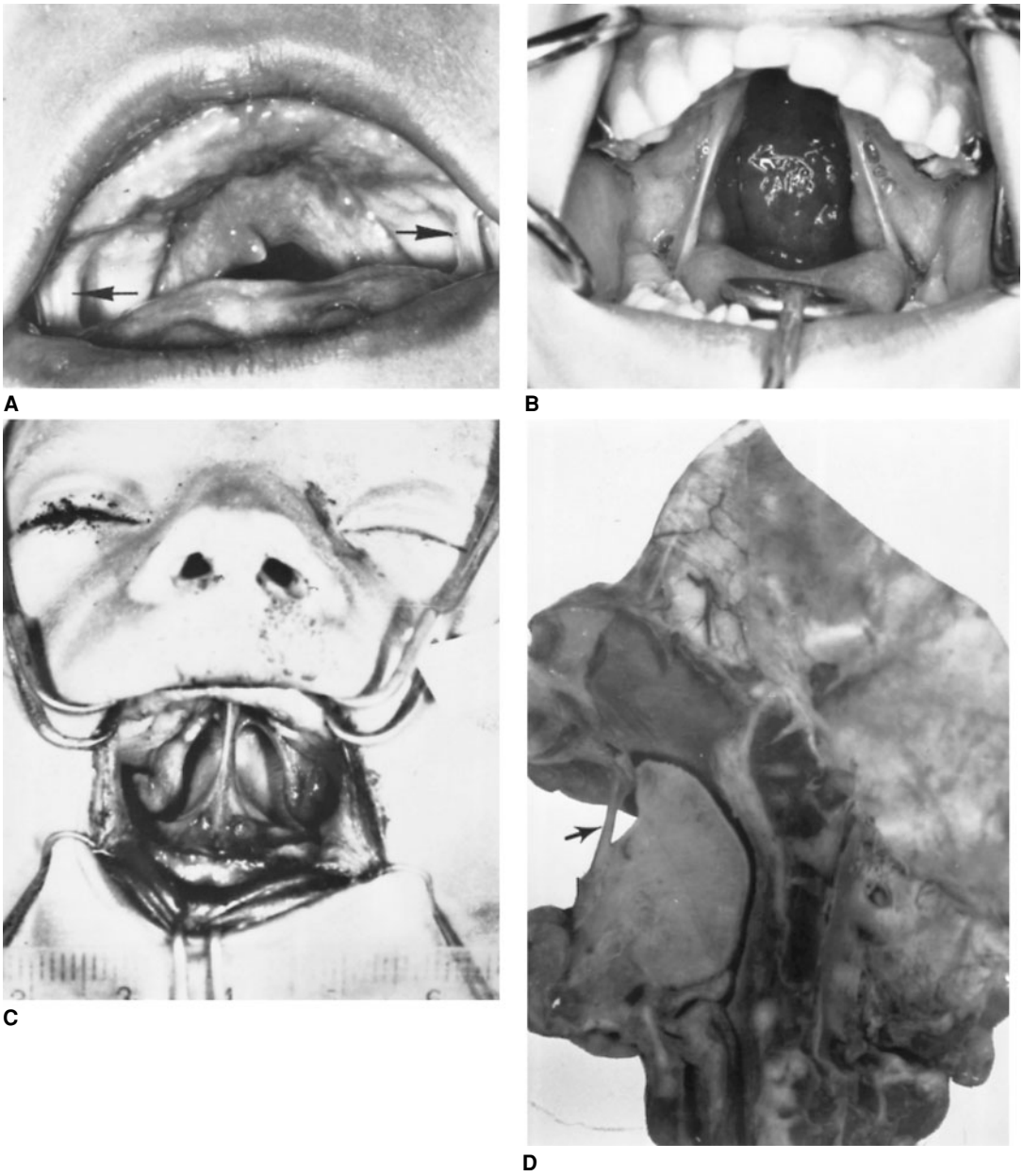

Fig. 22–43. *Cleft palate-lateral synechiae syndrome*. (A) Syngnathia; arrows point to fibrous bands joining upper and lower gingiva. (B) Autosomal dominantly inherited synechiae. (C,D) Cleft plate and persistence of buccopharyngeal membrane. (A courtesy of H Weyers, Cuxhaven, Germany. B courtesy of M Mazaheri, Lancaster, Pennsylvania. C,D from M Hub and J Jirásek, Cas Lek Ces 99:1297, 1960.)

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Lethal omphalocele and cleft palate

Czeisel (1) reported three female sibs with cleft palate and omphalocele. One sib had a bicornuate uterus, another internal hydrocephalus, and the third a hypoplastic uterus. The parents were nonconsanguineous. All three children died in infancy presumably from pneumonia.

Reference (Lethal omphalocele and cleft palate)

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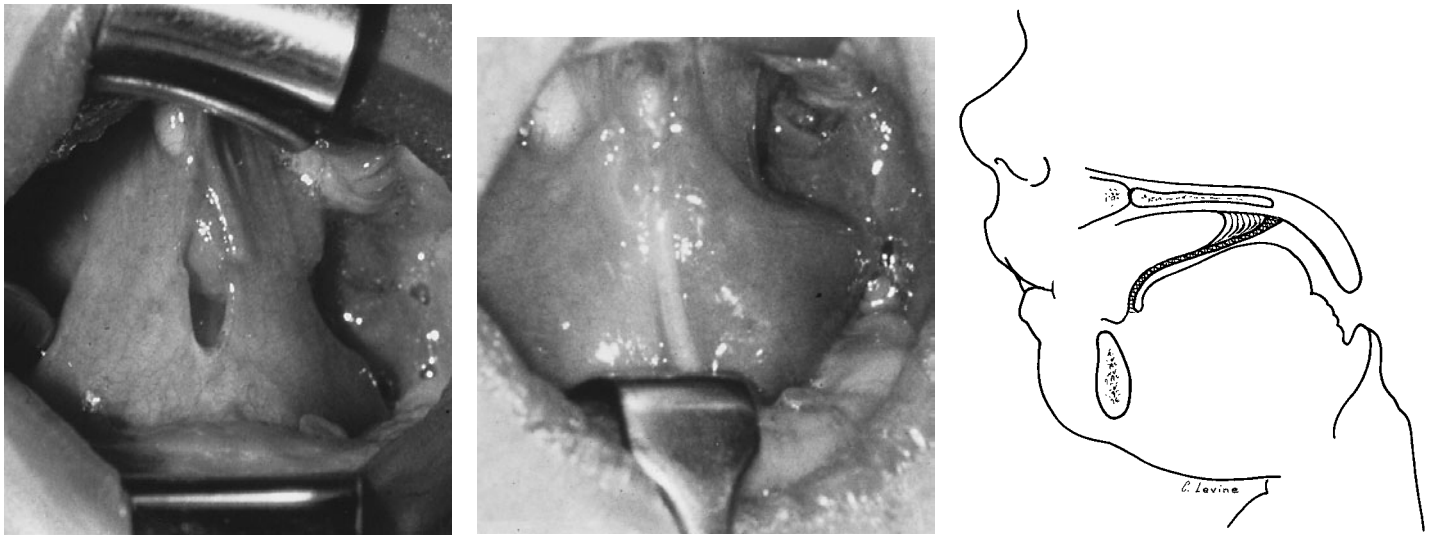


A B C

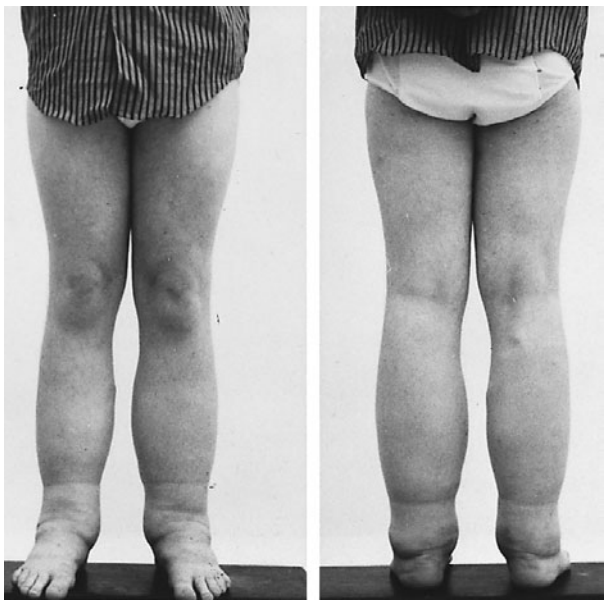
Fig. 22–44. *Posterior palatal synechiae and cleft palate*. (A) Oral web extending from subglossal region to palate. Surgical slit is present in midline. (B) Compare to similar case. (C) Schematic representation of subglossopalatal membrane. (A,C from GH Zalzal et al, Arch Otolaryngol Head Neck Surg 112:1101, 1986. B from T Nakajima et al, Plast Reconstr Surg 8:341, 1951.)

Lymphedema of pubertal onset and cleft palate

Figueroa et al (3) reported the association of lymphedema of pubertal onset (Meige type) with cleft palate. Inheritance is probably autosomal dominant with variable expressivity (2,4,6,7,12). The lymphedema is largely limited to the legs (Fig. 22–45). The arms, hands, and feet may also be involved. Among the latter group, the genitalia and intestines are more commonly affected. The etiology is thought to be hypoplasia or late development of the superficial lymphatic channels that inhibits effective drainage of a body part. There are many syndromes that involve lymphedema (microcephaly, distichiasis, yellow nails, ptosis, partial lower eyelid ectropion, spinal extradural cysts, vertebral anomalies, *Noonan syndrome, Turner syndrome*, etc.) (8,10,11). The patients reported by Jester (7) and Bartley and Jackson (2) also had distichiasis of the upper eyelids. *Hennekam syndrome*, which should be excluded, has autosomal recessive inheritance. Irons et al (5) described an autosomal recessive syndrome in sibs with lymphedema, hydroceles, atrial septal defect, and facial changes (epicanthic folds, wide nasal bridge). Anderson et al (1) reported associated lymphangiosarcoma.

The lymphedema-distichiasis gene, *MFH1*, maps to 16q24.3 (9) as does the gene for distichiasis-lymphedema-cleft palate (1a,2a).

Fig. 22–45. *Lymphedema of pubertal onset and cleft palate*. (A,B) Severe lymphedema affecting lower extremities. (From AA Figueroa et al, Cleft Palate J 20:151, 1983.)



A B

References (Lymphedema of pubertal onset and cleft palate)

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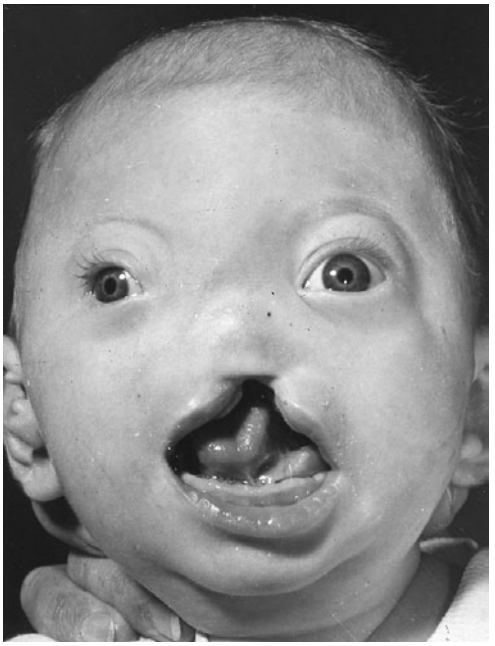

Fig. 22–46. *Median cleft upper lip, hypertelorism, and holoprosencephaly*. Median cleft upper lip and palate. (From WE Bell and WM Van Allen, Neurology 9:694, 1959.)

Median cleft upper lip, hypertelorism, and holoprosencephaly

Bell and Van Allen (1) described an infant with marked hypertelorism and unusual median cleft lip with cleft palate. There were microcephaly, agenesis of the corpus callosum, and ear tags (Fig. 22–46).

In what may be a second example, Ohtsuka (4) reported an 11-year-old female with hypertelorism and similar facial abnormalities. The child had seizures since birth and unilateral microphthalmos. Hydranencephaly and holoprosencephaly were demonstrated. Cleft palate was also present. Arthrogryposis was probably secondary to central nervous system alterations. Bony abnormalities included lumbar scoliosis, bilateral dislocation of hips, underdeveloped pelvic bones, and slender femora.

Both were isolated cases but consanguinity was documented by Ohtsuka (4). Hypertelorism is also known to be associated with semilobar holoprosencephaly with *del(18q)* and with *frontonasal malformation*. See *holoprosencephaly* for more detail. The combination of holoprosencephaly and hypertelorism has been described by Hartsfield et al (2) and Moore et al (3).

References (Median cleft upper lip, hypertelorism, and holoprosencephaly)

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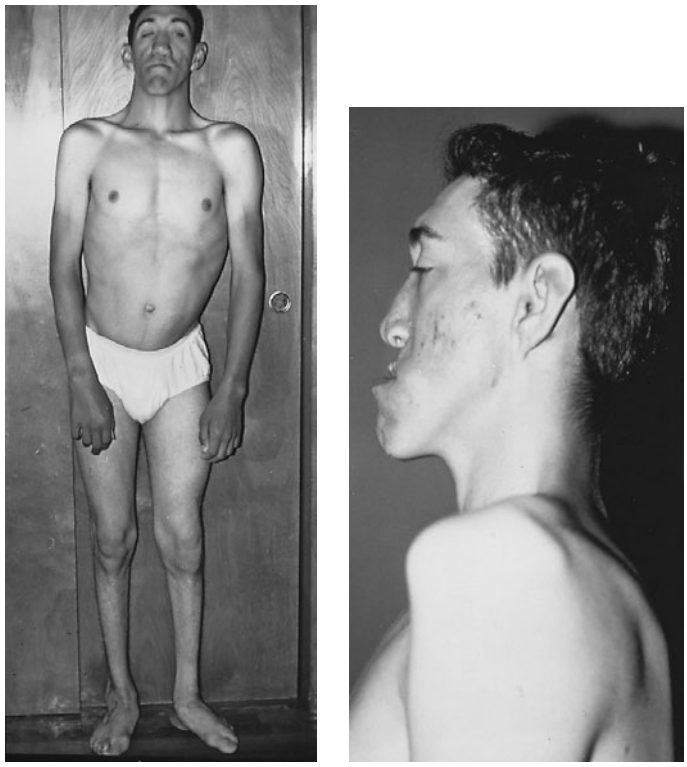
Median cleft upper lip, mental retardation, and pugilistic facies (W syndrome)

Pallister et al (4) described a mother and three children. The mother was reported by Bottani and Schinzel (1). The disorder may have X-linked dominant inheritance (2).



A B

Fig. 22–47. *Median cleft upper lip, mental retardation, and pugilistic facies (W syndrome)*. (A,B) Note frontal prominence, internal strabismus, flattened nasal bridge, midline notch of upper lip. Compare with Fig. 22–48. Although facies are similar, this probably is not the same disorder. The latter appears to have *cleft lip-palate, mental retardation, and holoprosencephaly syndrome*. [From PD Pallister et al, Birth Defects 10(7):51, 1974.]

The facies was characterized by high broad forehead, anterior cowlick, hypertelorism, downward slanting palpebral fissures, and alternating internal strabismus (Figs. 22–47 and 22–48). The nasal bridge was flattened. The upper lip had a midline notch because of a bifid frenum (Fig. 22–49). The hard palate exhibited anterior palatal cleft, and all probably had submucous cleft palate. The upper central incisors were missing.

Mental retardation, seizures, and mild spasticity were noted in a few individuals.

Musculoskeletal anomalies consisted of hernias, cubitus valgus with subluxation of the proximal radioulnar joints, lateral bowing of the radii, short ulnae, mild clinodactyly and camptodactyly of the fourth and fifth fingers, and pes cavus.

All had acne.

The syndrome should be differentiated from *otopalatodigital syndrome, Type I*, autosomal dominant *holoprosencephaly*, and *cleft lip-palate, microcephaly, mental retardation, and holoprosencephaly* (3).

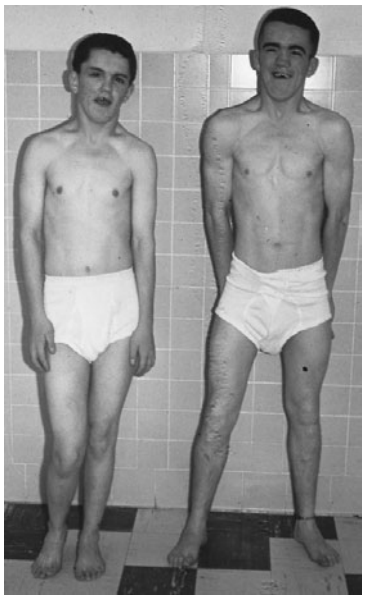
References [Median cleft upper lip, mental retardation, and pugilistic facies (W syndrome)]

1. Bottani A, Schinzel A: A third patient with median cleft upper lip, mental retardation and pugilistic facies (W syndrome). Corroboration of a hitherto private syndrome. Clin Dysmorphol 2:225–231, 1993.

2. Goizet C et al: W syndrome: Report of three cases and review. Am J Med Genet 87:446–449, 1999.

3. Martin AO et al: An autosomal dominant midline cleft syndrome resembling familial holoprosencephaly. Clin Genet 12:65–72, 1977.

4. Pallister PD et al: The W syndrome. Birth Defects 10(7):51–60, 1974.



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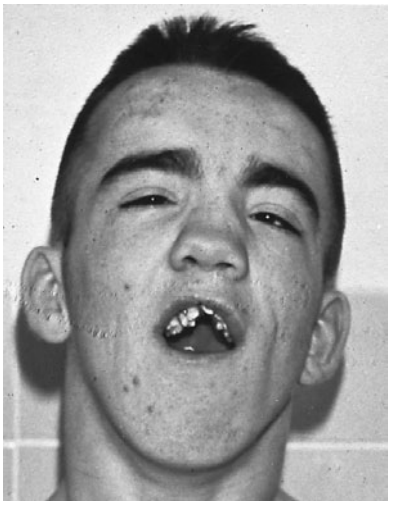


B

Fig. 22–48. *Median cleft upper lip, mental retardation, and pugilistic facies (W syndrome).* (A) Note downslanting palpebral fissures, pugilistic appearance, median cleft lip, hypoplasia of lower leg muscles. (B) Hypoplastic midface. (Courtesy of J Perrin, Birmingham, Michigan.)

Michels syndrome (oculopalatoskeletal syndrome; blepharophimosis-ptosis, inverse epicanthus, anterior segment anomalies, craniosynostosis, and cleft lip-palate)

Michels et al (5), in 1978, described four sibs, three brothers and a sister, with anterior chamber eye anomalies, other craniofacial anomalies, and skeletal defects. Added information was supplied by de la Paz et al (3). Other examples are those of Guion-Almeida and Rodini (4), Cunniff and Jones (2), and possibly those of Al Gazali et al (1). Inheritance is clearly autosomal recessive (1–6).

Height was generally below the 3rd centile as was head circumference (5). In some there was prenatal growth retardation (1,5). Mild mental retardation has been evident (3,5).

Eye anomalies seen in all affected included blepharoptosis, blepharophimosis, and inverse epicanthus. Mild hypertelorism, limited upward gaze, and corneal stromal opacities were noted in 65% (Figs. 22–50 and 22–51). The eyebrows were highly arched in 50%. Craniosynostosis of the lambdoidal sutures was observed in 60% (2–5). Cleft lip and palate were found in approximately 50% (2–5). Conductive hearing loss was noted in 80% (3,4).

Short clinodactylous fifth finger was present in most patients. Less common anomalies included radioulnar synostosis (3,5), arachnodactyly (1), long bowed fibulae (5), and talipes (5).

Fig. 22–49. *Median cleft upper lip, mental retardation, and pugilistic facies (W syndrome).* Midline cleft of upper lip, deep anterior palatal groove. [From PD Pallister et al, Birth Defects 10(7):51, 1974.]

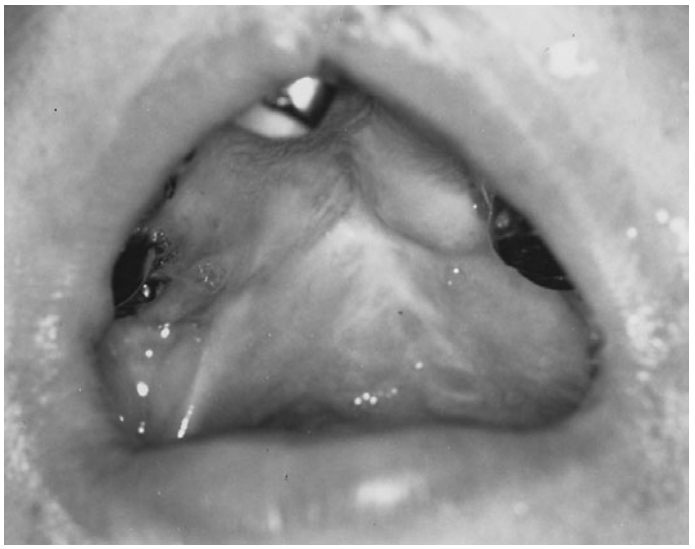
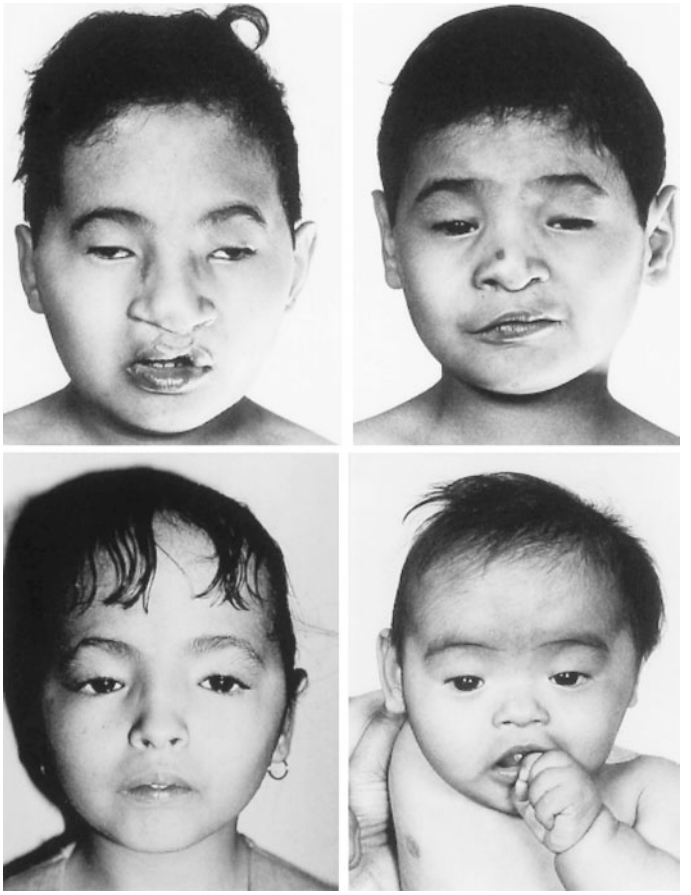


Fig. 22–50. *Michels syndrome*. Blepharoptosis, blepharophimosis, and epicanthus inversus. Note repaired cleft lip in upper two patients. (From VV Michels et al, J Pediatr 93:444, 1978.)



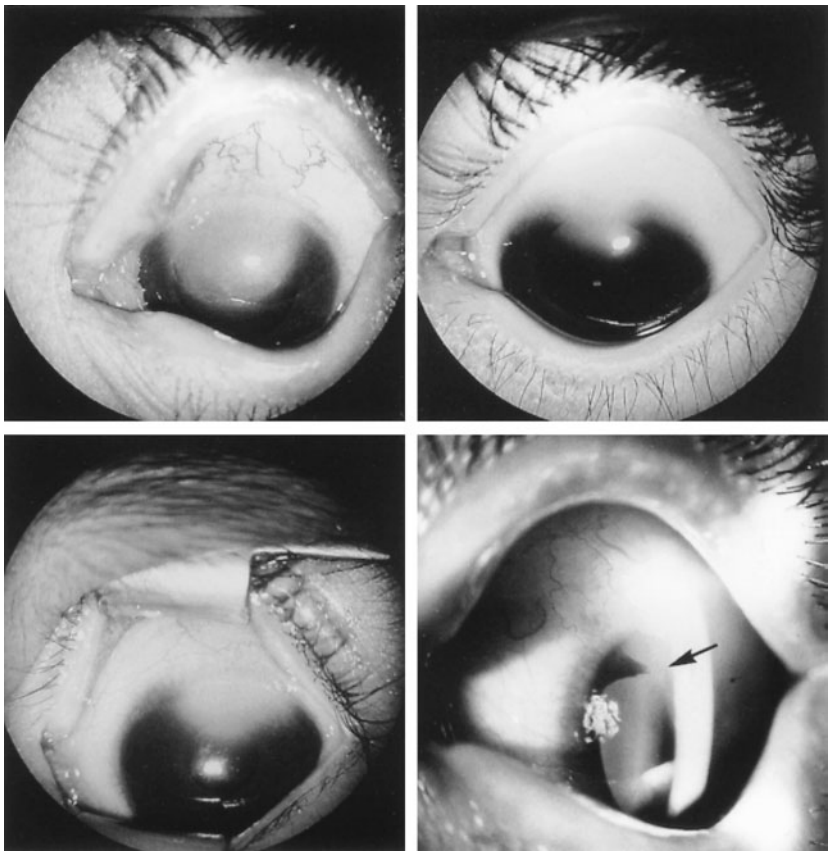


Fig. 22–51. *Michels syndrome*. Corneal opacities. Arrows point to iris adhesion in lower right. (From VV Michels et al, J Pediatr 93:444, 1978.)

An umbilical depression was noted in 70% (4,5).

The triad of *blepharophimosis, blepharoptosis, and inverse epicanthus* is a well-recognized autosomal dominant syndrome (eye triad) that has been mapped to 3q22.3. Also to be excluded are *Peters Plus syndrome* characterized by anterior segment eye anomalies, cleft lip and palate, and mental retardation but no anomalies of the skeleton other than short stature and brachydactyly.

Al Gazali et al (1) noted that the eye triad was absent in their patients. Some skeletal anomalies and congenital heart anomalies were found. They suggested that it may represent a different entity.

References [Michels syndrome (oculopalatoskeletal syndrome; blepharophimosis-ptosis, inverse epicanthus, anterior segment anomalies, craniosynostosis, and cleft lip-palate)]

1. Al Gazali LI et al: Anterior segment anomalies of the eye, clefting, and skeletal abnormalities in two sibs of consanguineous parents: Michels syndrome or a new syndrome. Clin Dysmorphol 3:238–244, 1994.
2. Cunniff C, Jones KL: Craniosynostosis and lid anomalies: Report of a girl with Michels syndrome. Am J Med Genet 37:28–30, 1990.
3. de la Paz M et al: A sibship with unusual lid anomalies of the eye and skeleton (Michels syndrome). Am J Ophthalmol 112:572–580, 1991.
4. Guion-Almeida ML, Rodini ESO: Michels syndrome in a Brazilian girl born to consanguineous parents. Am J Med Genet 57:377–379, 1995.
5. Michels VV et al: A clefting syndrome with ocular anterior chamber defect and lid anomalies. J Pediatr 93:444–446, 1978.
6. Paes-Alves AF et al: Autosomal recessive malformation syndrome with minor manifestation in the heterozygotes: A preliminary report of a possible new syndrome. Am J Med Genet 41:141–152, 1991.

Microcephaly and cleft palate

Halal (1) reported cleft palate and microcephaly in two sisters and their mother. The facies was somewhat unusual. There was mild hypotelorism and maxillary hypoplasia.

Abnormal retinal pigmentation with normal electroretinogram (ERG) findings was demonstrated. The microcephaly was at approximately the third centile. Mental retardation was mild. The mother had euthyroid goiter and bilateral camptodactyly at the DIP joints of fingers 2 to 5.

A similar combination of autosomal dominantly inherited cleft palate and microcephaly was reported by Say et al, but the patients also had short stature and large pinnae (see *Cleft palate, microcephaly, large ears, and short stature*). Microcephaly, mental retardation, persistent primary vitreous, and short stature have been reported as a recessive syndrome by Frydman (see *Oculo-palato-cerebral dwarfism*).

Reference (Microcephaly and cleft palate)

1. Halal F: Dominantly inherited syndrome of microcephaly and cleft palate. Am J Med Genet 15:135–140, 1983.

Oculo-palato-cerebral dwarfism

Frydman et al (1), in 1985, described a syndrome in three children of consanguineous parents. The syndrome consisted of cleft palate, microcephaly, mental retardation, spasticity, short stature, asthma, and persistent hypertrophic primary vitreous of the eye. Inheritance appears to be autosomal recessive.

Gestational hypertension was noted with all three sibs. Birthweight was approximately −2 SD. Stature fell to −2.5 to −4 SD. Hypotonia was noted in the neonatal period.

The facies was characterized by coarse hair, full cheeks, and deeply set eyes (Figs. 22–52 and 22–53). Hands and feet were small. The joints were mildly hypermobile. The skin was soft with a doughlike texture. The veins were visible beneath the skin.

Leukocoria became evident during the first month of life. Primary persistent hyperplastic primary vitreous and microphthalmia were evident.

Mental retardation ranged from mild to severe with microcephaly −3 to 5.5 SD. Spasticity ranged from a moderate degree to complete

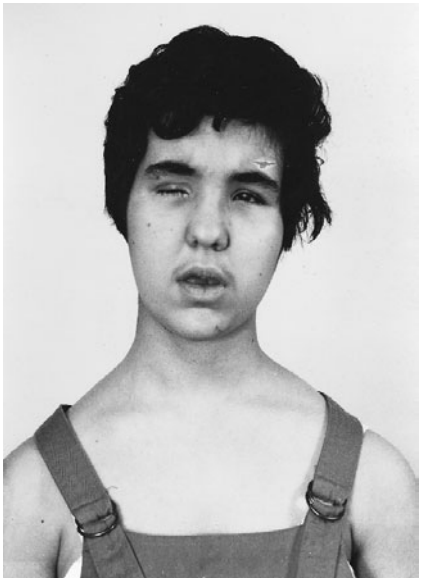


Fig. 22–52. *Oculo-palato-cerebral dwarfism*. Fifteen-year-old with microcephaly, mild mental retardation, hypotonia, cleft palate, short stature, long thin neck, and sloping shoulders. Patient had persistent hypertrophic primary vitreous, microphthalmia, mild hearing loss, small hands and feet, ankle spasticity, and asthma. (From M Frydman et al, Clin Genet 27:414, 1985.)

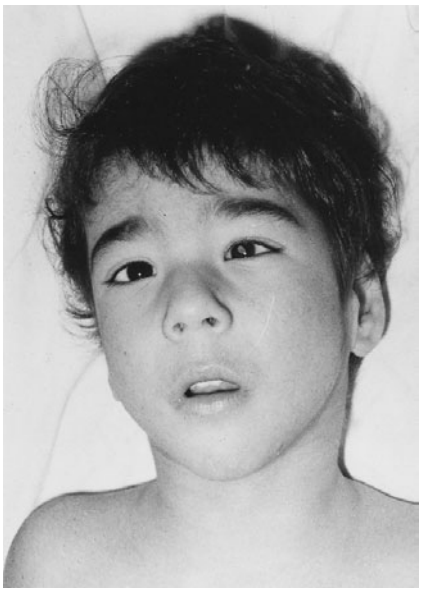
quadriplegia. Hearing loss was mild. All patients had severe asthma, pneumonitis, otitis media, pectus excavatum, and cleft palate.

A combination of microcephaly and cleft palate is seen in the syndromes described by Halal (see *microcephaly and cleft palate*) and by Say et al (see *Cleft palate, microcephaly, large ears, and short stature*).

Reference (Oculo-palato-cerebral dwarfism)

1. Frydman M et al: Oculo-palato-cerebral dwarfism: A new syndrome. Clin Genet 27:414–419, 1985.

Fig. 22–53. *Oculo-palato-cerebral dwarfism*. Sib having similar features: short stature, severe mental retardation, cleft palate, microphthalmia, persistent hypertrophic primary vitreous of left eye, quadriplegia, and asthma. (From M Frydman et al, Clin Genet 27:414, 1985.)



Odontotrichomelic syndrome (tetramelic deficiency, ectodermal dysplasia, and deformed pinnae)

Freire-Maia, Pinheiro, and co-workers (1–4,7) described a form of ectodermal dysplasia with tetramelic deficiency in four of eight Brazilian sibs. The parents were normal and apparently not consanguineous but were from a highly inbred region. Rather extensive bone deficiencies involved all extremities. Various skeletal abnormalities were reported. There was marked reduction in the amount of scalp and body hair, eyebrows, and lashes. The ears were large, thin, outstanding, and deformed. Oligodontia and conical crown form were noted. The nipples and areolas were hypoplastic, and hypogonadism was found, as well as mild mental retardation. Two of four affected sibs died in infancy. Cleft lip occurred in only one boy (Fig. 22–54). Some of these patients resemble those with *EEC syndrome* (6).

Herrmann et al (5) described a mentally retarded Amerindian boy with some of the stigmata seen in the syndrome noted above. However, their case probably represents another syndrome discussed under *Herrmann syndrome*.

References [Odontotrichomelic syndrome (tetramelic deficiency, ectodermal dysplasia, and deformed pinnae)]

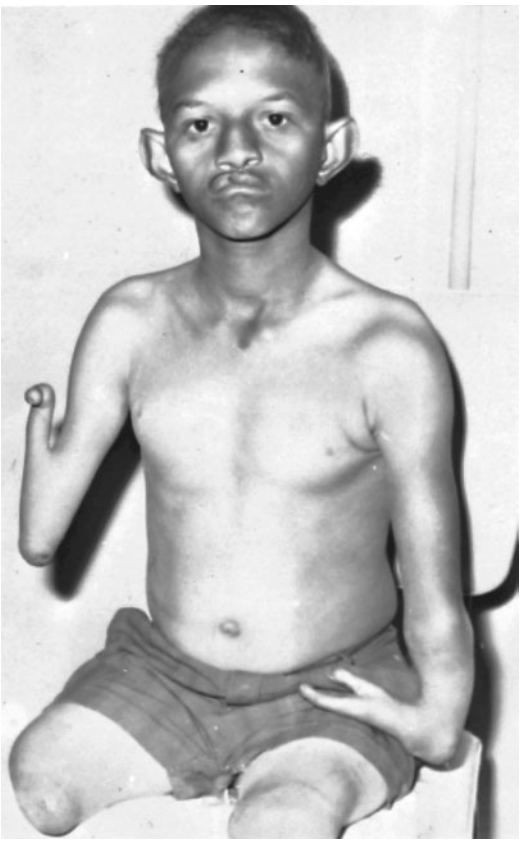
1. Cat I et al: Odontotrichomelic hypohidrotic dysplasia: A clinical reappraisal. Hum Hered 22:91–95, 1972.

2. Chautard EA, Freire-Maia N: Dermatoglyphic analysis in a highly mutilating syndrome. Acta Genet Med Gemellol 19:421–424, 1970.

3. Freire-Maia N: A newly recognized genetic syndrome of tetramelic deficiencies, ectodermal dysplasias, deformed ears and other anomalies. Am J Hum Genet 22:370–377, 1970.

4. Freire-Maia N, Pinheiro M: Ectodermal Dysplasias: A Clinical and Genetic Study. Alan R. Liss, New York, 1984, pp 106–108.

Fig. 22–54. *Odontotrichomelic syndrome*. Sparsity of hair, deformed ears, hypoplastic nipples, deficient teeth, and cleft lip-palate. A sister was similarly affected. (From N Freire-Maia, Am J Hum Genet 22:370, 1970.)



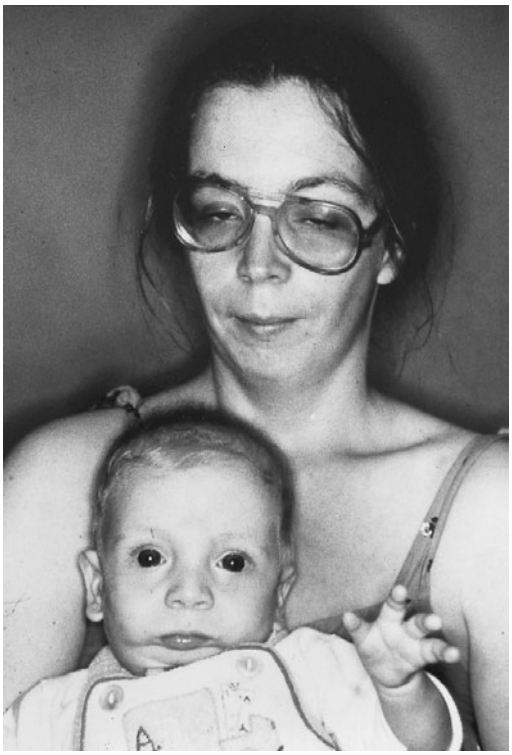


Fig. 22–55. *Oligodactyly and cleft palate*. Mother and son with cleft palate and micrognathia. (From M Robinow et al, Am J Med Genet 25:293, 1986.)

5. Herrmann J et al: Craniosynostosis and craniosynostosis syndromes. Rocky Mt Med J 66:145–156, 1969.
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7. Pinheiro M, Freire-Maia N: Ectodermal dysplasias: A clinical classification and a causal review. Am J Med Genet 53:153–162, 1994.

Oligodactyly and cleft palate

Robinow et al (2), in 1986, reported a mother and son with cleft palate, microretrognathia, and anomalies of the hands and feet. The first ray in the hands was hypoplastic and the fifth ray was absent. The fourth metacarpal was somewhat broadened. In the feet of the boy, the fifth rays were hypoplastic (Figs. 22–55 and 22–56). The mother had no abnormality of the toes. We are not aware of similar cases. Meinecke and Wiedemann (1) suggested that the syndrome represents incomplete expression of *postaxial acrofacial dysostosis*. Both Robinow et al (3) and RJ Gorlin express skepticism.

References (Oligodactyly and cleft palate)

1. Meinecke P, Wiedemann H-R: Robin sequence and oligodactyly in mother and son—probably a further example of the postaxial acrofacial dysostosis syndrome. Am J Med Genet 27:953–956, 1987.
2. Robinow M et al: Robin sequence and oligodactyly in mother and son. Am J Med Genet 25:293–298, 1986.
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Recurrent brachial plexus and neuropathy, characteristic facies, and cleft palate

Jacob et al (12) were probably the first to recognize the syndrome of recurrent brachial neuropathy (AD neuralgic amyotrophy), characteristic facies, and cleft palate. There have been a considerable number of other reports (1–8,11,12). Most patients with neuralgic amyotrophy do not have characteristic facies and cleft palate. Inheritance is autosomal dominant with variable expressivity and nearly complete penetrance. The gene has been mapped to 17q24–q25 (14,18). Heterogeneity has been alleged (10,19). Its frequency has been estimated as 1 per 60,000 in the general population (3).

The face is somewhat narrow and often there is mild facial asymmetry. The eyes appear deeply set and hypoteloric. There are epicanthal folds and mild upslanting of the palpebral fissures (Fig. 22–57). A number of patients have cleft palate or bifid uvula (1,2,4,6,7,9,12,13,16). Some patients experience hoarseness, implying involvement of the recurrent laryngeal nerve (9,12,15).

Usually beginning in the 4th to 8th year of life, the patient experiences sudden attacks of pain in the shoulder that radiate to the arms and hands. A few days after the pain subsides, paresthesia, weakness, and, later, atrophy of the upper extremities occur. Some patients exhibit wrist drop, whereas others cannot lift the arm above the horizontal level. Reflexes are reduced and there may be some transient sensory loss over the forearms and hands. Attacks may be more common during pregnancy, or following parturition, infectious disorders, or strenuous exercise. Recurrences occur at intervals of months or years. Electromyographic studies have shown partial denervation of several muscles of the upper extremities corresponding to a lesion of the brachial plexus. Stature is often small. Limitation of extension at the elbow and winging of the scapulae have also been noted. Rarely, other peripheral nerves or lower cranial nerves are involved. In most cases, there is complete resolution, but long-standing residual weakness and atrophy may occur.

The facies is remarkably similar to that described by Schilbach and Rott (17) in a dominantly inherited syndrome of *submucous cleft palate, hypotelorism, and hypospadias*. However, in that family, no brachial neuropathy was mentioned.

The disorder is not genetically related to hereditary neuropathy with liability to pressure palsies which has been mapped to 17p11.2 (5,19).

References (Recurrent brachial plexus and neuropathy, characteristic facies, and cleft palate)

1. Airaksinen EM et al: Hereditary recurrent brachial plexus, neuropathy with dysmorphic features. Acta Neurol Scand 71:309–316, 1985.
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3. Beghi E et al: Brachial plexus neuropathy in the population of Rochester, Minnesota. Ann Neurol 18:320–323, 1985.
4. Bradley WG et al: Recurrent brachial plexus neuropathy. Brain 98:381–398, 1975.
5. Chance PF et al: Hereditary neuralgic amyotrophy and hereditary neuropathy with liability to pressure palsies: Two distinct genetic disorders. Neurology 44:2253–2257, 1994.
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7. Erikson A: Hereditary syndrome consisting in recurrent attacks resembling brachial plexus neuritis, special facial features and cleft palate. Acta Paediatr Scand 63:885–888, 1974.
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9. Geiger LR et al: Familial neurologic amyotrophy: Report of three families with review of the literature. Brain 97:87–102, 1974.
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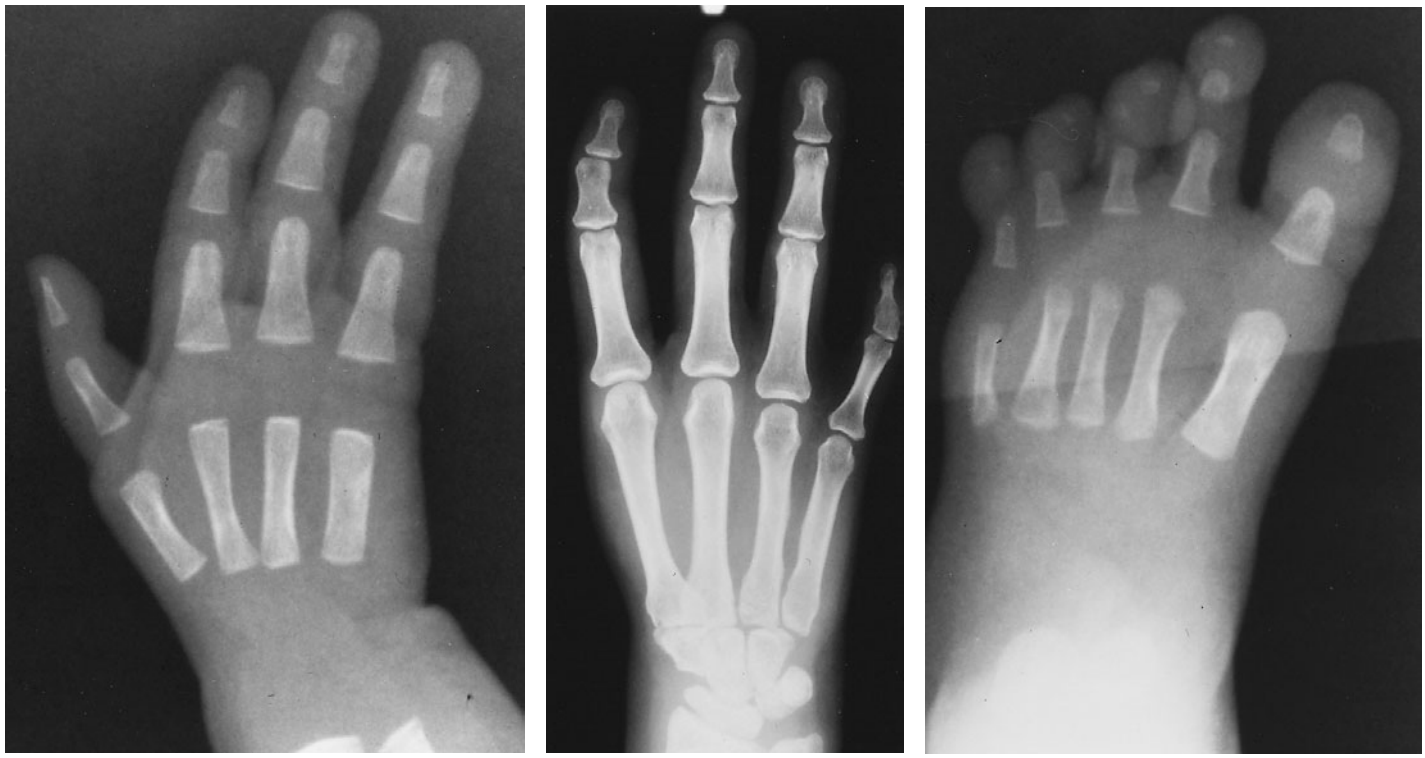

A B C

Fig. 22–56. *Oligodactyly and cleft palate*. (A,B) Both have hypoplastic or aplastic first and fifth rays of hands. (C) Child has hypoplastic fifth rays of feet. (From M Robinow et al, Am J Med Genet 25:293, 1986.)

14. Pellegrino JE et al: Hereditary neurologic amyotrophy: Evidence for genetic homogeneity and mapping to chromosome 17q25. Hum Genet 101:277–283, 1997.
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16. Rogers RC, Hamilton TB: Recurrent brachial neuritis. Proc Greenwood Genet Ctr 4:5–7, 1985.
17. Schilbach U, Rott HD: Ocular hypotelorism, submucous cleft palate, and hypospadias: A new autosomal dominant syndrome. Am J Med Genet 31: 863–870, 1988.
18. Stogbauer F et al: Refinement of the hereditary neuralgic amyotrophy (HNA) locus to chromosome 17q24–q25. Hum Genet 99:685–687, 1997.
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Ring-shaped skin creases and cleft palate

Kunze and Riehm (8) reported two families each with autosomal dominant transmission of ring-shaped creases (Fig. 22–58) which gradually improve with age (5,9,13). In one family, a son had cleft palate and in the other family, a daughter had cleft palate. Cleft palate has been described in other reports (4,7,15). However, most patients with ring-shaped skin creases have not had cleft palate (9,13). We view the term "Michelin tire baby" as pejorative (3). An early report is that of Ross (13). The creases are associated with lipomatosus nevus or smooth muscle hamartoma (5,6,10,11,14–16). We cannot accept the case of Burgdorf et al (2).

There has been evidence of autosomal dominant inheritance (1,7–9). However, there is surely etiologic heterogeneity.

In addition to cleft palate, facial anomalies have included microcephaly, high forehead, microphthalmia and microcornea, broad nasal bridge, hypotelorism, microstomia and dysmorphic pinnae, and microtia with stenotic canals (4,5,7,8). A similar example is that of Case 1 of Cohen et al (3). Macrostomia was noted in Case 2 of Cohen (3).

Miscellaneous abnormalities include lax joints (16), hirsutism (10, 12,16), seizures (16), mental retardation (4,5,16), obesity (5,8), retinopathy (12), neuroblastoma (8), ureterocele (8), and mastocytosis (11).

References (Ring-shaped creases and cleft palate)

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10. Oku T et al: Folded skin with an underlying cutaneous smooth muscle hamartoma. Br J Dermatol 129:606–608, 1993.
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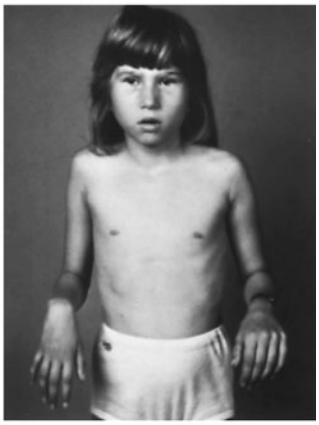

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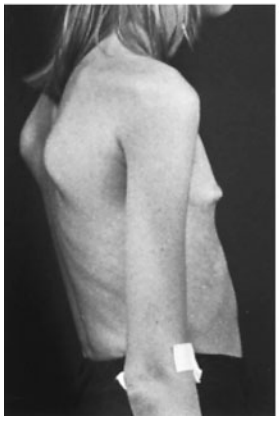

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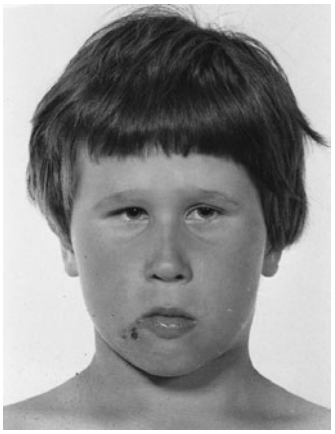

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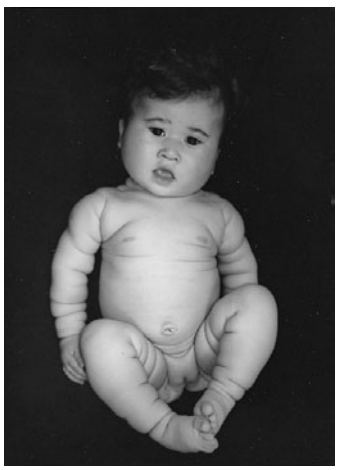
Fig. 22–57. *Recurrent brachial plexus neuropathy, characteristic facies, and cleft palate*. (A) Father and two daughters. Note deeply set eyes, ocular hypotelorism, and mongoloid obliquity of palpebral fissures. (B) Patient exhibiting wrist drop during attack of recurrent brachial neuritis. (C) Winged scapulae are clearly evident. (D) Typical facies. (A–C from A Erikson, Acta Paediatr Scand 63:885, 1974. D from EM Airaksinen et al, Acta Neurol Scand 71:309, 1985.)

babies") with specific histologic findings and/or karyotype abnormalities: Clues to molecular pathogenesis? Am J Med Genet 69:221, 1997.

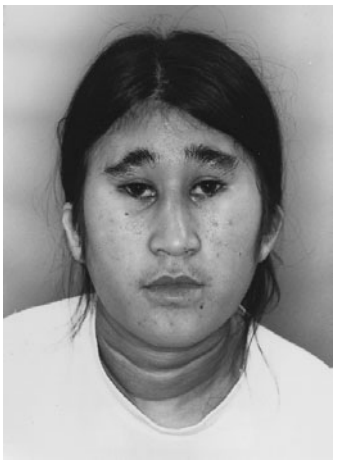
15. Schnur RE et al: Variability in the Michelin tire syndrome. J Am Acad Dermatol 28:364–370, 1993.

16. Wallach D et al: Naevus musculaire généralisé avec aspect clinique de "bébé Michelin." Ann Dermatol Venereol 107:923–927, 1980.

Fig. 22–58. *Ring-shaped skin creases and cleft palate*. (A) Multiple ring-shaped deep creases distributed over body. (B) Mother exhibits residual skin creases on neck. Also note hypotelorism. (From ML Guion-Almeida et al, Braz J Dysmorphol Speech Hearing Dis 2:13–18, 1998.)



A



B

Rüdiger syndrome

Rüdiger et al (1) described a lethal, probably autosomal recessive, syndrome in sibs, the infants succumbing within the first year of life. The disorder is characterized by somatic retardation, flexion contractures of hands with thick, single palmar creases, small fingers and nails, and ureterovesical stenosis. The male sib had micropenis and inguinal hernias; the female sib had bicornuate uterus and cystic ovaries. Arches were noted on2all fingers. The facies was coarse with prominent forehead, flat nasal bridge, stubby nose, and prominent upper lip. The soft palate was cleft (Fig. 22–59).

Reference (Rüdiger syndrome)

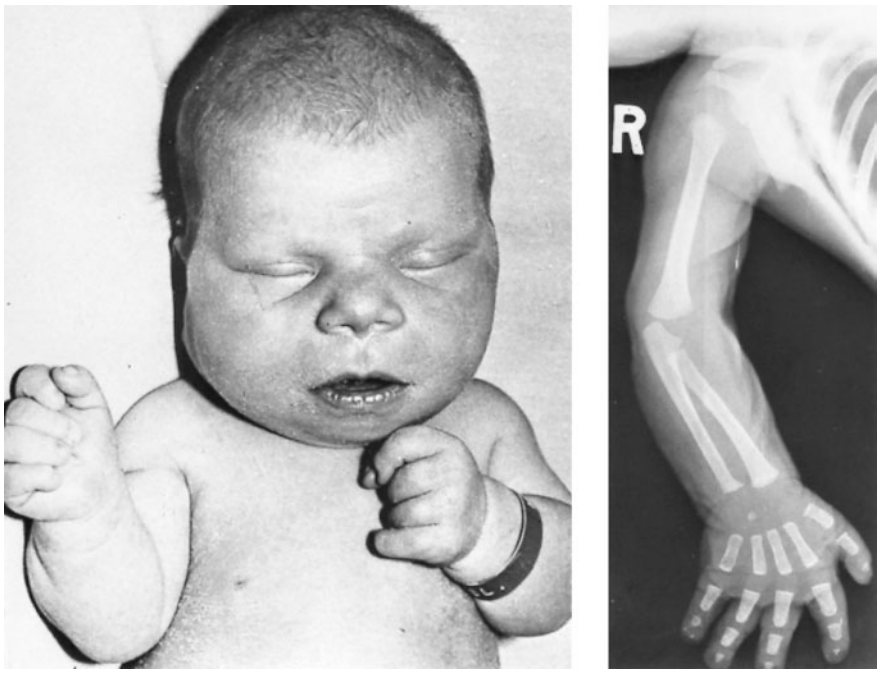
1. Rüdiger RA et al: Severe developmental failure with coarse facial features, distal limb hypoplasia, thickened palmar creases, bifid uvula and ureteral stenosis: A previously undescribed familial disorder with lethal outcome. J Pediatr 79:977–981, 1971.

Short stature and cleft palate

Gareis and Smith (1) reported a kindred in which several affected members had short stature below the third centile because of relative shortness of the extremities. All affected males and approximately half the affected females had cleft palate or submucous cleft palate and bifid uvula. Micrognathia was present in approximately half those affected. The condition is dominantly inherited, possibly X-linked.

Reference (Short stature and cleft palate)

1. Gareis FJ, Smith DW: Diminished stature-defective palate syndrome: A dominantly inherited disorder. J Pediatr 79:470–472, 1971.



A B

Fig. 22–59. *Rüdiger syndrome*. (A) Coarse facies, finger contractures. (B) Small middle phalanges and small triangular terminal phalanges. (From RA Rüdiger et al, J Pediatr 79:977, 1971.)

Submucosal cleft palate, hypotelorism, and hypospadias

Schilbach and Rott (1) described 10 affected individuals in 5 generations of a family. All exhibited hypotelorism and submucosal cleft palate. In addition, the facies was characterized by epicanthic folds, blepharophimosis, and upslanting palpebral fissures (Fig. 22–60). Males exhibited hypospadias of variable degrees.

There was very mild cutaneous syndactyly of the third and fourth fingers and the second and third toes. In the hands, the syndactyly correlated with an abnormally low ridge count of digital triradii *b* and *c*.

The face is similar to that seen in *recurrent brachial plexus neuropathy*.

Inheritance is clearly autosomal dominant.

Reference (Submucosal cleft palate, hypotelorism, and hypospadias)

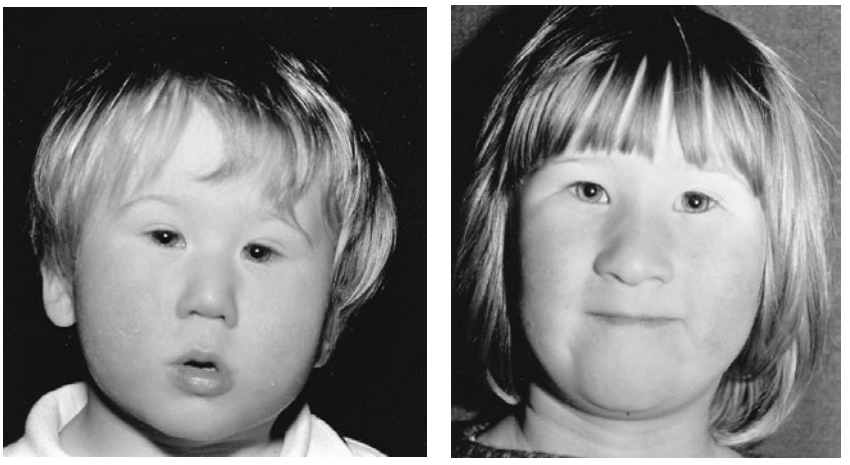
1. Schilbach U, Rott H-D: Ocular hypotelorism, submucosal cleft palate, and hypospadias: A new autosomal dominant syndrome. Am J Med Genet 31:863–870, 1988.

Cleft lip-palate, mental and growth retardation, sensorineural hearing loss, and postaxial polydactyly

RJ Gorlin and J Cervenka have seen a family in 1985 with autosomal dominant inheritance of cleft lip-palate, micrognathia, sensorineural hearing loss, mental and somatic retardation, and postaxial polydactyly.

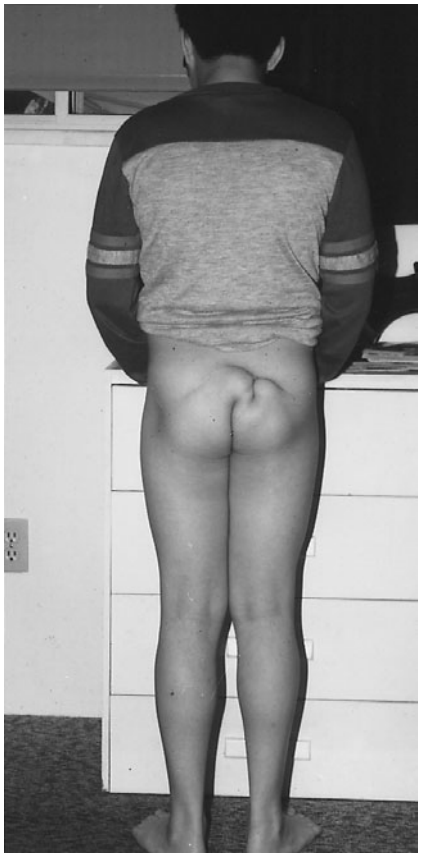
Cleft lip-palate, sensorineural hearing loss, sacral lipomas, and aberrant fingerlike appendages—*disorganization* homologue?

Lowry and Yong (4) observed two male Chinese sibs with cleft lip and palate, profound sensorineural hearing loss, and sacral lipomas. In one child, there was connection of the lipoma with the spinal cord. An anterior sacral meningocoele was found. The other child had two separate aberrant fingerlike appendages of the heel and thigh and a dislocated hip. Both suffered from functional constipation and lower limb asymmetry. Intelligence and growth were normal (Fig. 22–61).



A B

Fig. 22–60. *Submucosal cleft palate, hypotelorism, and hypospadias*. (A,B) Affected sibs with blepharophimosis, upslanting palpebral fissures, and hypotrichosis. (From U Schilbach and H-D Rott, Am J Med Genet 31:863–870, 1988.)



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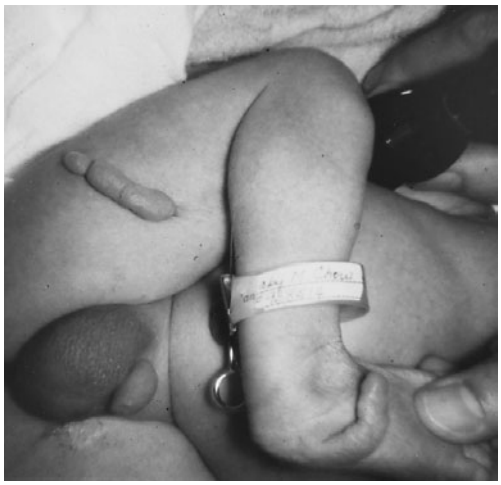

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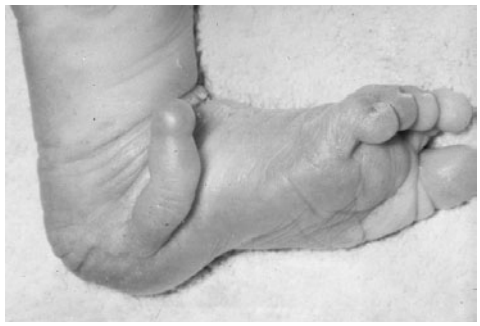

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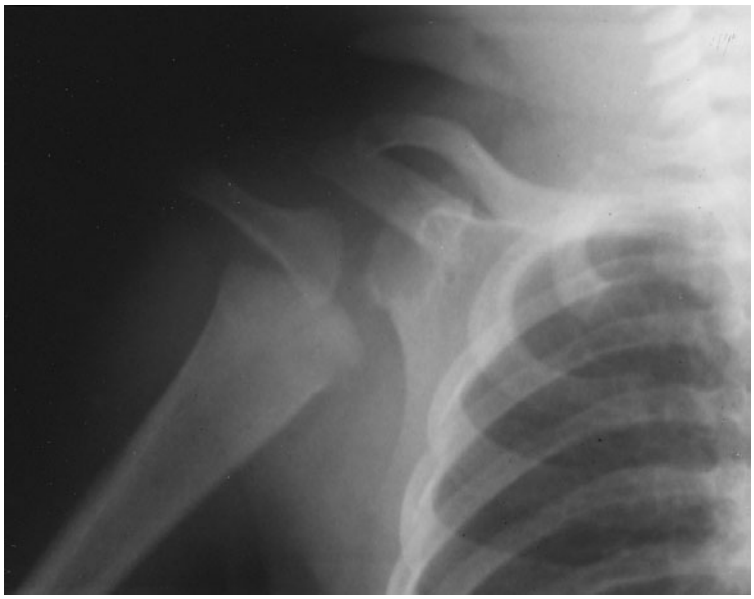


D

Fig. 22–61. *Cleft lip-palate, sensorineural hearing loss, sacral lipomas, and aberrant fingerlike appendages—disorganization homologue*? (A) Sacral lipoma. (B) Digit-like appendages of thigh and foot. (C) Close-up view of pedal growth. (D) Radiograph of boy with extra bone of shoulder. (A–C courtesy of RB Lowry, Calgary, Alberta. D courtesy of J Murray, Iowa City, Iowa.)

Nasal bone and cartilage were poorly developed, resulting in a flattened facial profile. A small area of cutis aplasia congenita was evident in the scalp on one boy. An accessory calcaneus was present on the lateral heel of the same sib and a rotational anomaly of the penis in the other.

Van Langen and Hennekam (9) described a male child of consanguineous parents with cleft lip-palate, hypertelorism, natal teeth, digit-like appendage of the chest wall, prominent coccyx, profound sensorineural hearing loss, ptosis, divergent strabismus, abnormal EEG, and global retardation. *Malpuech syndrome* should also be considered.

One of us (RJG) has seen a similarly affected boy at the University of Iowa Medical Center (Fig. 22–61).

All reported patients are males. Inheritance may be autosomal or X-linked recessive.

Winter and Donnai (12) noted a possible relationship to the mouse mutant "disorganization" (Ds). A number of other "disorganization" homologues have been noted, but we cannot find much common thread to bind them to the syndrome considered here (1–3,5–8,10,11). Each appeared to be unique. Especially bizarre was one child with three facial appendages (1).

References (Cleft lip-palate, sensorineural hearing loss, sacral lipomas, and aberrant fingerlike appendages—*disorganization* homologue?)

1. de Michelena MI, Stachurska A: Multiple anomalies possibly caused by human homologue to the mouse disorganization (Ds) gene. Clin Dysmorphol 2:131–134, 1993.
2. Elliott AM et al: Developmental anomalies suggestive of the human homologue of the mouse mutant disorganization. Am J Med Genet 55:240–243, 1995.
3. Lin AE: Two additional patients representing the possible human homologue for the mouse mutant disorganization (Ds). J Med Genet 28:645–647, 1991.
4. Lowry RB, Yong S-L: Cleft lip and palate, sensorineural deafness, and sacral lipoma in two brothers: A possible example of the disorganization mutant. J Med Genet 28:135–137, 1991.
5. Naguib KK et al: Human homologue for the mouse mutant disorganization: Does it exist? J Med Genet 28:138–139, 1991.
6. Petzel MA, Erickson RP: Disorganization: A possible cause of apparent conjoint twinning. J Med Genet 28:712–714, 1991.
7. Robin NH et al: Human malformations similar to those in the mouse mutant disorganization (Ds). Hum Genet 92:461–464, 1993.
8. Teebi AS, Elliott AM: Another case of the human homologue of the mouse mutant disorganization. Am J Med Genet 61:94, 1996.
9. Van Langen IM, Hennekam RCM: Another example of the human homologue of the mouse mutant disorganization? Clin Dysmorphol 3:361–362, 1994.
10. Viljoen DL, Kidson SH: Mirror polydactyly: Pathogenesis based on a morphogen gradient theory. Am J Med Genet 35:229–235, 1990.
11. Wainwright H, Viljoen D: Developmental anomalies in monozygotic twins resembling the human homologue of the mouse mutant disorganization. Clin Dysmorphol 2:135–139, 1993.
12. Winter RM, Donnai D: A possibly human homologue for the mouse mutant disorganization. J Med Genet 26:417–420, 1989.

Macrosomia, microphthalmia, plus or minus cleft palate, and early infant death

Teebi et al (1) described a consanguineous Kuwaiti family with 5 of 10 siblings exhibiting early macrosomia, wide anterior fontanel, bilateral severe microphthalmia, protuberant abdomen, and respiratory infections leading to early infant death. Three of the five had cleft palate.

Inheritance appears to be autosomal recessive.

To be excluded is *macrosomia, obesity, macrocephaly, and ocular abnormalities (MOMO) syndrome*.

Reference (Macrosomia, microphthalmia, plus or minus cleft palate, and early infant death)

1. Teebi AS et al: Macrosomia, microphthalmia, cleft palate and early infant death: A new autosomal recessive syndrome. Clin Genet 36:174–177, 1989.

Cleft lip-palate and X-linked mental retardation

Siderius et al (4), in 1999, described a three-generation family with a form of X-linked mental retardation. Three affected males exhibited mild to borderline mental retardation and cleft lip-palate, some unilateral, some bilateral. The face was long, and the nasal tip was broad but may have been secondary to the cleft. A somewhat similar syndrome in which there was X-linked mental retardation with variable stature, head circumference, and testicular volume has been linked to Xq12–q21. Two of this kindred had cleft lip-palate (1). A still further X-linked syndrome incorporates mental retardation with short stature, small hands and feet, seizures, glaucoma, and cleft palate. Linkage was established to Xq28 (2). The X-linked cerebropalatocardiac syndrome has microcephaly, short stature, cleft palate, cupped ears, bulbous nose, short philtrum, and tented upper lip (3).

References (Cleft lip-palate and X-linked mental retardation)

1. Abidi F et al: X-linked mental retardation with variable stature, head circumference, and testicular volume linked to Xq12–q21. Am J Med Genet 85:223–229, 1999.
2. Armfield K et al: X-linked mental retardation syndrome with short stature, small hands and feet, seizures, cleft palate, and glaucoma is linked to Xq28. Am J Med Genet 85:236–242, 1999.
3. Hamel BCJ et al: Mental retardation, congenital heart defect, cleft palate, short stature and facial anomalies. Am J Med Genet 51:591–596, 1994.
4. Siderius LE et al: X-linked mental retardation associated with cleft lip/palate maps to Xp11.3–q21.3. Am J Med Genet 85:216–220, 1999.

Cleft lip-palate, ectrodactyly, holoprosencephaly, and hypertelorism

Hartsfield et al (1) in 1984, Young et al (3) in 1992, and Imaizumi et al (2) in 1988 reported examples of association of holoprosencephaly, ectrodactyly, hypertelorism, cleft lip-palate, and dysmorphic pinnae.

One patient had craniosynostosis (1). In the only child who survived there was mental retardation (2).

References (Cleft lip-palate, ectrodactyly, holoprosencephaly, and hypertelorism)

1. Hartsfield JK et al: Case report 119: Hypertelorism associated with holoprosencephaly and ectrodactyly. J Clin Dysmorphol 2:27–31, 1984.
2. Imaizumi K et al: Association of holoprosencephaly, ectrodactyly, cleft lip/cleft palate and hypertelorism: A possible third case. Clin Dysmorphol 7: 213–216, 1998.
3. Young ID et al: Holoprosencephaly, telecanthus and ectrodactyly: A second case. Clin Dysmorphol 1:47–51, 1992.

Cleft palate, micrognathia, ptosis, facial weakness, hypotonia, and lateral ophthalmoplegia (Carey-Fineman-Ziter syndrome)

In 1982, Carey et al (2) described a brother and sister with hypotonia, bilateral ptosis, lateral ophthalmoplegia, downslanting palpebral fissures, and Robin sequence. Additional examples were provided by Schimke et al (5), Baraitser and Reardon (1), and Ryan et al (4).

Normal intelligence, feeding and swallowing problems, facial weakness, bilateral ptosis, downslanting palpebral fissures, external ophthalmoplegia, triangular nose, long philtrum, micrognathia, and small tongue have been essentially constant features (Fig. 22–62). More than one-third die in infancy, and more than one-third exhibit mental retardation.

Hypotonia and weakness, hypoplastic pectoral muscles, scoliosis, generalized-poor muscle mass, brachydactyly, poor flexion creases, talipes and wrist dimples have been noted in most.

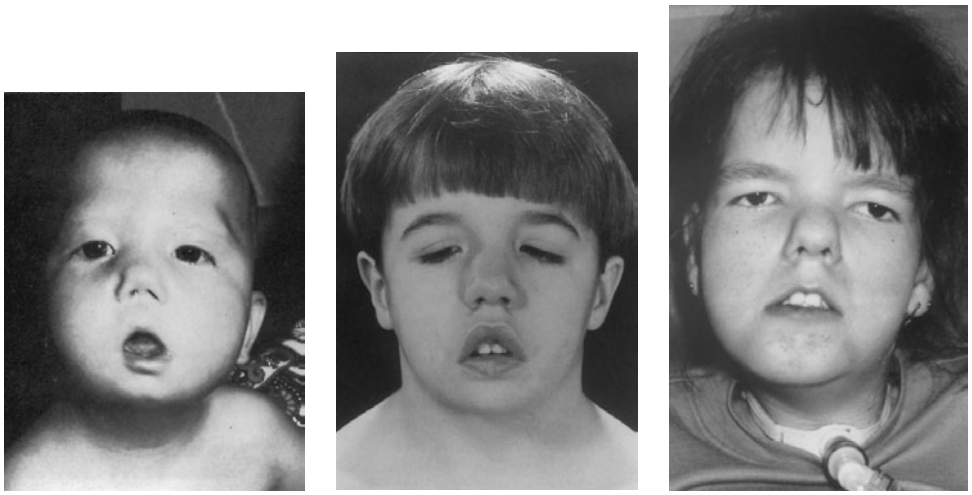
Miscellaneous findings have included: talipes (1,4,5), scoliosis (2,4), cleft palate (2,5), microcephaly (2,5), and short stature (1,2,5).

Inheritance may possibly be autosomal recessive (2,4), but caution is needed in counseling.

It is possible that the syndrome may be a form of *Moebius syndrome* (3).

References [Cleft palate, micrognathia, ptosis, facial weakness, hypotonia, and lateral ophthalmoplegia (Carey-Fineman-Ziter syndrome)]

1. Baraitser M, Reardon W: New case of the Carey-Fineman-Ziter syndrome. Am J Med Genet 53:163–164, 1994.
2. Carey JC et al: The Robin sequence as a consequence of malformation, dysplasia, and neuromuscular syndromes. J Pediatr 101:858–864, 1982.
3. Cortez SC, Kinney HC: Brainstem tegmental necrosis and olivary hypoplasia: A lethal entity associated with congenital apnea. J Neuropathol Exp Neurol 55:841–849, 1996.
4. Ryan A et al: Carey-Fineman-Ziter (CFZ) syndrome: Report on affected sibs. Am J Med Genet 82:110–113, 1999.
5. Schimke RN et al: Congenital nonprogressive myopathy with Möbius and Robin sequence—the Carey, Fineman-Ziter syndrome. A confirmatory report. Am J Med Genet 46:721–723, 1993.



A B C

Fig. 22–62. *Cleft palate, micrognathia, ptosis, facial weakness, hypotonia, and lateral ophthalmoplegia (Carey-Fineman-Ziter syndrome).* (A) Note facial weakness in 1-year-old child. (B) Down-slanting palpebral fissures, ptosis, and facial weakness in 5-year-old. (C) Short bulbous nose, myopathic facies. (A from JC Carey, J Pediatr 101:858, 1982. B from M Baraitser and W Reardon, Am J Med Genet 53:163, 1994. C from A Ryan et al, Am J Med Genet 82:110, 1999.)

Cleft palate, multiple epiphyseal dysplasia (Ribbing), and micrognathia

Lowry et al (1), in 1996, reported two unrelated patients with cleft palate and micrognathia (Robin sequence) with short extremities because of multiple epiphyseal dysplasia of the Ribbing type.

Facial changes that were minimal included mild hypertelorism, mild upslanting palpebral fissures, and broad nasal tip.

There was delay in appearance of epiphyses of the long bones. Later the epiphyses appeared fragmented and, finally, very flat. The fibulae were short and the radial heads dislocated. Marked genu valgum and scoliosis developed.

Reference [Cleft palate, multiple epiphyseal dysplasia (Ribbing), and micrognathia]

1. Lowry RB et al: Syndrome of multiple epiphyseal dysplasia (Ribbing type) with rhizomelic shortness, cleft palate and micrognathia in two unrelated patients. Am J Med Genet 63:55–61, 1996.

Cleft palate, unusual facies, generalized hypotonia, and congenital hydronephrosis

Okamoto et al (1), in 1997, described two unrelated Japanese patients with severe growth failure, severe mental retardation, generalized floppiness, unusual facies characterized by microcephaly, midface hypoplasia, synophrys, long eyelashes, prominent eyes, epicanthic folds, apparently low-set pinnae with long ear lobes, flat nasal bridge, short upturned nose, long philtrum, open mouth, and webbed neck. Both had cleft palate and generalized hypertrichosis. The joints were hypermobile. Cardiac anomalies included VSD, ASD, and endocardial cushion defect. Both exhibited congenital hydronephrosis.

Reference (Cleft palate, unusual facies, generalized hypotonia, and congenital hydronephrosis)

1. Okamoto N et al: New MCA/MR syndrome with generalized hypotonia, congenital hydronephrosis, and characteristic face. Am J Med Genet 68:347–349, 1997.

Oto-facio-cervical syndrome

A family with abnormalities of the external ear, face, and neck was described by Fára et al (2) in 1967. The father and four of seven children were affected. A sporadic case was reported by Dallapiccola and Mingarelli (1). Another possible example is that of Allanson (personal communication, 1989). We suspect that the patient of Pennie and Marres (4) also had the syndrome.

Autosomal dominant inheritance is evident.

The face is long and of an inverted triangular shape, with a relatively broad forehead and narrow mandible (Fig. 22–63). In most cases, lateral cervical fistulas are also present either unilaterally or bilaterally. Lacrimal duct atresia has also been seen. The auricles are prominent with large conchae. Preauricular fistulas are present just in front of the helix. The sporadic case of Allanson had a right-sided preauricular fistula and a tag anterior to the left ear. Audiometric testing of four affected family members showed bilateral conductive hearing loss of 60–70 dB, more marked in low and high frequencies with 40–50 dB loss in middle frequencies (2). Sensorineural hearing loss has also been seen (1).

The neck appears long with weak musculature, and the shoulders and clavicles sloped downward markedly. The scapulae are located more laterally than normal and showed mild winging. A Sprengel shoulder was noted in the sporadic patient of Allanson, that of Dallapiccola and Mingarelli (1), and in the patient of Pennie and Marres (4). All affected persons have been short in stature.

Unilateral renal agenesis was found in one family member.

There was mild to moderate hyporeflexia, more marked in the arms than the legs. Mild intellectual deficit was noted in the family members.

Radiographs were similar in all affected members of the family. The skull showed narrowing in the middle third of the face, the sella turcica was deep with a slanting clivus, and there was a marked difference in the level of the orbital roof and the cribriform plate (Fig. 22–63G). The temporal pyramids were asymmetric with poor mastoid pneumatization. The clavicles slanted obliquely downward (Fig. 22–63H). Radiographs of the carpal bones showed moderately retarded bone age in three children in the affected family.

In the isolated patient there was spina bifida occulta of the fifth lumbar and first sacral vertebrae.

The combination of the characteristic facies, sloping shoulders, auricular abnormalities, and hearing loss appears unique. There is marked overlap, however, between this syndrome and the *branchio-oto-renal syndrome* (3). The latter syndrome lacks anomalies of the shoulder and short stature, whereas renal anomalies are much more common. Although the family of Fára et al did not have preauricular tags or lacrimal duct stenosis, the sporadic patient of Allanson had both a preauricular tag and lacrimal duct stenosis, increasing the overlap between these two conditions.

References (Oto-facio-cervical syndrome)

1. Dallapiccola B, Mingarelli R: Otofaciocervical syndrome: A sporadic patient supports splitting from the branchio-oto-renal syndrome. J Med Genet 32: 816–818, 1995.

2. Fára M et al: Dismorphia oto-facio-cervicalis familiaris. Acta Chir Plast 9:255–268, 1967.

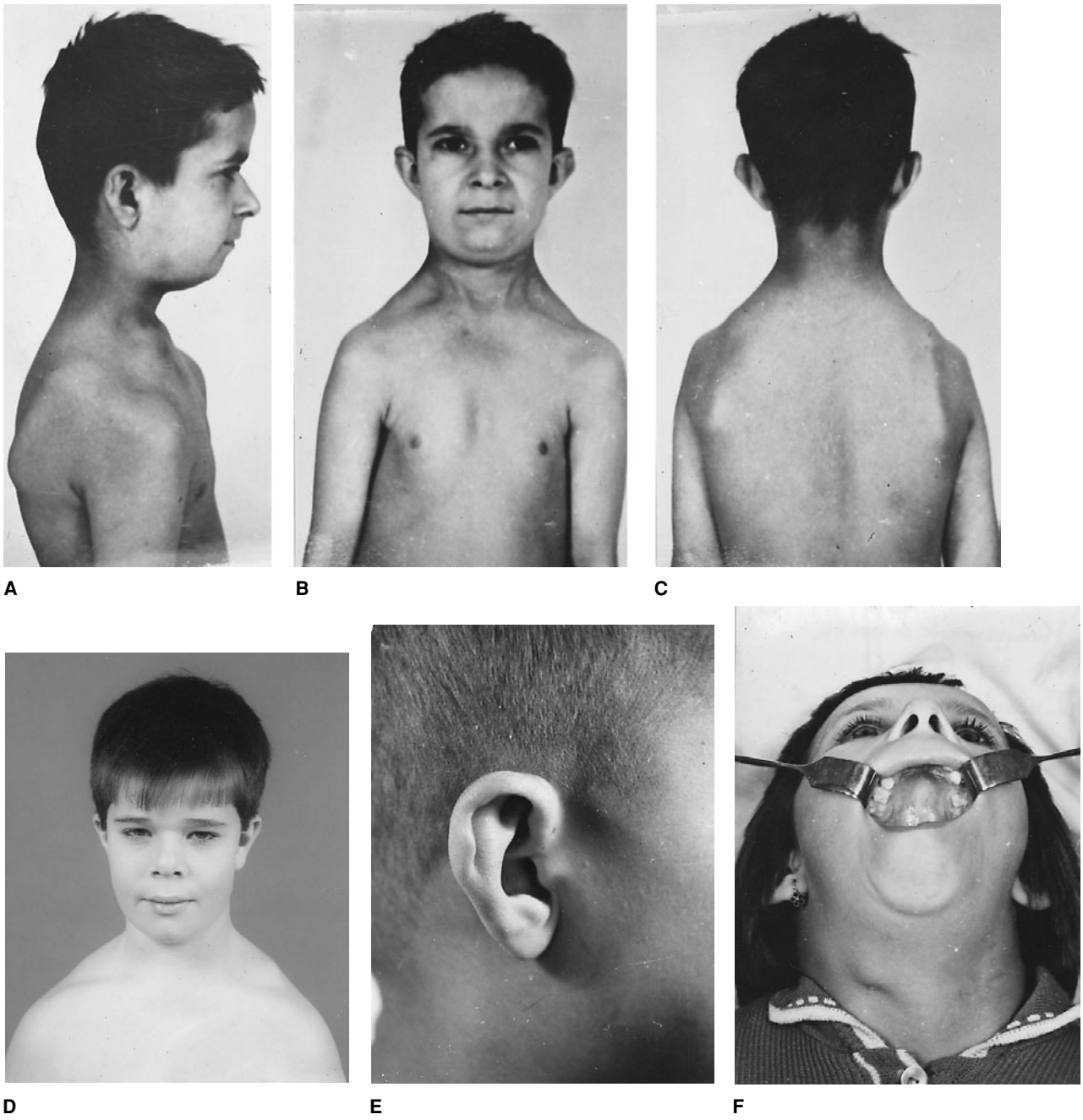


Fig. 22–63. *Oto-facio-cervical syndrome*. (A–C) Three views showing sloping shoulders and abnormal position of clavicles and scapulae. (D) Compare patient of J Allanson with that of Fára et al (A–C). (E) Prominent ears, Darwinian tubercle, and fistula at insertions of helix. (F) Highly arched palate; right cervical fistula was present; left cervical fistula had been removed surgically. (G) Lateral view of father's skull showing vertical elongation of head, deep sella turcica, steep clivus, low sphenoid bone, and poor mastoid pneumatization. (H) Radiograph showing depressed position of shoulders. Clavicles are at level of third rib, their outer ends running obliquely downward. The scapulae project at level of axillae. [A–C,E–G from M Fára et al, Acta Chir Plast (Praha) 9:255, 1967. D courtesy of J Allanson, Ottawa, Ontario, Canada.]

3. Fraser FC et al: Genetic aspects of the BOR syndrome—branchial fistulas, ear pits, hearing loss and renal anomalies. Am J Med Genet 2:241–252, 1978.

4. Pennie BH, Marres HAM: Shoulder abnormalities in association with branchio-oto-renal dysplasia in a patient who also has familial joint laxity. Int J Pediatr Otorhinolaryngol 23:269–273, 1992.

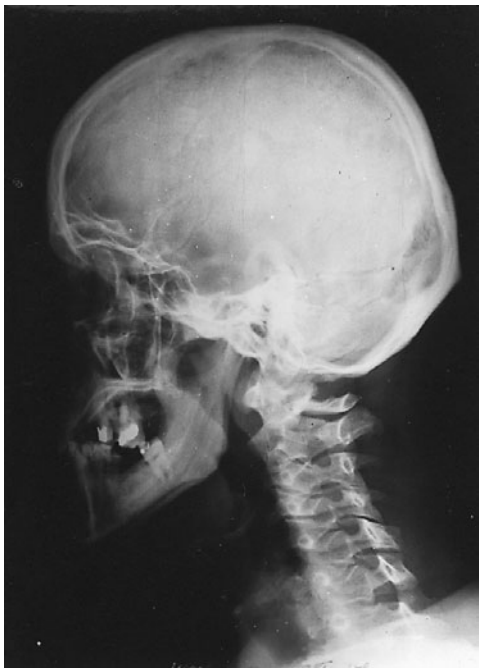
Midline malformations, limb abnormalities, and hypopituitarism (Dincsoy syndrome)

In 1995, Dincsoy and colleagues (1) reported male and female Saudi Arabian sibs, born to first cousin parents. The sibs exhibited midline anomalies that included cleft lip and palate, flat nose, ocular hypotelorism, and dysgenesis of the corpus callosum and/or Dandy-Walker anomaly. Skeletal changes included short limbs and unusual radiolucent anterior tibial notch and digital anomalies such as overlapping fingers and camptodactyly.

In addition, the patients had hypopituitarism and secondary ambiguous genitalia that included perineal hypospadias and cryptorchidism.

Inheritance is probably autosomal recessive.

One must exclude *hydrolethalus syndrome* and *pseudotrisomy 13 syndrome*. Neither sib exhibited preaxial or postaxial polydactyly (although that is not an absolute requirement). The radiolucent notch in the midshaft of the tibia is seen in neither of those syndromes.



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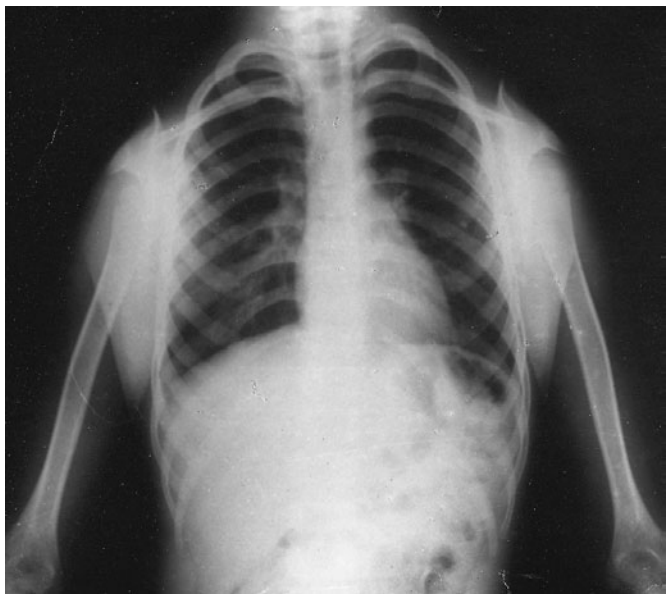


H

Fig. 22–63. *(Cont.)*

Reference [Midline malformations, limb abnormalities, and hypopituitarism (Dincsoy syndrome)]

1. Dincsoy MY et al: Multiple congenital malformations in two sibs reminiscent of hydrolethalus and pseudotrisomy 13 syndromes. Am J Med Genet 56:317–321, 1995.

Tetra-amelia with pulmonary hypoplasia

Rosenak et al (1) described a Muslim Arab family with autosomal recessive inheritance of symmetric tetra-amelia and pulmonary hypoplasia. One had cleft lip. Death occurred soon after birth. Zlotogora et al (2) added two Palestinian families with the same combination of findings. An enlarged head (hydrocephalus?) was described.

Inheritance is autosomal recessive (1,2).

The reader should also see *amelia* and *cleft lip-palate* and *unusual facies, tetra-amelia, hypotrichosis, and developmental retardation*.

References (Tetra-amelia with pulmonary hypoplasia)

1. Rosenak D et al: Recurrent tetraamelia and pulmonary hypoplasia with multiple malformations in sibs. Am J Med Genet 38:25–28, 1991.
2. Zlotogora J et al: Syndrome of tetra amelia with pulmonary hypoplasia. Am J Med Genet 47:570–571, 1993.

Robin sequence, cleft mandible, pre- and postaxial hand anomalies, and clubfoot (Richieri-Costa and Pereira syndrome)

Richieri-Costa and Pereira (3), in 1992, described five unrelated female Brazilian children with short stature, Robin sequence, agenesis of mandibular incisors, pre- and postaxial hand anomalies, and talipes. Two additional male examples were presented by Richieri-Costa and Pereira (4) in 1993. Another was added in 1998 (2). A non-Brazilian infant was described (6).

Inheritance is clearly autosomal recessive. Parental consanguinity was noted in five of eight families. All affected male patients died.

Birth weight and length were generally unremarkable, but subsequent growth showed the children to be below the 3rd centile for height, weight, and OFC. Intelligence was normal.

Craniofacial findings. Mild ocular hypertelorism, outstanding low-set pinnae, retromicrognathia, microstomia, cleft lower alveolar ridge with ankyloglossia in some, and variable degrees of cleft palate are characteristic (Fig. 22–64). The lower central and lateral incisors were absent and radiographs showed a cleft through the midline of the mandible (Fig. 22–64D). In some cases, the mandible is so small that a tracheostomy must be done. Laryngeal malformations include: short round larynx, absent or reduced epiglottis, hypertrophic aryepiglottic folds, and a fold in the posterior larynx above the glottis (5).

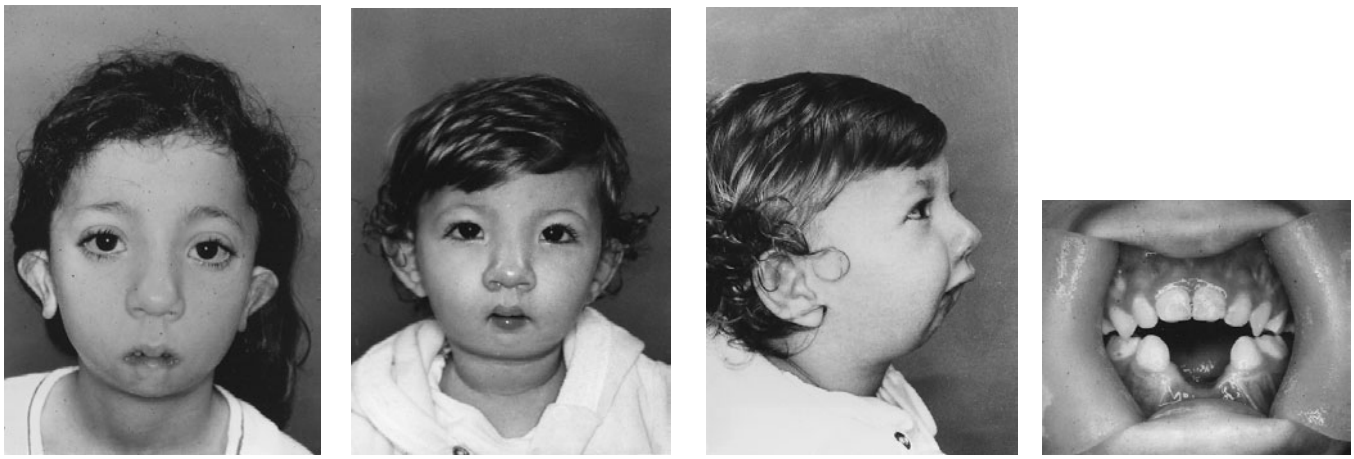
Musculoskeletal system. There was radial deviation of the hands. The thumbs were hypoplastic and the fifth fingers were clinodactylous. Clubfoot and short lower extremities were evident. The halluces were short and, in the rare case, duplicated (1) (Fig. 22–65A,B).

Radiographs showed hypoplastic radii and first rays. Metacarpals 4–5 were fused proximally. The middle phalanx of the fifth fingers were hypoplastic, carpal bone age was delayed, and carpal coalition was common. The distal tibiae were hypoplastic, the fibulae had proximal and lateral displacement, and there was talipes (Fig. 22–65C,D).

Diagnosis. The clinical picture clearly distinguished this condition from all other cleft syndromes.

References [Robin sequence, cleft mandible, pre- and postaxial hand anomalies, and clubfoot (Richieri-Costa and Pereira syndrome)]

1. Guion-Almeida ML, Richieri-Costa A : Autosomal recessive short stature, Robin sequence, cleft mandible, pre/postaxial limb anomalies and club feet: Report of a patient with preaxial polydactyly of the halluces. Braz J Dysmorphol Speech Hear 1:27–30, 1998.
2. Richieri-Costa A, Brandão-Almeida IL: Short stature, Robin sequence, cleft mandible, pre/postaxial hand anomalies, and clubfoot. Another affected Brazilian patient born to consanguineous parents. Am J Med Genet 71:233–235, 1997.
3. Richieri-Costa A, Pereira SCS: Short stature, Robin sequence, cleft mandible, pre-postaxial hand anomalies, and clubfoot: A new autosomal recessive syndrome. Am J Med Genet 42:681–687, 1992.
4. Richieri-Costa A, Pereira SCS: Autosomal recessive short stature, Robin sequence, cleft mandible, pre/postaxial hand anomalies, and clubfeet in male patients. Am J Med Genet 47:707–709, 1993.



A B C D

Fig. 22–64. *Robin sequence, cleft mandible, pre- and postaxial hand anomalies, and clubfoot (Richieri-Costa and Pereira syndrome).* (A–C) Note hypertelorism, small mouth, low-set posteriorly rotated and outstanding pinnae, micrognathia. (D) Absence of lower incisors. (From A Richieri-Costa and SCS Pereira, Am J Med Genet 42:681, 1992.)

5. Tabith A Jr, Bento-Gonçalves CGA: Laryngeal malformations in the Richieri-Costa and Pereira form of acrofacial dysostosis. Am J Med Genet 66: 399–402, 1996.

6. Walter-Nicolet E et al: The Richieri-Costa and Pereira form of acrofacial dysostosis: First case in a non-Brazilian infant. Am J Med Genet 87:430–433, 1999.

Cleft lip-palate, congenital contractures, ectodermal dysplasia, and psychomotor and growth retardation

Ladda et al (1) reported two brothers with congenital contractures of all major joints as well as the fingers and toes (Fig. 22–66).

Hair was brittle and thin with little pigmentation. Brachycephaly, deep-set eyes, blepharophimosis, ptosis, and microretrognathia were evident. One brother had cleft lip-palate, the other had cleft palate. Oligodontia and conical crown form were documented.

Both growth and marked mental retardation were described in the brother that lived. The other died soon after birth.

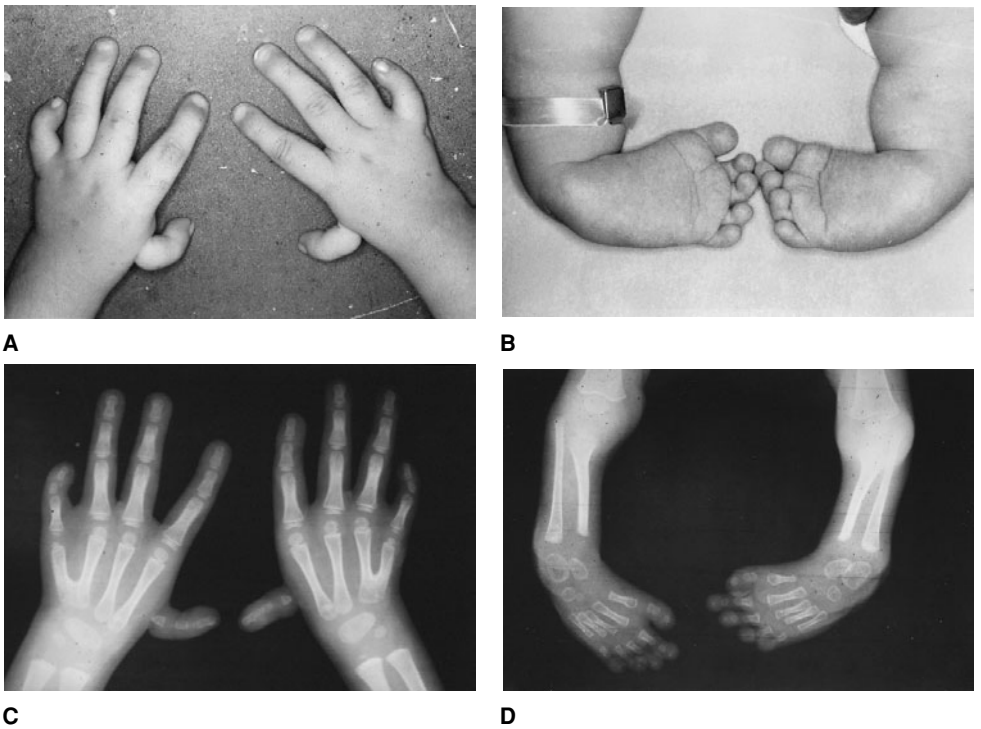
Inheritance may be X-linked or autosomal recessive.

Reference (Cleft lip-palate, congenital contractures, ectodermal dysplasia, and psychomotor and growth retardation)

1. Ladda RL et al: Congenital contractures, ectodermal dysplasia, cleft lip/palate, and developmental impairment: A distinct syndrome. Am J Med Genet 47:550–555, 1993.

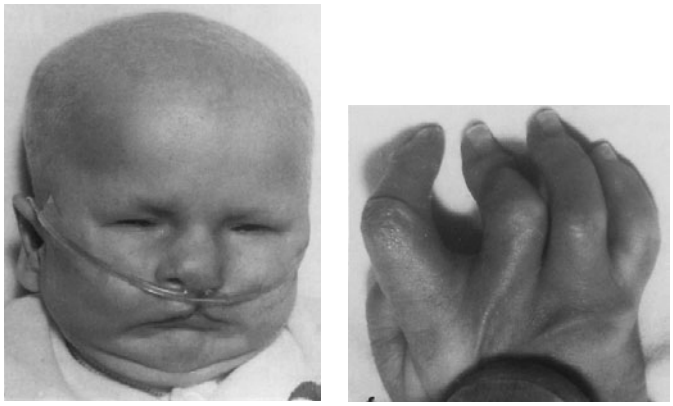
Cleft lip-palate, microbrachycephaly, eye anomalies, short stature, and mental retardation

Richieri-Costa and Guion-Almeida (2), in 1992, reported three Brazilian brothers with a unique syndrome of microbrachycephaly,



A B C D

Fig. 22–65. *Robin sequence, cleft mandible, pre- and postaxial hand anomalies, and clubfoot (Richieri-Costa and Pereira syndrome).* (A) Hypoplastic displaced thumb, short middle phalanx of fifth finger. (B) Club feet. (C) Radiograph showing hypoplastic thumbs and first metacarpals, fused metacarpals IV–V. (D) Radiograph showing club feet, abbreviated tibiae, and proximal and lateral fibulae. (From A Richieri-Costa and SCS Pereira, Am J Med Genet 42:681, 1992.)



A B

Fig. 22–66. *Cleft lip-palate, congenital contractures, ectodermal dysplasia, and psychomotor and growth retardation*. (A) Note cleft and sparse hair growth. (B) Congenital contractures of fingers. (From RL Ladda et al, Am J Med Genet 47:550, 1993.)

prominent supraorbital ridges, deep-set eyes, asymmetric palpebral fissures, palpebral ptosis, coloboma of iris and retina, nystagmus, strabismus, malar hypoplasia, cleft lip-palate, short stature, and mental retardation (Fig. 22–67). There was no parental consanguinity. Another probable example was that of Natacci et al (1).

One must rule out *Michels syndrome* (cleft lip-palate, blepharophimosis, ptosis, corneal stromal opacities, sensorineural hearing loss, radioulnar synostosis).

References (Cleft lip-palate, microbrachycephaly, eye anomalies, short stature, and mental retardation)

1. Natacci F et al: New case of the Richieri-Costa/Guion-Almeida syndrome. Am J Med Genet 83:419–421, 1999.
2. Richieri-Costa A, Guion-Almeida ML: Short stature, mental retardation, eye anomalies, and cleft lip/palate. Am J Med Genet 42:449–452, 1992.

Cleft palate, abnormal pinnae, short stature, and monodactylous tetraectrodactyly

Richieri-Costa and de Miranda (3) described a male child, the offspring of unrelated parents.

Height was below the 3rd centile as was birthweight.

The face was normal except for small low-set outstanding pinnae. Cleft palate was noted. The teeth, hair, and eyes were normal (Fig. 22–68).

The hands and feet exhibited bilateral symmetrical monodactylous ectrodactyly.

Differential diagnosis includes *ectrodactyly-cleft palate syndrome* (2). There is neither short stature nor ear anomalies in that disorder.

A somewhat similar example was described by Herrmann et al (1) in association with *alcohol embryopathy*.

References (Cleft palate, abnormal pinnae, short stature, and monodactylous tetraectrodactyly)

1. Herrmann J et al: Tetraectrodactyly and other skeletal manifestations in the fetal alcohol syndrome. Eur J Pediatr 133:221–226, 1980.
2. Opitz JM et al: The ECP syndrome. Another autosomal dominant cause of monodactylous ectrodactyly. Eur J Pediatr 133:217–220, 1980.
3. Richieri-Costa A, de Miranda E: Short stature, abnormal ears, monodactylous tetraectrodactyly, cleft palate in a Brazilian boy. Am J Med Genet 31:559–564, 1988.

Unusual facies, blepharophimosis, and contractural arachnodactyly (van den Ende-Gupta syndrome)

van den Ende et al (3), in 1992, Gupta et al (1), in 1995, and Phadke et al (2), in 1998, reported patients with blepharophimosis, arachnodactyly, and camptodactyly (Fig. 22–69).

Inheritance appears to be clearly autosomal recessive.

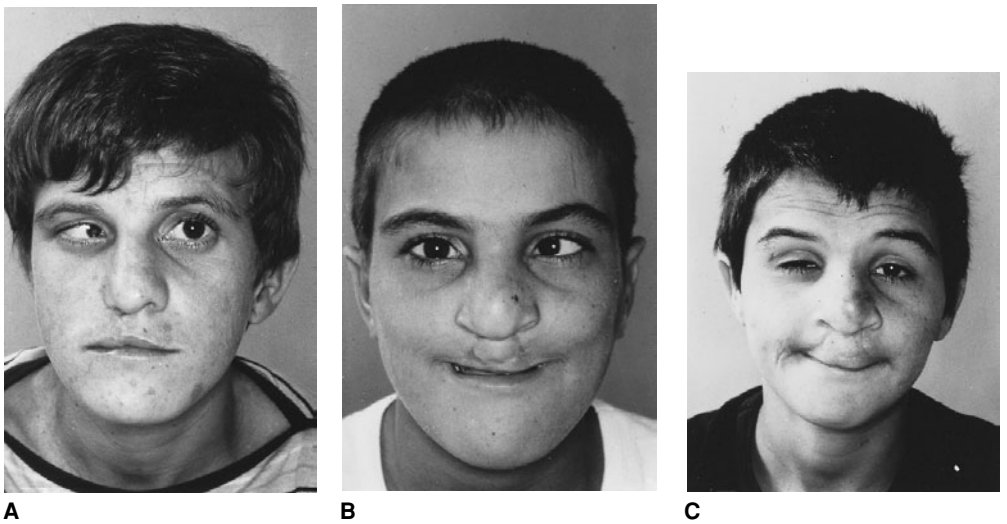
The facies is characterized by blepharophimosis, triangular face, malar hypoplasia with downslanting eyebrows and possibly upslanting palpebral fissures. The pinnae have been prominent, and the nose narrow and beaked. Lips are everted. Cleft palate and velopharyngeal insufficiency have been reported (1,3).

The hands and feet are long, and arachnodactyly, camptodactyly, and valgus deformity of the hallux have been constant findings. The elbow is deformed with posterior dislocation of the head of the radius. Radiographically, the ribs are slender. Intelligence has been normal.

Marden-Walker syndrome can be excluded by absence of microcephaly, mental retardation, hypotonia, and joint limitation.

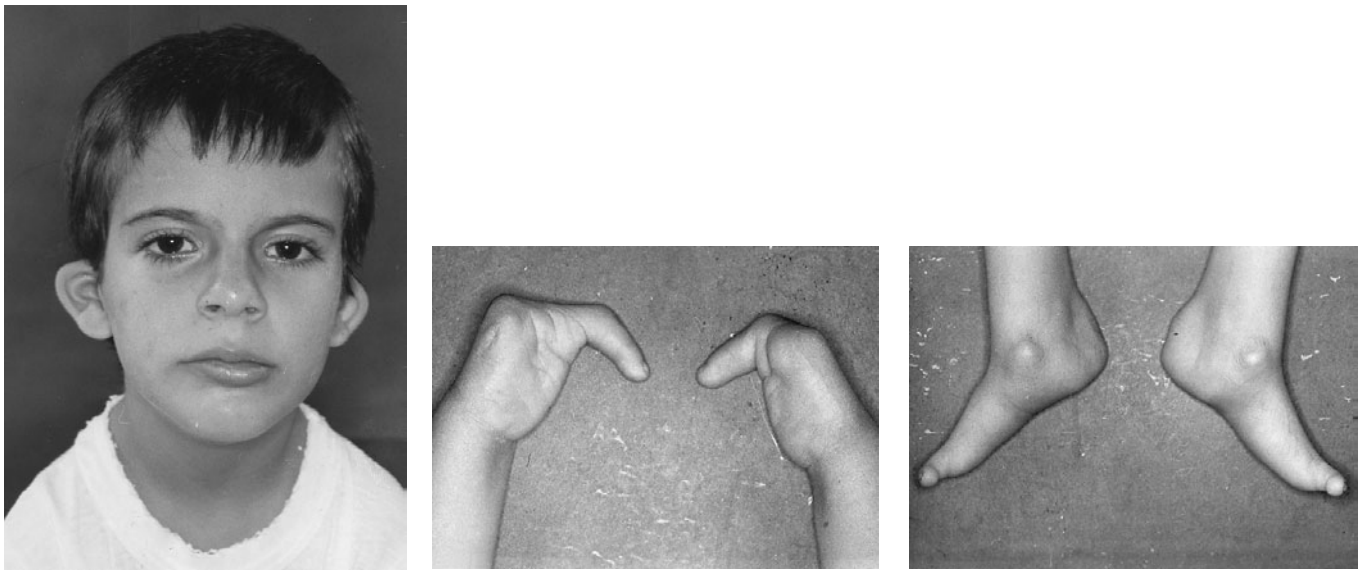
References [Unusual facies, blepharophimosis, and contractural arachnodactyly (van den Ende-Gupta syndrome)]

1. Gupta A et al: A new autosomal recessive syndrome of characteristic facies, joint contractures, skeletal abnormalities and normal development: Second report with further clinical delineation. J Med Genet 32:809–812, 1995.
2. Phadke SR et al: Further delineation of a new (van den Ende-Gupta) syndrome of blepharophimosis, contractural arachnodactyly, and characteristic face. Am J Med Genet 77:16–18, 1998.



A B C

Fig. 22–67. *Cleft lip-palate, microbrachycephaly, eye anomalies, short stature, and mental retardation*. (A–C) Three brothers with short stature, mental retardation, microbrachycephaly, deep-set eyes, and nystagmus. (From A Richieri-Costa and ML Guion-Almeida, Am J Med Genet 42:449, 1992.)



A B C

Fig. 22–68. *Cleft palate, abnormal pinnae, short stature, and monodactylous tetraectrodactyly.* (A) Somewhat low-set protruding pinnae. (B,C) Monodactylous tetraectrodactyly. (From A Richieri-Costa and E de Miranda, Am J Med Genet 31:559, 1988.)

3. van den Ende JJ et al: Marden-Walker-like syndrome without psychomotor retardation. Report of a Brazilian girl born to consanguineous parents. Am J Med Genet 42:467–469, 1992.

Cleft lip, microbrachycephaly, long thin face, ptosis, hypotelorism, lumbosacral/pelvic anomalies, and mental retardation

Richieri-Costa et al (1), in 1992, noted two sisters with a strikingly similar facial phenotype: microbrachycephaly, hypoplastic supraorbital ridges, long thin face, ptosis, hypotelorism, strabismus, midface hypoplasia, dysmorphic pinnae, and cleft lip. The bitemporal distance was reduced. The chin was large and prominent, and the mandibular angle was obtuse (Fig. 22–70).

Both sisters exhibited large fontanelles with delayed closure, pectus excavatum, wrinkled skin, lymphedema, abnormally modeled lumbosacral and pelvic bones, lumbar lordosis, brachydactyly, and short flat feet. Clasped thumbs were noted at birth.

Low birthweight, short adult stature, and moderate mental retardation were evident.

Radiologic studies showed hypoplastic distal epiphyses of radius and ulna, capitate/hamate coalition, short hypoplastic metacarpals 4–5, hypoplastic phalanges, hallux valgus, scoliosis, broad pelvis, vertically-shaped pubic and ischial bones, and shallow acetabulae.

The parents were not consanguineous. Inheritance is probably autosomal recessive.

The facies is very similar to that of *facio-cardio-renal syndrome*.

Reference (Cleft lip, microbrachycephaly, long thin face, ptosis, hypotelorism, lumbosacral-pelvic anomalies, and mental retardation)

1. Richieri-Costa A et al: Mental retardation, microbrachycephaly, hypotelorism, palpebral ptosis, thin/long face, cleft lip and lumbosacral/pelvic anomalies. Am J Med Genet 43:565–568, 1992.

Cleft palate, sickle-shaped scapulae, and talipes equinovarus

Bezirdjian and Szucs (1) documented a female with micrognathia, cleft palate, and an unusual sickle shaped deformity of both scapulae (Fig. 22–71). She also had bilateral club foot deformity.

Reference (Cleft palate, sickle-shaped scapulae, and talipes equinovarus)

1. Bezirdjian DR, Szucs R: Sickle-shaped scapulae in a patient with the Pierre Robin syndrome. Br J Radiol 62:171–173, 1989.

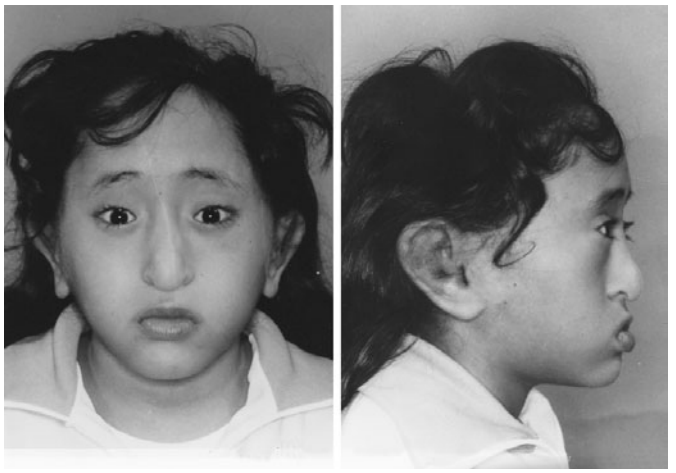
Unusual smiling face, cleft palate, and absence of middle ear space

Morris (1) described a mother and daughter with craniofacial anomalies and hearing loss. Both exhibited a striking appearance: a smiling face with lateral creases extending from the corners of the mouth to a point midway between the tragus and mouth. The daughter had submucous cleft palate, lacrimal duct stenosis, and a 40 dB conductive hearing loss. CT scan of the temporal bone showed normal ossicles, inner ear structures, and external auditory canals, but the mastoid air cells were poorly developed with abnormal soft tissue filling both the air cells and the middle ear space. On surgery, there was a thick vascular scar-like tissue in place of the middle ear cleft. External ear length was at the lower end of normal (5th centile). The mother had exhibited a repaired cleft of the soft palate, lacrimal duct stenosis, and mixed hearing loss.

The etiology is unknown. Failure of expansion of the distal portion of the first pharyngeal pouch that forms the tympanic cavity and mastoid air cells could have resulted in lack of middle ear space. The unusual appearance of the smiling face is apparently because of the lateral cleft-like extensions of the smile and may be caused by mandibular deficiency, facial muscle hypoplasia, or abnormal facial muscle insertion. The last possibility would suggest abnormal insertion of the zygomaticus major muscle into the orbicularis auris muscle.

Vance and Brei (2) also reported a case of a male with bilateral cheek dimples, the facial creases becoming more evident upon smiling or crying, lacrimal duct stenosis, and bilateral conductive hearing loss. Also noted were epicanthal folds, mild ptosis, upturned nose, high-arched palate, micrognathia, laryngomalacia, and pectus excavatum.

Wiedemann et al (3) described a 6-year-old girl that they labeled *Wildervanck syndrome* (Fig. 22–72). There was bony malformation at the atlantoccipital junction and block formation of cervical vertebrae 2–4 and synostosis of the spinous processes to C-6. The soft palate was immobile. The same facies was present as that seen in the above-mentioned cases, and there was conductive hearing impairment.



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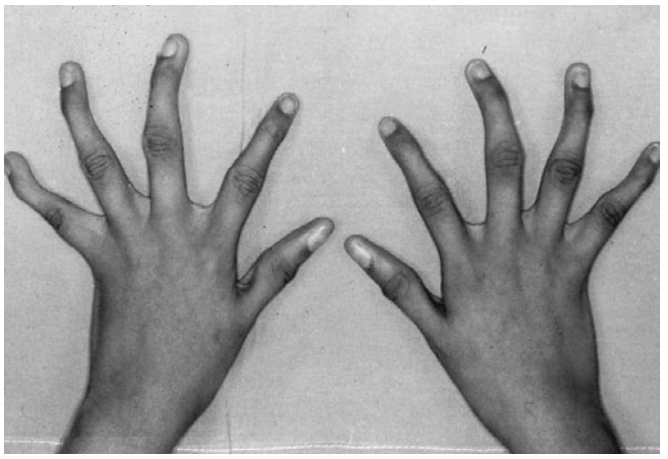
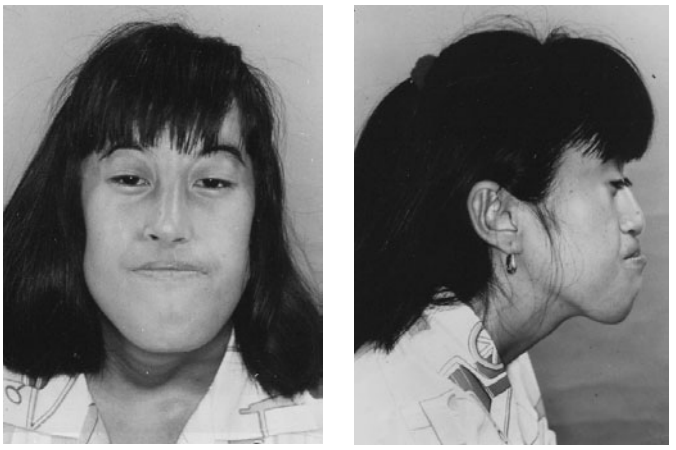


C

Fig. 22–69. *Unusual facies, blepharophimosis, and contractural arachnodactyly (van den Ende-Gupta syndrome)*. (A,B) Blepharophimosis, triangular face, midface hypoplasia, narrow beaked nose, everted lips. (C) Arachnodactyly and camptodactyly. (From JJ van den Ende et al, Am J Med Genet 42:467, 1992.)

Fig. 22–70. *Cleft lip, microbrachycephaly, long thin face, ptosis, hypotelorism, lumbosacral-pelvic anomalies, and mental retardation*. (A,B) Microbrachycephaly, long thin face, ptosis, hypertelorism, and midface hypoplasia. (From A Richieri-Costa et al, Am J Med Genet 43:565, 1992.)



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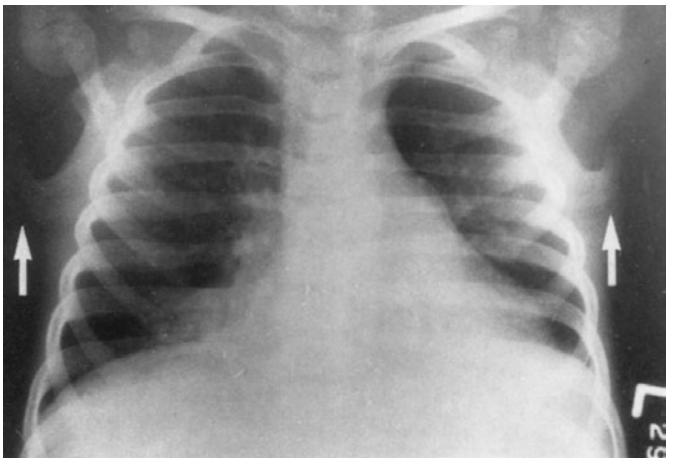
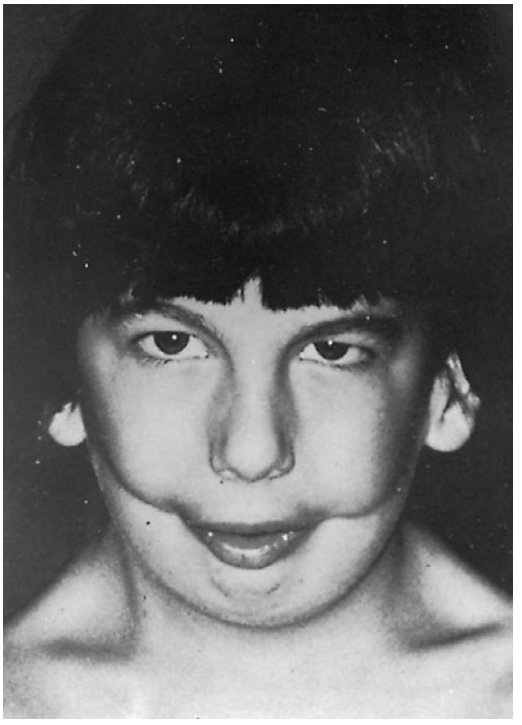


Fig. 22–71. *Cleft palate, sickle-shaped scapulae, and talipes equinovarus*. Arrows point to bilateral sickle-shaped scapulae. (From DR Bezirdjian and R Szucs, Br J Radiol 62:171, 1989.)

References (Unusual smiling face, cleft palate, and absence of middle ear space)

1. Morris CA: An unusual smiling face, cleft palate, and absence of the middle ear space—a unique branchial arch syndrome? Abstract 15th David W. Smith Workshop on Malformations and Morphogenesis, Tampa, Florida, 4–9 August 1994.
2. Vance GH, Brie T: Facial dimpling and hearing loss. Abstract 15th David W. Smith Workshop on Malformations and Morphogenesis, Tampa, Florida, 4–9 August 1994.
3. Wiedemann H-R et al: An Atlas of Characteristic Syndromes. Wildervanck syndrome, Wolfe Med Pub Ltd, London, 1985, pp 216–217.

Fig. 22–72. *Unusual smiling face, cleft palate, and absence of middle ear space*. Note bilateral grooves extending from corners of mouth when jaw is closed. (From HR Wiedemann et al, Wildervanck syndrome. In: An Atlas of Characteristic Syndromes, Wolfe Med Pub Ltd, London, p 216, 1985.)



Coloboma, hearing loss, hematuria, and cleft lip-palate

Collum (4) and Kingston et al (8) described a three-generation family in which colobomata of iris and choroid were segregating, sometimes accompanied by clefting and mental retardation. The family was updated by Ravine et al (13). Autosomal dominant inheritance with wide variation is obvious. No chromosomal localization is known. Most family members have required remedial teaching, and one male was institutionalized. It has remained uncertain whether the learning difficulties have been primary or secondary.

Craniofacial findings. Six patients had cleft lip with or without cleft palate. The range of expression was wide.

Ocular system. The most common finding was coloboma of the chorioretina and, to a lesser extent, coloboma of the iris, optic pits, and colobomatous microphthalmia. Presenile cataracts and retinal detachment were also found as complication of the colobomata. Impairment of extraocular movements was also prevalent. Three members had anomalous branching of retinal vessels.

Auditory system. The most common hearing loss was mid-frequency sensorineural, but in some patients with clefting, there was superimposed conductive hearing loss because of recurrent otitis media.

Hematuria. Seven members had hematuria without renal impairment.

Other findings. An anencephalic child with cleft lip and palate was born within the family, but this may have been aleatory.

Differential diagnosis. Hussels (6) described an adult female with uveal coloboma, clefting, and deafness, and microphthalmia in her son. Wenstrom et al (16) reported familial coloboma including microphthalmia, cataracts, hearing loss, and mild mental retardation. Other entities to be excluded are *Waardenburg syndrome*, *CHIME syndrome*, ocular-renal syndrome caused by PAX2 mutations (12,15), and the case report by Richieri-Costa and Guion-Almeida (14).

Atkin and Patil (3) reported a child and his maternal uncle with cleft lip-palate, microphthalmia, cloudy cornea, congenital heart defect, hemivertebrae, ureteral anomalies, hypospadias, cryptorchidism, and ectrodactyly. Pinsky et al (11) reported three sisters with microphthalmia, cloudy cornea, cleft lip, variable anomalies of the pinnae, mental retardation, and spasticity. Their mother had microphthalmia. Ho et al (5) noted the association of various forms of ocular coloboma with congenital heart anomalies, mental retardation, skeletal defects, and cleft palate. *Pilotto syndrome* consists of brachycephaly, cleft lip-palate, high nasal bridge, mildly dysmorphic pinnae, congenital heart defect, vertebral anomalies, short stature, and mental retardation (10). A similarly affected child was noted by Pena (9). The latter patient had microphthalmia, coloboma of the optic discs and choroid, and scoliosis. S Kapur (personal communication, 1989) described male and female sibs with cleft lip-palate, bulbous nasal tip, microphthalmia, iris coloboma, cataract, ASD, VSD, tetralogy of Fallot, displaced kidneys, hypoplastic thumbs, finger contractures, anal stenosis, and severe mental retardation.

The association of clefting with eye colobomas is also found in *Abruzzo-Erickson syndrome, Baraitser syndrome*, and *Michels syndrome*. Female sibs with cleft lip-palate, corneal opacities, optic nerve coloboma, profound psychomotor retardation, and congenital heart defects were reported by Anyane-Yeboa et al (1). James et al (6) noted the association of cleft lip and/or palate with uveal colobomas. The eye coloboma/cleft lip-palate association overlaps with *CHARGE* association (2).

References (Coloboma, hearing loss, hematuria, and cleft lip-palate)

1. Anyane-Yeboa K et al: Cleft lip and palate, corneal opacities and profound psychomotor retardation. Cleft Palate J 20:246–250, 1983.
2. Awrich PD et al: CHARGE association anomalies in siblings. Am J Hum Genet 34:80A, 1982.
3. Atkin JF, Patil S: Apparently new oculo-vertebro-acral syndrome. Am J Med Genet 19:585–587, 1984.
4. Collum LMT: Uveal colobomata and other anomalies in three generations of one family. Br J Ophthalmol 55:458–461, 1971.
5. Ho CK et al: Ocular colobomas, cardiac defect and other anomalies. A study of seven cases including two sibs. J Med Genet 12:289–292, 1975.
6. Hussels IE: Midface syndrome with iridochoroidal coloboma and deafness in a mother: Microphthalmia in her son. Birth Defects OAS 7(7):269, 1971.
7. James PLM et al: Systemic association of uveal colobomata. Br J Ophthalmol 58:917–921, 1974.
8. Kingston HM et al: An autosomal dominant syndrome of uveal colobomata, cleft lip and palate, and mental retardation. J Med Genet 19:444–446, 1982.
9. Pena SDJ: Cleft lip and palate, congenital heart disease, scoliosis, short stature, and mental retardation: The Pilotto syndrome. Birth Defects 18(3B): 183–186, 1982.
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12. Ramer JC et al: Previously apparently undescribed syndrome: Shallow orbits, coloboma, trigonocephaly, gyral malformations, and mental and growth retardation. Am J Med Genet 57:403–409, 1995.
13. Ravine D et al: Dominant coloboma-microphthalmos syndrome associated with sensorineural hearing loss, hematuria, and cleft lip/palate. Am J Med Genet 72:227–236, 1997.
14. Richieri-Costa A, Guion-Almeida ML: Short stature, mental retardation, eye anomalies, and cleft lip-palate. Am J Med Genet 42:449–452, 1992.
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16. Wenstrom KD et al: Unique phenotype associated with a pericentric inversion of chromosome 6 in three generations. Am J Med Genet 39:102–105, 1991.

Agenesis of the corpus callosum, profound mental retardation, oculocutaneous albinism, combined immunodeficiency, and cleft palate

Vici et al (3), in 1988, reported two brothers with agenesis of the corpus callosum with profound developmental delay, seizures, bilateral cataract, oculocutaneous albinism, combined immunodeficiency, and cleft lip-palate. They died at 2–3 years. A male and female sib with similar findings, but without cleft palate, were described by del Campo et al (1). In addition, there was marked hypoplasia of the cerebellar vermis and neuronal white matter heterotopia as well as polymicrogyria and pachygyria.

Inheritance is probably autosomal recessive (1).

While there is some overlap with Chediak-Higashi syndrome and Griscelli syndrome, the autosomal recessive disorder considered here appears to be distinct. Toriello and Carey (2) reported four children, three of whom were sibs, with cleft palate, agenesis of the corpus callosum, and unusual facies.

References (Agenesis of the corpus callosum, profound mental retardation, oculocutaneous albinism, combined immunodeficiency, and cleft palate)

1. del Campo M et al: Albinism and agenesis of the corpus callosum with profound developmental delay: Vici syndrome, evidence for autosomal recessive inheritance. Am J Med Genet 85:479–485, 1999.
2. Toriello HV, Carey JC: Corpus callosum agenesis, facial anomalies, Robin sequence, and other anomalies: A new autosomal recessive syndrome? Am J Med Genet 31:17–23, 1988.
3. Vici CD et al: Agenesis of the corpus callosum, combined immunodeficiency, bilateral cataract, and hypopigmentation in two brothers. Am J Med Genet 29:1–8, 1988.

Anophthalmia, heminasal a/hypoplasia, atypical facial clefting, growth and mental retardation, and agenesis of corpus callosum

Guion-Almeida and Richieri-Costa (1), in 1999, noted four unrelated children with growth and mental retardation, agenesis of corpus callosum, prominent forehead, facial asymmetry, anophthalmia, heminasal a/hypoplasia, preauricular skin tags, dysmorphic pinnae and atypical facial clefting.

To be excluded are *oculoauriculofrontonasal spectrum, heminasal aplasia*, and *oculo-auriculo-vertebral spectrum*.

Reference (Anophthalmia, heminasal a/hypoplasia, atypical facial clefting, growth and mental retardation, and agenesis of corpus callosum)

1. Guion-Almeida ML, Richieri-Costa A: New syndrome of growth and mental retardation, structural anomalies of the central nervous system, and first branchial arch, anophthalmia, heminasal a/hypoplasia, and atypical clefting. Report on four Brazilian patients. Am J Med Genet 87:237–244, 1999.

Anophthalmia, pulmonary hypoplasia, and cleft palate

Spear et al (2) and Seller et al (1) described sibs with anophthalmia and pulmonary hypoplasia. Cleft palate was noted (1).

References (Anophthalmia, pulmonary hypoplasia, and cleft palate)

1. Seller MJ: Two sibs with anophthalmia and pulmonary hypoplasia (the Matthew-Wood syndrome). Am J Med Genet 62:227–229, 1996.
2. Spear GS et al: Bilateral pulmonary agenesis and microphthalmia. Am J Med Genet (Suppl) 3:379–382, 1987.

Cleft lip and cone-rod dystrophy

Ausems et al (1) reported three sibs, the product of a consanguineous marriage, with cleft lip. Two developed a progressive retinopathy identified as cone-rod dystrophy.

Inheritance appears to be autosomal recessive.

Impaired color vision (because of cone dystrophy) followed by night blindness and peripheral field diminution (because of rod dystrophy) leads to early vision loss. It is usually found in otherwise normal individuals but other findings have been reported: hereditary ataxia, alopecia, mental retardation with hypogonadism and sensorineural hearing loss (4) and renal dysfunction and sensorineural hearing loss (2).

Inheritance has been autosomal dominant in some kindred, autosomal recessive in others, and X-linked recessive in still others (3).

References (Cleft lip and cone-rod dystrophy)

1. Ausems MGEM et al: Cleft lip and cone-rod dystrophy in a consanguineous sibship. Clin Dysmorphol 5:307–311, 1996.
2. Beighton P et al: Rod-cone dystrophy, sensorineural deafness and renal dysfunction: An autosomal recessive syndrome? Am J Med Genet 47:832–836, 1993.
3. Moore AT: Cone and cone-rod dystrophies. J Med Genet 29:289–290, 1992.
4. Warburg M et al: Deletion mapping of a retinal cone-rod dystrophy: Assignment to 18q21.1. Am J Med Genet 39:288–293, 1991.

Cleft lip-palate and "anophthalmia plus"

Fryns et al (1) described a female fetus with bilateral anophthalmia, bilateral cleft lip-palate, microtia with mild bilateral lateral facial clefting, myelomeningocoele, and uterus unicornis. A second child, a male, had bilateral anophthalmia and a lobeless ear.

Inheritance may possibly be autosomal recessive.

Reference (Cleft lip-palate and "anophthalmia plus")

1. Fryns J-P et al: Apparently new "anophthalmia-plus" syndrome in sibs. Am J Med Genet 58:113–114, 1995.

Cleft lip-palate and XY gonadal dysgenesis (Brosnan syndrome)

Brosnan et al, in 1980, reported two female sibs with 46,XY gonadal dysgenesis, short stature, narrow forehead with metopic ridge, broad squashed nose, pretragal pits, narrow external ear canals, overfolded helices, cleft lip-palate, enamel dysplasia, punched-out scalp defects, broad hands and feet with spatulate thumbs and halluces, VSD, umbilical hernia, and mild mental retardation.

Both had streak gonads, 46,XY chromosome constitution, and small bicornuate uterus.

Follow-up was carried out by Schimke and Ardinger (2).

References [Cleft lip-palate and XY gonadal dysgenesis (Brosnan syndrome)]

1. Brosnan PG et al: A new familial syndrome of 46,XY gonadal dysgenesis with anomalies of ectodermal and mesodermal structures. J Pediatr 97:586–590, 1980.
2. Schimke RN, Ardinger HH: Brosnan syndrome: Twenty years later. XX David W Smith Workshop on Malformations and Morphogenesis. Schlangenbad, Germany 3–9 August 1999.

Cleft lip-palate, agenesis of corpus callosum, microcephaly, seizures, psychomotor retardation, and preaxial polydactyly

Several patients have been described with microcephaly, agenesis or hypoplasia of the corpus callosum, mental retardation, seizures or infantile spasm, and cortical atrophy. At least three patients had cleft lip-palate (1–3). One had inguinal hernia (2).

Two had preaxial polydactyly; another had exophthalmos. Such conditions as *acrocallosal syndrome; cleft lip and palate, prominent eyes, and congenital heart disease; Lin-Gettig syndrome* and *Lowry-MacLean syndrome* must be excluded.

References (Cleft lip-palate, agenesis of corpus callosum, microcephaly, seizures, psychomotor retardation, and preaxial polydactyly)

1. Howard FM, Young ID: Unknown syndrome: Microcephaly, facial clefting, and preaxial polydactyly. J Med Genet 25:272–273, 1988.
2. Marles SL, Chudley AE: Another case of microcephaly, facial clefting, and preaxial polydactyly. J Med Genet 27:593–594, 1990.
3. Tütüncüoglu S et al: Corpus callosum dysgenesis, microcephaly, infantile spasm, cleft lip-palate, exophthalmos and psychomotor retardation. Clin Genet 49:220–222, 1996.

Cleft lip-palate, antecubital pterygia, and the nail-patella syndrome

Cleft lip-palate may be associated with antecubital pterygia as part of the nail-patella syndrome. This combination has been documented in two cases (1,4).

The nail-patella syndrome is an autosomal dominant condition characterized by patellar a/hypoplasia, finger nail dysplasia (especially of the thumbs and index fingers), arthrodysplasia of elbows, iliac horns, and nephropathy (5). The usual elbow alterations involve subluxation or luxation of the radial and/or ulnar heads with limitation of pronation, supination, and extension. However, it has been reported with antecubital pterygia (2–4).

References (Cleft lip-palate, antecubital pterygia, and the nail-patella syndrome)

1. Duncan JG, Souter WA: Hereditary onycho-osteodysplasia. The nail-patella syndrome. J Bone Joint Surg Br 45:242–258, 1963.
2. Fenske HD, Spitalny LA: Hereditary osteo-onychodysplasia. Am J Ophthalmol 70:604–608, 1970.
3. Hall JG et al: Limb pterygium syndromes: A review and report of eleven patients. Am J Med Genet 12:377–409, 1982.
4. Richieri-Costa A: Antecubital pterygium and cleft lip/palate presenting as signs of the nail-patella syndrome: Report of a Brazilian family. Am J Med Genet 38:9–12, 1991.
5. Simila S et al: Hereditary onycho-osteodysplasia (the nail-patella syndrome) with nephrosis-like renal disease in a newborn boy. Pediatrics 46:61–65, 1970.

Cleft lip-palate, blepharoptosis, oligodontia, and ectrodactyly

Rodini and Richieri-Costa (1) reported the female offspring of consanguineous parents. The father has cleft lip-palate. His daughter presented with ectrodactyly of the feet, syndactyly of toes, bilateral ptosis, cleft lip-palate, and oligodontia.

We suspect that in spite of the parental consanguinity that this case may be incomplete expression of the *EEC syndrome*, which often has variable expression.

Reference (Cleft lip-palate, blepharoptosis, oligodontia, and ectrodactyly)

1. Rodini ESO, Richieri-Costa A: Autosomal recessive, blepharoptosis, cleft lip/palate, dental anomalies and ectrodactyly. Am J Med Genet 42:340–342, 1992.

Cleft lip-palate, facial, eye, heart, and intestinal anomalies (Kapur-Toriello syndrome)

Kapur and Toriello (2) reported a brother and sister with cleft lip-palate, nose with bulbous tip and columella below nares, microphthalmia (one with cataract and colobomata of iris and retina), and low-set pinnae with atretic canal and ear tags.

Congenital heart anomalies (ASD, VSD, tetralogy of Fallot), hypoplastic thumbs, finger contractures, hypoplastic labia in the female, small penis in the male, rectal stenosis, and malrotation of the intestine were also observed. Growth and development were significantly retarded.

Similar cases were described by Zelante et al (3) and Graham et al (1).

Inheritance may be autosomal recessive.

References [Cleft lip-palate, facial, eye, heart, and intestinal anomalies (Kapur-Toriello syndrome)]

1. Graham GE et al: A fourth patient with the Kapur-Toriello syndrome: Nesidioblastosis, digital hypoplasia and late parental age as novel findings. Am J Hum Genet 67:Abst 685, 2000.
2. Kapur S, Toriello HV: Apparently new MCA/MR syndrome in sibs with cleft lip and palate and other facial, eye, heart, and intestinal anomalies. Am J Med Genet 41:423–425, 1991.
3. Zelante L et al: Confirmation of Kapur-Toriello syndrome in an Italian patient. Clin Dysmorphol 8:151–153, 1999.

Cleft lip-palate, leptomeningeal angiomatosis, absent olfactory tracts, Dandy-Walker malformation, and congenital heart anomalies

Hurst et al (1) described a stillborn male with an unusual combination of cleft lip-palate, broad nasal root, downslanting palpebral fissures, small posteriorly rotated pinnae, congenital heart anomalies (small atria, hypoplastic left ventricle, atretic aorta and aortic valve), leptomeningeal angiomatosis, absent olfactory tracts, thin corpus callosum, absent septum pellucidum, and hypoplasia of the cerebellar vermis.

Reference (Cleft lip-palate, leptomeningeal angiomatosis, absent olfactory tracts, Dandy-Walker malformation, and congenital heart anomalies)

1. Hurst JA et al: Leptomeningeal angiomatosis, absent olfactory tracts, hypoplasia of cerebellar vermis, cleft lip and palate, and congenital heart disease in a stillborn infant. Clin Dysmorphol 1:168–171, 1992.

Cleft lip-palate, microcephaly, cardiac malformations, and digital anomalies

Perçin et al (1) reported two sibs with atrial septal defect in one, tetralogy of Fallot in the other, small middle phalanges of fingers II and V, and long, broad halluces. Cone-shaped epiphyses were noted on X-ray examination.

One had cleft lip-palate, the other occult cleft lip.

There is some similarity to *Juberg-Hayward syndrome*.

Reference (Cleft lip-palate, microcephaly, cardiac malformations, and digital anomalies)

1. Perçin EF et al: A new syndrome with cardiac malformations, cleft lip-palate, microcephaly, and digital anomalies. Clin Genet 48:264–267, 1995.

Cleft lip-palate, pigmentary retinopathy, and cholestasis

Hardikar et al (2), in 1992, reported two unrelated children with a syndrome of cleft lip-palate, pigmentary retinopathy, multisystem obstruction with cholestasis and pulmonary outflow murmur. Another example is that of Cools and Jaeken (1).

The facies is characterized by long narrow palpebral fissures, depressed nasal tip, preauricular dimples, and moderate psychomotor development. The patient of Hardikar et al (1) manifest a stenotic hepatic duct responsible for the obstruction. This could not be demonstrated in the case of Cools and Jaeken (2). A jejunal web or rotation anomaly of the gut was present in all three patients as was hydronephrosis. Congenital heart anomalies were found in two of the three patients. There is some resemblance to *Kabuki syndrome*.

Various disorders were excluded such as *Alagille syndrome*, Norwegian cholestasis, congenital hepatic fibrosis, and Caroli disease.

References (Cleft lip-palate, pigmentary retinopathy, and cholestasis)

1. Hardikar W et al: Multisystem obstruction with cholestasis, pigmentary retinopathy, and cleft palate. A new syndrome? Am J Med Genet 44:13–17, 1992.
2. Cools F, Jaeken J: Hardikar syndrome: A new syndrome with cleft lip/palate, pigmentary retinopathy, and cholestasis. Am J Med Genet 71:472–474, 1997.

Cleft lip-palate, scoliosis, congenital heart disease, and mental retardation (Pilotto syndrome)

Pilotto et al (2) reported a syndrome of bilateral cleft lip-palate, microbrachycephaly, facial asymmetry, high nasal bridge, dysmorphic pinnae, short neck, retarded bone age, kyphoscoliosis with vertebral body defects, 13 pairs of ribs, pseudoepiphyses of metacarpals, and skeletal anomalies, congenital heart anomalies (PDA, ASD), genital hypoplasia, and growth and mental retardation. Additional possible examples were recorded by Pena (1) and Strømme et al (3).

Inheritance is unknown. Pilotto et al (2) noted two other sibs who died in infancy with malformations (scoliosis, congenital heart anomaly).

References [Cleft lip-palate, scoliosis, congenital heart disease, and mental retardation (Pilotto syndrome)]

1. Pena SDJ: Cleft lip and palate, congenital heart disease, scoliosis, short neck and mental retardation: The Pilotto syndrome. Birth Defects 18(3B):183–186, 1982.
2. Pilotto RF et al: Study of a child with "idiopathic" malformation/mental retardation syndrome. Birth Defects 11(3):51–53, 1975.
3. Strømme P et al: Cleft lip and palate, scoliosis, skeletal and cardiac malformations and other dysmorphic features in a child. Scand J Plast Reconstr Hand Surg 27:71–74, 1993.

Cleft lip-palate, severe psychomotor retardation, characteristic facies, hypospadias, and limb contractures

Wolff et al (1) described severely mentally retarded male sibs, one of whom had seizures. Both had a facies marked by low hair line, hypertelorism, bulbous nose, upslanting palpebral fissures, large pinnae, micro/retrognathia, and thick lips. One had cleft lip-palate, the other convergent strabismus and abnormal nasal septum.

Both exhibited hypospadias; one had cryptorchidism, the other inguinal hernia.

Both had delayed skeletal maturation, large hands, progressive postnatal limb contractures, hypoplasia of the terminal phalanges, talipes, and camptodactyly. One had scoliosis and clinodactyly, the other rough skin.

There is some overlap with the *branchio-skeleto-genital syndrome, acro-fronto-facio-nasal dysostosis* and *Opitz (BBB/G) syndrome*.

Inheritance is either autosomal or X-linked recessive.

Reference (Cleft lip-palate, severe psychomotor retardation, characteristic facies, hypospadias, and limb contractures)

1. Wolff G et al: Two brothers with characteristic facial appearance, severe psychomotor retardation, hypospadias, contractures, and other symptoms: A new recessive syndrome? J Med Genet 31:65–67, 1994.

Cleft lip-palate, unusual facies, intestinal malrotation, and congenital heart anomalies

McPherson and Clemens (1) reported male and female sibs with bilateral cleft lip-palate, hypertelorism, flat profile and occiput, malrotation of intestine, and complex congenital heart anomalies leading to death. The female had bifid thumbs; and the male was large for gestational age and had a bilobed tongue. The neck appeared short and broad in the male and with nuchal edema in the female sib. Visceromegaly and glial heterotopias were found in the male infant. Three male sibs were added by Nevins et al (2). They manifested similar anomalies but did not have bifid tongue, malrotation of the intestine, or bifid thumbs.

Excluded were *Simpson-Golabi-Behmel syndrome* and *Fryns syndrome*.

Inheritance is probably autosomal recessive.

References (Cleft lip-palate, unusual facies, intestinal malrotation, and congenital heart anomalies)

1. McPherson E, Clemens M: Cleft lip and palate, characteristic facial appearance, malrotation of the intestine, and lethal congenital heart disease in two sibs. A new autosomal recessive condition? Am J Med Genet 62:58–60, 1996.
2. Nevin NC et al: Cleft lip and palate, hypertelorism, brachycephaly, flat facial profile, and congenital heart disease in three brothers. Am J Med Genet 73:412–415, 1997.

Cleft palate, atresia of the auditory meati, and limb reduction defects

Glass et al (1), in 1994, reported male and female sibs with common anomalies of cleft palate, auditory meatal atresia, and limb reduction in spite of marked dissimilarity in other abnormalities.

Inheritance may be autosomal recessive. One child had macrocephaly, porencephaly, spastic tetraplegia, seizures, and severe mental retardation. Preauricular tag, slit-like auditory meati, cleft palate were also found. The other sib had cleft palate, bilateral ear tags, narrow meati, lack of one arm, absence of proximal humerus of the other arm with humero-radio-ulnar synostosis at the elbow. The third digit had camptodactyly.

There was no evidence of *Delleman syndrome*. Teratogen exposure was excluded.

Reference (Cleft palate, atresia of the auditory meati, and limb reduction defects)

1. Glass IA et al: Ear anomalies, clefting, and limb reduction defects: A new autosomal recessive condition? Clin Dysmorphol 3:150–156, 1994.

Cleft palate, congenital hypothyroidism, curly hair, and choanal atresia

Bamforth et al (1) reported two brothers with congenital hypothyroidism, sparse curly/spiky hair, low-set dysmorphic pinnae, micrognathia, and cleft palate. Choanal atresia and bifid epiglottis were found as well as developmental delay. A similarly affected female was described by Buntincx et al (2). Bilateral choanal atresia was found. The eyelashes were long. The scalp hair extended low in the forehead. Late polyhydramnios was noted in all cases (1,2).

Inheritance may be autosomal recessive.

It may be the same as *hypothyroidism and hypohidrotic ectodermal dysplasia* (3–5). Zadik et al (6) reported a female with congenital hypothyroidism, dermoid cysts of the upper eyelids, convergent strabismus, oligodontia, and cleft palate.

ANOTHER syndrome should be excluded.

References (Cleft palate, congenital hypothyroidism, curly hair, and choanal atresia)

1. Bamforth JS et al: Congenital hypothyroidism, spiky hair, and cleft palate. J Med Genet 26:49–51, 1989.
2. Buntincx IM et al: Syndrome association of cleft palate, bilateral choanal atresia, curly hair, and congenital hypothyroidism. J Med Genet 30:427–428, 1995.
3. Morris CA et al: Another case of ANOTHER syndrome (hypohidrotic ectodermal dysplasia with hypothyroidism). Proc Greenwood Genet Ctr 6:145–146, 1987.
4. Pabst HF et al: Hypohidrotic ectodermal dysplasia with hypothyroidism. J Pediatr 98:223–227, 1987.
5. Pike MG et al: A distinctive type of hypohidrotic dysplasia featuring hypothyroidism. J Pediatr 108:109–111, 1986.
6. Zadik Z et al: Dermoid cysts, hypothyroidism, cleft palate, and hypodontia. J Clin Dysmorphol 1(4):24–27, 1983.

Cleft palate, craniosynostosis, joint contractures, anomalous pinnae, and scoliosis

Iida et al (1) described a female infant with coronal synostosis, trismus, outstanding pinnae with flat helices, flat nasal root, and finger contractures. The palate was widely cleft and there was scoliosis.

There was some resemblance to *Antley-Bixler syndrome*, but the child had no radiohumeral synostosis, choanal atresia, congenital heart or urogenital anomalies.

Reference (Cleft palate, craniosynostosis, joint contractures, anomalous pinnae, and scoliosis)

1. Iida A et al: Craniosynostosis with joint contractures, ear deformity, cleft palate, scoliosis, and other features. Cleft Palate Craniofac J 32:489–491, 1995.

Cleft palate, microphthalmia, dextrocardia, choreoathetosis, and mental retardation

Aughton (1) and Nachlieli and Gershoni-Baruch (2) reported male infants born to consanguineous Arab parents. The infants had sloping foreheads, anophthalmia/microphthalmia, small deep-set palpebral fissures, prominent nasal root and nasal bridge, and large pinnae. One had cleft palate (2).

Both had dextrocardia, one had vertebral rib defects and supernumerary ribs. One had mental retardation, choreoathetosis, and seizures (2). Both had folding of the plantae pedis.

Inheritance appears to be autosomal recessive.

Other conditions to be excluded are *cerebro-oculo-facial (COFS) syndrome*, Waardenburg microphthalmia syndrome (3), and *Lenz microphthalmia syndrome*.

References (Cleft palate, microphthalmia, dextrocardia, choreoathetosis, and mental retardation)

1. Aughton DJ: New syndrome? Clinical anophthalmia, dextrocardia, and skeletal anomalies in an infant born to consanguineous parents. Am J Med Genet 37:178–181, 1990.
2. Nachlieli T, Gershoni-Baruch R: Dextrocardia, microphthalmia, cleft palate, choreoathetosis, and mental retardation in an infant born to consanguineous parents. Am J Med Genet 42:458–460, 1992.
3. Traboulsi EI et al: Waardenburg's recessive anophthalmia syndrome. Ophthalmol Paediatr Genet 1:13–18, 1983.

Cleft palate, Potter sequence, congenital heart anomalies, and mesoaxial polydactyly (Holzgreve-Wagner-Rehder syndrome)

Cleft palate, persistent buccopharyngeal membrane, mesoaxial hexadactyly, and congenital heart anomalies was discussed as a syndrome by Holzgreve et al (2) in 1984. To date there have been only isolated examples (1–3).

Craniofacial findings. Marked acrocephaly without craniosynostosis has been present. Posterior cleft palate with glossoptosis and persistent buccopharyngeal membrane are constant features (1–3).

Respiratory and cardiovascular systems. The lungs are hypoplastic. Congenital heart and great vessel anomalies have included VSD, hypoplastic left heart, aortic arch hypoplasia, and single umbilical artery.

Musculoskeletal findings. Mesoaxial hexadactyly, postaxial polydactyly, Y-shaped fusion of metacarpals 4–5, ossification defects of ribs and sacral vertebral defects have been noted. The fifth finger may be abbreviated. Eleven ribs have been documented. The lower limbs have been fixed.

Renal anomalies. All have bilateral renal agenesis with associated Potter sequence.

Differential diagnosis. One must exclude the various *oral-facial-digital syndromes* and Kaufman syndrome (polydactyly, hematocolpos, cardiopathy, *Thomas syndrome, Gillessen-Kaesbach syndrome*, and *Pallister-Hall syndrome*. Potter sequence is associated with a veritable host of other anomalies in single gene disorders and in *amnion rupture sequence* (see Chapter 1). Thomas et al (4) and Zlotogora et al (5) described sibs with hypoplastic left heart, ASD, renal hypoplasia/agenesis, and cleft lip-palate but no anomalies of the extremities.

References [Cleft palate, Potter sequence, congenital heart anomalies, and mesoaxial polydactyly (Holzgreve-Wagner-Rehder syndrome)]

1. Bonnet J et al: Hypoplasie rénale, polydactylie, cardiopathie; Un nouveau syndrome? J Genet Hum 335:279–289, 1987.
2. Holzgreve W et al: Bilateral renal agenesis with Potter phenotype, cleft palate, anomalies of the cardiovascular system, skeletal anomalies including hexadactyly, and bifid metacarpals. A new syndrome? Am J Med Genet 18:177–182, 1984.
3. Legius E et al: Holzgreve-Wagner-Rehder syndrome: Potter sequence associated with persistent buccopharyngeal membrane. A second observation. Am J Med Genet 31:269–272, 1988.
4. Thomas IT et al: Holzgreve syndrome: Recurrence in sibs. Am J Med Genet 45:767–769, 1993.
5. Zlotogora J et al: Thomas syndrome: Potter sequence with cleft lip/plate and cardiac anomalies. Am J Med Genet 62:224–226, 1996.

Cleft lip-palate, Potter sequence, and cardiac abnormalities (Thomas syndrome)

Thomas et al (3), in 1993, and Zlotogora et al (4), in 1996, both reported sibs with Potter sequence, cleft lip or cleft palate and congenital heart anomalies. Sibs reported earlier by Curry (2) probably had the same syndrome. Additional affected sibs were described by Briscioli et al (1).

Inheritance is clearly autosomal recessive.

Several had intrauterine growth retardation (4).

Kidney abnormalities ranged from hypoplasia (3,4) to cystic dysplasia (2,4) to agenesis (1,4). All infants exhibited Potter sequence.

Cleft palate (2,3) and cleft lip with cleft palate (1,4) were found.

Congenital heart anomalies included VSD, mitral valve atresia, aortic valve atresia, PDA, tetralogy of Fallot, coarctation of aorta, and bicuspid pulmonary valve.

Holzgreve-Wagner-Rehder syndrome is similar but does not have extremity anomalies and all examples have been isolated. *Gillessen-Kaesbach syndrome* is characterized by Potter sequence, microbrachycephaly, and brachymelia.

References [Cleft lip-palate, Potter sequence, and cardiac abnormalities (Thomas syndrome)]

1. Briscioli V et al: Thomas syndrome: Clinical variability and autosomal recessive inheritance. Am J Med Genet 71:373–374, 1997.
2. Curry CJR et al: The Potter sequence. Am J Med Genet 19:679–702, 1984.
3. Thomas IT et al: Holzgreve syndrome: Recurrence in sibs. Am J Med Genet 45:767–769, 1993.
4. Zlotogora J et al: Thomas syndrome: Potter sequence with cleft lip/palate and cardiac anomalies. Am J Med Genet 62:224–226, 1996.

Cleft palate, radial and patellar aplasia/hypoplasia, and short stature (RAPADILINO syndrome)

Kääriänen et al (2) reported a syndrome, employing the acronym RAPADILINO: *R*A (*ra*dial anomalies), *P*A (absent/hypoplastic *pa*tellae), *D*I (*di*arrhea, *di*slocated joints), *L*I (*li*ttle size, *li*mb malformations), *N*O (long thin *no*se, *no*rmal intelligence).

Their four patients exhibited radial aplasia or hypoplasia, absence of thumbs, absent or hypoplastic patellae, dislocation of joints, diarrhea in infancy, long slender nose, and small chin.

Intelligence was normal. The voice was high-pitched. Two of the four patients had cleft palate.

Vargas et al (4) described an isolated male with similar phenotype. In addition, there was partial anal stenosis. The ulnae were short and bowed. An ASD was also described. Kant et al (3) reported a male who, in addition, had a poikilodermatous skin rash, somewhat resembling that seen in *Rothmund-Thompson syndrome*.

Inheritance may be autosomal recessive.

One must exclude TAR syndrome, VATER association, Fanconi anemia, and *Aase-Smith syndrome II*.

References [Cleft palate, radial and patellar aplasia/hypoplasia, and short stature (RAPADILINO syndrome)]

1. Jam K et al: RAPADILINO syndrome. A multiple malformation syndrome with radial and patellar aplasia. Teratology 60:37–38, 1999.
2. Kääriänen H et al: RAPADILINO syndrome with radial and patellar aplasia/hypoplasia as main manifestations. Am J Med Genet 33:346–351, 1989.
3. Kant S et al: Rapadilino syndrome—a non-Finnish case. Clin Dysmorphol 7:135–138, 1998.
4. Vargas FR et al: RAPADILINO syndrome. Am J Med Genet 44:716–719, 1992.

Cleft palate, whistling face, distal arthrogryposis, and mental retardation

Illum et al (2), Schrander-Stumpel et al (4) and Di Rocco et al (1), and others (3,5) described patients with Robin sequence, distal arthrogryposis type IID or E, severe encephalopathy, mental retardation, hypotonia, seizures, postnatal growth retardation, and a face characterized by small mandible and a somewhat whistling face appearance. Polyhydramnios was noted in several cases (2,4). Death occurred relatively early. Calcium deposits were found throughout the brain.

Inheritance may possibly be autosomal recessive (2).

References (Cleft palate, whistling face, distal arthrogryposis, and mental retardation)

1. Di Rocco M et al: Distal arthrogryposis, mental retardation, whistling face, and Pierre Robin sequence: Another case. Am J Med Genet 44:391, 1992.
2. Illum N et al: Lethal autosomal recessive arthrogryposis multiplex congenita with whistling face and calcifications of the nervous system. Neuropediatrics 19:186–192, 1988.
3. Lev D et al: Progressive neurologic deterioration in a child with distal arthrogryposis and whistling face. J Med Genet 37:231–233, 2000.
4. Schrander-Stumpel C et al: Association of distal arthrogryposis, mental retardation, whistling face, and Pierre Robin sequence: Evidence for nosologic heterogeneity. Am J Med Genet 38:557–561, 1991.
5. Zampino D et al: Severe form of Freeman-Sheldon syndrome associated with brain anomalies and hearing loss. Am J Med Genet 62:294–296, 1996.

Distal arthrogryposis, unusual facies, cleft lip with/without cleft palate, short stature, hydronephrosis, and normal intelligence

Sonoda and Kouno (1) reported two brothers with joint contractures of the distal limbs, an unusual facies characterized by marked hypertelorism, and blepharophimosis, one with cleft lip, the other with cleft lip and palate, short stature, hydronephrosis, undescended testes, and normal intelligence. Although the authors suggested that they represented a form of oto-palato-digital syndrome, we disagree, and further suggest that it represents a new entity.

Reference (Distal arthrogryposis, unusual facies, cleft lip with/without cleft palate, short stature, hydronephrosis, and normal intelligence)

1. Sonoda T, Kouno K: Two brothers with distal arthrogryposis, peculiar facial appearance, cleft palate, short stature, hydronephrosis, retentio testis, and normal intelligence: A new type of distal arthrogryposis? Am J Med Genet 91:280–285, 2000.

Microcephaly, preauricular skin tags, cleft palate, camptodactyly, and distal limb anomalies

Guion-Almeida et al (1), in 1999, reported two unrelated children born to nonconsanguineous parents. The children had microcephaly, growth and mental retardation, telecanthus, hypoplastic tragus, short nose, preauricular skin tags/pits, short neck, micrognathia, camptodactyly, long thin fingers, and foot abnormalities.

Both children exhibited hypotonia; one had seizures. There were abnormal palmar creases.

Differential diagnosis would include *Toriello-Carey syndrome, cerebro-facio-articular syndrome*, and *oculo-auriculo-vertebral spectrum*.

Reference (Microcephaly, preauricular skin tags, cleft palate, camptodactyly, and distal limb anomalies)

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Chapter 23
Orofacial Clefting Syndromes: Associations

Aicardi syndrome and cleft lip-palate

Aicardi syndrome consists of seizures, callosal agenesis, severe mental retardation, delayed development, and ocular abnormalities (chorioretinal lacunae, microphthalmia) occurring in retarded females. It is believed to be caused by an X-linked dominant gene that is lethal in the hemizygous male. The gene maps to Xp22.3 (1). Death usually occurs during the first decade of life. The syndrome has been reported in association with porencephaly, corticoheterotopias, Arnold-Chiari malformation, papilloma of the choroid plexus, lissencephaly, ventricular cyst, polygyria, microgyria, arhinencephaly, and Dandy–Walker malformation. It has been estimated that cleft lip-palate (1–6) is found in about 3% of the cases. *Holoprosencephaly* (5) has also been described

References (Aicardi syndrome and cleft lip-palate)

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Anencephaly and/or cleft lip-palate

Anencephaly, a disorder due to failure of closure of the anterior neuropore and resultant lack of brain development, is characterized by absence of cranial vault and brain, hypoplastic and/or deformed pituitary gland, and absent hypothalamus. Associated are protruding eyeballs and tongue, aquiline nose, malformations of the cranial base, short neck, and changes secondary to lack of neural connections between the pituitary and the generally absent hypothalamus, such as hypoplasia of the adrenal glands and gonads (4). The protruding tongue may be due to an abnormally small oral cavity. The mandible is relatively large. A general account of *anencephaly* appears in chapter 16. The reader is referred to the comprehensive work of Lemire et al (18) for detailed information.

The association of clefting and anencephaly is certainly higher than chance would dictate. Khoury et al (16) found a relationship with neural tube defects and CL(P) especially significant. Heintel (13) stated that every anencephalic had submucous cleft palate. Although this may be an exaggeration, palatal form is certainly bizarre with a pronounced midline palatal raphe, suggesting to us altered temporal fusion of the palatal shelves with the nasal septum. Similar palatal changes are seen in holoprosencephaly (see Fig. 20–22). Among 114 infants with isolated cleft palate, MacMahon and McKeown (19) found one anencephalic, but three with this condition were noted among 105 infants with cleft lip and palate among 34 Japanese anencephalics. A number of authors (9,10,24) have also noted the association. Conversely, several investigators examining infants with anencephaly have found cleft lip-palate (2,3, 5,6,14,26) or cleft palate or uvula (1,11,14,15,22,26). However, since no systematic large survey has been done, clefting has ranged from 2% to 20% (7,8,14,18,21,25,26). Gleeson and Stovin (12) described an anencephalic child with cleft palate, Klippel-Feil-like anomaly, and neuroenteric cyst. Rejjal and Abu-Osba (23) reported discordant anencephaly with cleft lip-palate in a triplet pregnancy. Medeira et al (20) noted anencephaly, spina bifida, limb anomalies, and cleft lip-palate.

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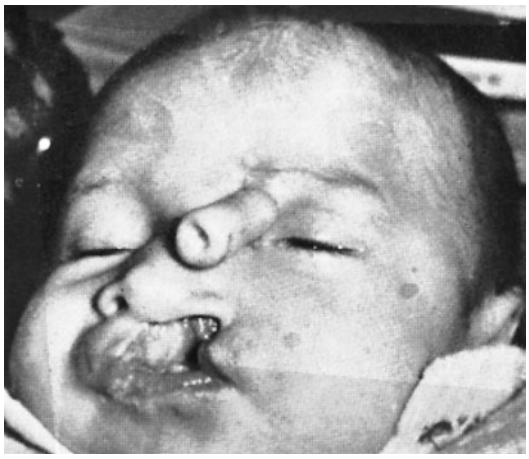

Fig. 23–1. *Lateral proboscis and cleft lip-palate*. (Courtesy of LR McLaren, Br J Plast Surg 8:57, 1955.)

Lateral nasal proboscis and its associations

Lateral nasal proboscis is characterized by a tubular proboscis-like structure (similar to that seen in the midline above the eye in cyclopia), usually 2–4 cm in length and 0.5–1.0 cm in width extending from an area just lateral to the glabella or nasal root (2,5,6,8) (Fig. 23–1). Ocular hypertelorism may be present (7,11). It usually is accompanied by agenesis of one-half of the nose (vide supra). Rarely, the proboscis is located in the midline. A bizarre example associated with holoprosencephaly and oblique facial cleft was located above the eyebrow lateral to the eye (1). In a few cases, there has been normal nose formation (4,13). Bilateral proboscides have also been described (12).

The proboscis is usually blind-ended, rarely solid. It represents the missing nostril and lateral half of the nose. The lacrimal duct, nasal bone, vomer, maxillary sinus, cribriform plate, and ethmoid cells are often missing on the involved side and there may be unilateral choanal atresia. In several cases, colobomas of the iris and upper and lower eyelids were found (3,9). The olfactory bulb is usually rudimentary on the involved side (13). An intraorbital cyst has been found (10,14).

The frequency has been estimated to be less than 1 in 100,000 live-born infants. There is no sex or racial predilection.

Embryologically, as indicated earlier, the external nose is derived from the medial and lateral nasal prominences. The median nasal prominence gives rise to half of the septum and the medial crus of the lower lateral cartilage. Each lateral nasal prominence forms the nasal bone, the lateral crus of the lower lateral cartilage, the upper lateral cartilage and the anterior end of the lower turbinal complex. The lateral nasal proboscis arises from defective formation of the lateral nasal prominence sometime during the 4th–5th week of embryonal life.

Boo-Chai (3) classified proboscis lateralis into four groups: (*1*) proboscis with normal nose, (*2*) proboscis with nasal defect, (*3*) proboscis with nasal defect plus defects of eye and adnexa, and (*4*) proboscis with nasal defect plus abnormality of eye and adnexa plus cleft lip or palate.

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Duane anomaly and cleft palate

The Duane retraction syndrome is a congenital eye movement disorder characterized by marked limitation of abduction, limitation of adduction, palpebral fissure narrowing, and globe retraction on attempted adduction. The anomaly may be unilateral or bilateral. The sixth nerve nucleus or nuclei have been found to be hypoplastic, the lateral rectus fibrotic, and the medial rectus hypertrophic.

Occasionally, Duane anomaly is associated with cleft palate. Although some patients clearly have *Klippel–Feil anomaly* or *Wildervanck syndrome* (Klippel–Feil anomaly plus), others have only the binary combination (1,2). Kirkham (3), describing patients with Duane anomaly, cleft palate, and profound hearing loss, suggested that the patients had incomplete expression of the wider spectrum. The Okihiro syndrome consists of Duane anomaly, hypoplasia of the thenar eminence, and sensorineural hearing loss (4). Gorlin et al (4) have reviewed the general problem.

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Retinoblastoma and cleft palate

Bonaïti-Pellié et al (1) reported two sibs with cleft palate and retinoblastoma. Their mother had retinoblastoma but no cleft palate. The children also had severe micrognathia. Jensen and Miller (2) noted a child with Robin sequence and retinoblastoma; and Walker (3) described identical twins, one having cleft palate and the other retinoblastoma.

References (Retinoblastoma and cleft palate)

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Cleft larynx, laryngeal web, and cleft palate

Cleft lip–palate is rarely associated with cleft larynx with or without extension into the trachea and/or esophagus (3,6–8,10). It presents with stridor, respiratory distress, or choking during feeding. Several patients have had multiple malformations (malformed pinnae, hypertelorism, tracheoesophageal fistula, congenital heart anomalies, urogenital anomalies).

Many have succumbed in early infancy. Some surely represent examples of the *G syndrome* (10). Laryngeal cleft is also seen in *Pallister–Hall syndrome*. Lim et al (8) and Tyler (11) listed other associated anomalies.

Laryngeal webs, most often (75%) glottic, may rarely be found with cleft lip–palate or submucous palatal cleft (1,2,4,5). The clinical manifestations are hoarseness, dyspnea, and inspiratory stridor. Excellent reviews of the early and recent literature have been published (9,10).

Both combinations are usually sporadic. Cleft larynx is probably a developmental field defect, occurring with separation of the larynx and esophagus and closure of the larynx.

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Oral duplication and cleft palate

The occurrence of supernumerary mouth and/or jaws is rare indeed. Although these cases have differed enough from one another to make each one relatively unique, for purposes of general discussion, we will briefly consider four forms: (*1*) single mouth with duplication of maxillary arch, (*2*) supernumerary mouth laterally placed with rudimentary mandible, (*3*) single mouth with replication of mandibular segments, and (*4*) true facial duplication (diprosopus) with or without anencephaly. Duplication, in most cases, probably arises from forking of the notochord, partial doubling of the prosencephalon or olfactory placodes, or duplication of growth centers around the stomodeal plate (40).

Our interest here will largely be limited to the first and last forms. Reduplication of the mouth and mandible alone is quite rare (1,16,29) as is duplication of the upper lip and maxilla (17). We suspect that the mildest form is doubling of the pituitary gland (27a). The child reported by Avery and Hayward (3) had hypertelorism and a single mouth with two palates, each of which was cleft. There were two arcades of maxillary teeth and a bilaterally grooved or bifid or trifid tongue. We believe that the third lobe represents the tuberculum impar (Fig. 23–2). She was also moderately mentally retarded and had tetralogy of Fallot. Many similarly affected children have been described (8,10,18,20,26,27,32,33,35,38–41). Two pituitary glands have been found in several of these children (5,32,36). Two of the children had hamartomatous tissue hanging from the palate. An unusual variant of the condition was reported by Fish (22). This child also had a nasal dermoid, a median cleft of the upper lip, and a fleshy hamartomatous mass (fat, cartilage, nevus cells) on the chin. Similar cases but without cleft palate have been described (14,23,36). Some have encephaloceles (6).

A child with two mouths, one of which had cleft palate, was documented by Bacsich et al (5). We are also aware of several examples of children with an extra tongue. The children have other stigmata which would classify them in the *oculo-auriculo-vertebral spectrum*. Some of these infants had cleft palate.

Calomeni and Jordan (12) described a male with large lower lip, doubling of tongue, cleft palate, incomplete fusion of mandibular symphysis, nasal dermoid, hirsutism, fusion defects of cervical spine, and anomalous aorta. Bartholdson et al (7) reported a male with two tongues, cleft palate, and mild ocular hypertelorism. Variants have been reported by Britto et al (8a), Chen and Noordhoff (16a), and Tharanon et al (36a).

Diprosopus is the most extreme form of facial doubling. There may be two lateral eyes, a median eye, and doubling of the hypophysis, mouth, and nose. Clefting of the lip or palate is common (37). There have been several examples, some of which have been anencephalic (2,4,9,11,15,19, 21,24,28,30,34), not all of which have cleft palate (31).

Lateral facial clefts with maxillary duplication are discussed elsewhere in this text (13,25).

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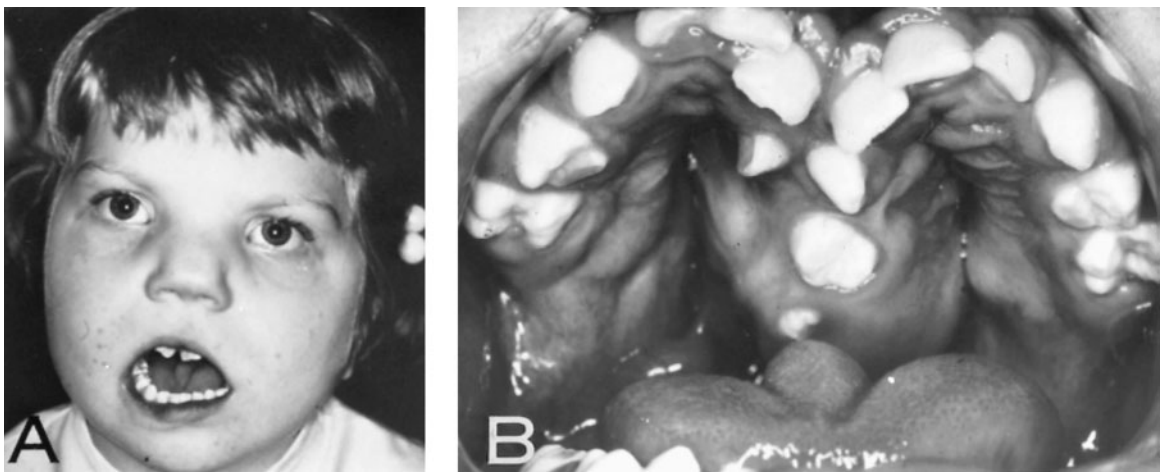
Fig. 23–2. *Oral duplication and cleft palate*. (A,B) Ocular hypertelorism, two hard palates, and two dental arches. Note two cleft palates and partial duplication of the tongue. (From JK Avery and JR Hayward, Cleft Palate J 6: 505, 1969.)



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Thoracopagous twins and cleft lip-palate

Knowledge of conjoined twins dates back to the Neolithic period (31). There are early reports from the sixteenth century (4,6). The four basic types of conjoined twins are: (*1*) thoracopagus (73%), exhibiting various degrees of thoracic fusion, (*2*) pygopagus (19%), generally fused at the level of the sacral spine, (*3*) ischiopagus (6%), in which each twin has a single leg and a common fused leg, and (*4*) craniopagus (2%), exhibiting fusion of the skulls (26).

Investigators agree that conjoined twins result from incomplete separation of a single fertilized ovum, prior to the end of the third week (21,22,34). The degree and site of incomplete splitting determine the type of conjoined twins. It has been suggested that a defect in the primitive streak, aging of the ovum, and environmental factors may play a causative role. Experimental manipulation of the primitive streak in amphibian and chick embryos has induced complete and incomplete twinning (34).

Epidemiologic studies, based on data from the Birth Defects Monitoring Program of the CDC, indicated that 81 sets of conjoined twins were found among 7,903,000 births from 1970 to 1977, representing an incidence of roughly 1 per 100,000 births. The International Clearing House for Birth Defects Monitoring Systems (13), in 1991, found 1.3 per 100,000 births. Similar findings were presented by Machin (17). Thoracoomphalopagus represented 28%, followed by thoracopagus 18%, omphalopagus 10%, parasitic twins 10%, and craniopagus 6%. There was an approximately 3F:2M sex predilection. The birth prevalence among nonwhites (16/million) is greater than among whites (9/million). No maternal age effect is found. Conjoined twins have higher rates of malformation than monozygotic separate twins. About 80% are malformed in areas other than at the union and 20% are discordant (19). Among the 81 cases, six presented orofacial clefts, five being cleft lip–palate and one isolated cleft palate (8). The six cases of clefts all occurred in thoracopagous twins, representing 7% of all cases or 13% of thoracopagus cases. Other studies have shown similar data (1,13,21,22). Thoracopagous twins thus have a higher rate of facial clefting than that expected by chance (8,10,13). Mirror image cleft lip has been reported in several instances (9,15,18–22,28) (Fig. 23–3). Discordance for cleft lip in thoracopagous twins has also been found (4a,21,22,24,26,27). Cleft palate (3,7) and cleft lip and palate (11,12) have been reported in cephalothoracopagus. Ayer and Mariappa (2) observed unilateral cleft lip and palate in both thoracopagous twins and bilateral cleft lip and palate in both faces of a diprosopic child. Similar cases were documented by Latteier and Anderson (16), Ueo et al (29), and Pavone et al (23). Ivy (14) and Vestergaard (30) described a two-headed fetus, one with cleft lip–palate and the other normal. Buchta (5) described anencephaly in thoracopagous twins with facial clefting. Cleft palate has been reported in craniopagus (31,33). Rowlatt (25) noted a double tongue and a single pituitary fossa containing two pituitary glands in thoracocephalopagous twins.

References (Thoracopagous twins and cleft lip-palate)

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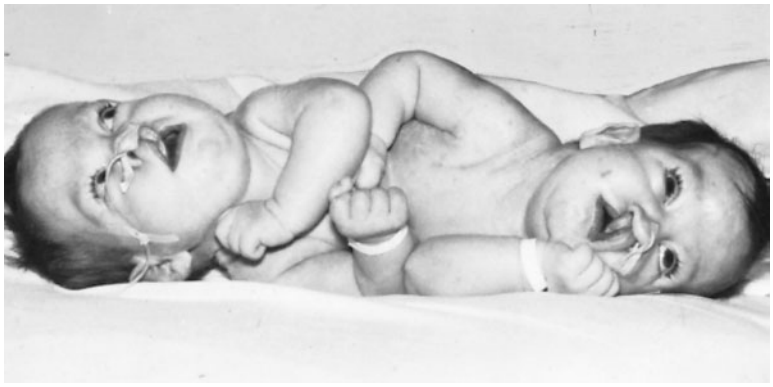

Fig. 23–3. *Thoracopagous twins and cleft lip-palate*. Conjoined twins with mirror image clefts. (From R Stellmach and G Frenkel, Dtsch Zahnarztl Z 25:28, 1970.)

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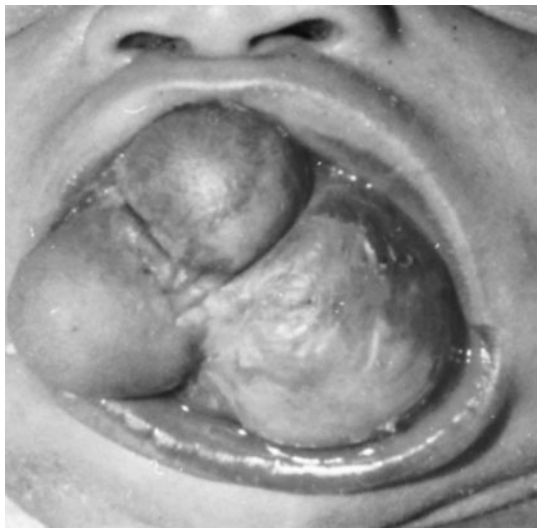
Oral teratoma, encephalomeningocele, and cleft palate

Epignathus is a term used to describe a congenital teratoma protruding from the mouth of an infant (1–9,16,18,19,25,26,34,35). It has been shown that these growths usually develop in the area of Rathke's pouch and project and fill the pharynx or oral cavity between the palatal shelves (8,34) (Fig. 23–4). Among 81 cases of teratomas seen in infancy and childhood, cleft palate was found in 1.2% (15). In general, oral teratomas constitute no more than a few percent of all teratomas (3,22). Affected infants rarely survive the neonatal period. The mass interferes with swallowing in the fetus, thereby causing polyhydramnios in the mother (6).

Erich (8), reviewing 22 cases of oral teratomas, noted that 11 were attached to the sphenoid bone, six to the lateral wall of the epipharynx near the opening of the eustachian tube, two to the soft palate, and one to the hard palate. They may even be attached to the lower jaw (13,29). The size of the teratoma varies from several centimeters to huge parasitic masses. The smaller and simpler cases are compatible with life and, as a rule, arise further back in the oral cavity (2,18). The larger examples often cause deformity of the mandible due to mechanical interference in growth (18). A teratoma of the tongue associated with cleft was reported by Grier and MacNerland (11). Congenital oral teratomas are far more common in females (6F:1M) and are benign.

Fig. 23–4. *Oral teratoma and cleft palate*. (Courtesy of CO Dummett, Los Angeles, California.)



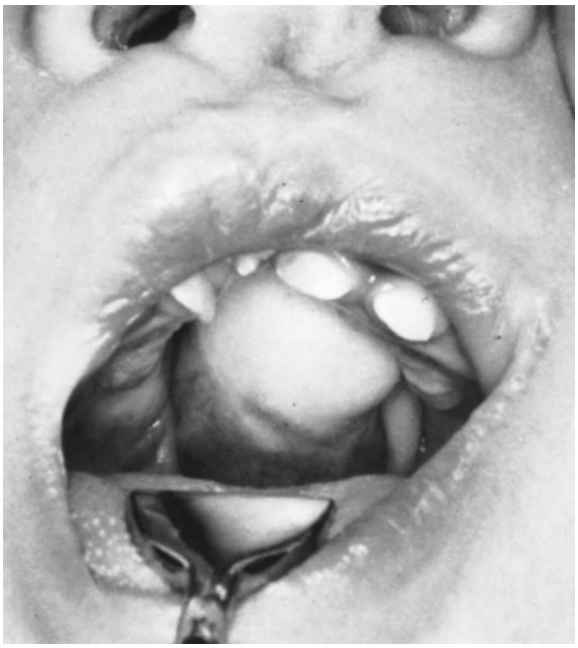


Fig. 23–5. *Encephalomeningocele and cleft palate*. Repaired cleft lip, unrepaired cleft palate.

The cleft, in most cases, has involved both hard and soft palates, but in others only the soft palate is cleft (2,18,25). The cleft may be submucosal (34). Hirshowitz et al (14) reported a case of congenital intraoral teratoma with bifid nose. The teratoma was attached to the area normally occupied by the maxillary central incisors.

Histologically, the teratomas can be solid and/or cystic. They consist of tissues derived from the three germ layers, including skin and adnexa, mucous and nonmucous secreting glands, muscle, cartilage, lymphoid tissue, nervous tissue, and bone. Some are covered with hair (1,2,5,25,35). Wynn et al (35) found a perfectly formed finger with bones, joints, and nail inside the mass. Malignant changes have not been observed in these tumors.

Cleft lip and/or palate has also been described in association with glioma or encephalomeningocele which herniates through the sphenoid bone to present in the mouth (7,10,17,20,21,26,29,32,33,36) (Fig. 23–5). The encephalocele may also present as a bulge on the frontal bone (20) and may be associated with ocular hypertelorism.

The cleft can involve both lip and palate (9,20,26,29) or only the palate (10,21,28,30,36).

Naidich et al (24), in a survey of 30 cases of basal (sphenoidal, sphenoethmoidal, ethmoidal) encephaloceles, noted that in addition to optic nerve dysplasia (rarely microphthalmia) (40%) and callosal agenesis (rarely lipoma) (40%), about 50% were associated with median cleft of the upper lip. Conversely, Grogono's (12) analysis of 50 patients with callosal agenesis showed one (2%) with median cleft upper lip. Carpenter and Druckemiller (4), surveying 45 patients with callosal agenesis, also found midline cleft upper lip, cleft lip, and cleft palate. It would, thus, appear that midline cleft of the upper lip in the presence of hypertelorism should suggest further examination of the child for midline dysraphic anomalies such as basal encephalocele, callosal agenesis, or optic nerve dysplasia (28).

Histologically, these masses are composed of glial tissue or choroid plexus (10,36) or even melanocytes (10).

References (Oral teratoma, encephalomeningocele, and cleft palate)

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Hypogonadotropic hypogonadism and cleft lip and/or palate (includes Kallmann syndrome)

Cleft lip and/or cleft palate have been reported in both males and females with low urinary gonadotropin levels due to defective release of hypothalamic gonadotropin-releasing hormone. This results in low levels of LH

and FSH, which in males, for example, normally simulate testosterone production and spermatogenesis, respectively (16). Such individuals have normal sexual differentiation, but females manifest oligomenorrhea, poor breast development, and scanty axillary and pubic hair while males have infantile testes with cryptorchidism, aspermia, and absent Leydig cells. About 60% of males have gynecomastia and eunuchoid habitus, and about. Forty percent exhibit anosmia (Kallmann syndrome, olfactogenital dysplasia) (1,3,7–10,12,13,17); others do not (14,15). The anosmia results from absence of olfactory tracts and bulbs (5). Conversely, it has been estimated that about 15% of patients with Kallmann syndrome have clefts. About 20% have sensorineural hearing loss (2). Kallmann syndrome has several patterns of transmission: autosomal dominant, autosomal recessive, and X- linked (17), the last being the most frequent form. It has been estimated that there are 5M:1F. The X-linked form has been mapped to Xp22.3 (6,11). The gene is involved in neuronal cell migration, there being a common developmental pathway for olfactory neurons and those synthesizing gonadotropin-releasing hormone. Some carrier females exhibit anosmia (4,12). See *holoprosencephaly* for related material.

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Hypophyseal short stature and cleft lip-palate

Francés et al (2) and other (3,5–10) described cleft lip and/or palate associated with either panhypopituitarism or isolated growth hormone deficiency. A converse study was done in which 200 children with isolated clefts of the lip, palate, or both were examined. Among those that were short, about 30% showed partial or complete growth hormone deficiency. However, normal values were found by Köster et al (4) in an unselected group of 200 patients with clefts. The second patient reported by Francés et al (2) appeared to have some degree of the premaxillary agenesis form of holoprosencephaly.

The patient described by Zuppinger et al (11) also exhibited colobomata of the choroid and optic nerve with resultant retinal detachment. Brewer (1) described bilateral cleft lip and agenesis of the pituitary gland. Also see *hypogonadotropic hypogonadism and cleft lip and/or cleft palate* and *holoprosencephaly*.

Growth hormone deficiency may be found in association with a number of congenital malformations: *anencephaly, holoprosencephaly, frontonasal malformation, Rieger syndrome*, microcephaly, *single central incisor, EEC syndrome*, and septo-optic dysplasia.

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Amelia and cleft lip-palate

Centa and Rovei (2) described amelia, micrognathia, and cleft palate in a child described as having the Robin sequence. Holthusen (6) reported a less severely affected child. The arms, femurs, and fibulas were absent. Perhaps this case should be classified with absent femurs and cleft palate. Frantz and O'Rahilly (3) noted the association between amelia and cleft lip and cleft palate. Thomas and Donnai (10), Yim and Ebbin (11), and Froster et al (4) reported brachial amelia with cleft lip–palate and forebrain anomalies (encephalocele, hydrocephaly, holoprosencephaly) (Fig. 23–6).

Zimmer et al (12), Gershoni-Baruch et al (5), and Kosaki et al (7) described tetra-amelia, lung abnormalities, hydrocephalus, midfacial clefts, absence of ears and nose, and anal atresia as an X-linked recessive syndrome affecting seven male children in an Arab-Muslim family. This has been termed "Zimmer phocomelia"(7). There is evidence of sex reversal (11). Rosenak et al (9) also reported male and female sibs with tetra-amelia, lung hypo–aplasia, and anomalies of the pulmonary arteries. Başaran et al (1) noted male sibs with tetra-amelia, cleft lip–palate, lung agenesis, and cardiovascular malformations. The tetraphocomelic infant with neural tube defects and facial clefts had an unidentified condition (9).

One must exclude *odontotrichomelic syndrome* and the *Ohdo syndrome (unusual facies, tetra-amelia, congenital hypothyroidism, and severe mental retardation)*. Michaud et al (8) reported autosomal recessive amelia unassociated with other anomalies.

References (Amelia and cleft lip-palate)

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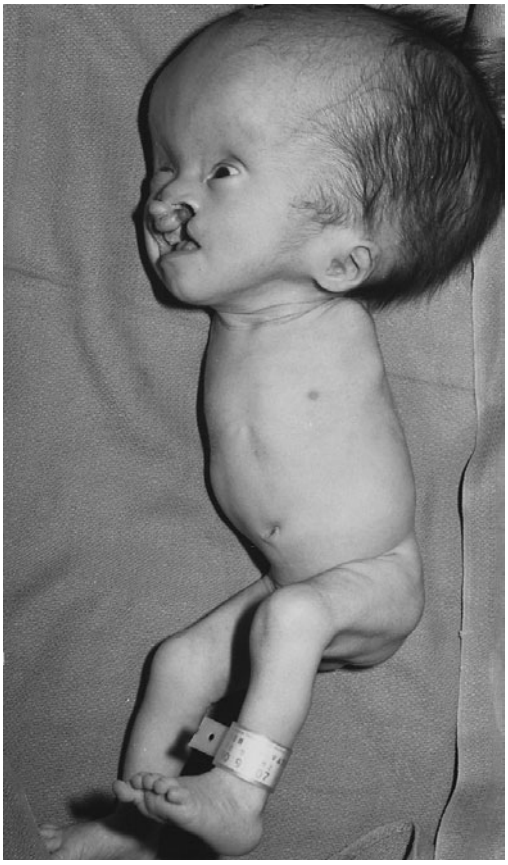

Fig. 23–6. *Amelia and cleft lip-palate*. Complete brachial amelia with hydrocephaly and bilateral cleft lip-palate. [From DKC Yim and AJ Ebbin, Syndrome Ident 8(1):3, 1982.]

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Cleft lip-palate and congenital heart defects

Clefting can be associated with a wide spectrum of congenital heart defects. Boeson et al (2) noted 11 cases of cleft lip and/or cleft palate among 516 patients with congenital heart anomalies. The cardiac defects were of various types, the most common being ASD and VSD. Rabl and Schulz (8) noted the association of cleft lip–palate with pulmonary valvular atresia and septal defect in twins. They also described two sibs with clefts. Geis et al (4) found that 6% of their cleft lip–palate population had congenital heart defects of various forms. Baetz-Greenwalt et al (1) found 14% of infants with hypoplastic right-sided heart to have cleft palate.

Pradat (7), in examination of 2618 infants with major heart malformations, noted that 73 had facial clefts. No specific heart anomalies were associated.

Shah et al (10), in an extensive review of congenital cardiac malformations in children with facial clefts, found no consistent pattern of heart anomalies. Among 32 children with cleft lip or cleft palate who died, cardiac anomalies were present in 66%. Seventeen had cleft palate, six had Robin sequence, four had tetralogy of Fallot, four had tricuspid stenosis, three had coarctation of the aorta, and three had ASD of the secundum type. There were no cases of transposition of the great vessels or examples of a single ventricle among the group. Similar observations were made by Okada et al (6), who also noted that the Robin sequence was associated with coarctation of the aorta and tetralogy of Fallot. It is quite possible that some had *velocardiofacial syndrome* (9).

An equally diverse group with congenital heart anomalies and hypoplastic, aplastic, or triploid thumbs is described in Holt-Oram syndrome (3,5). The reader is also referred to *cleft lip-palate and extrathoracic ectopia of the heart*. Shamberger and Welch (11) described tetralogy of Fallot, omphalocele and cleft palate.

References (Cleft lip-palate and congenital heart defects)

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Enlarged parietal foramina and cleft lip and/or palate

Enlarged parietal bone defects (Catlin marks, cranium bifidum), usually bilateral, frequently represent an isolated autosomal dominant trait. They may be associated with clefting of the lip or palate with a possibly greater-than-chance frequency.

The nature of these cranial defects has been discussed by numerous authors (7–11). The fenestrae are usually symptom free, but occasionally there is associated headache (10). The frequency of the parietal bone defects would appear to be less than 1 in 25,000 individuals. Over 300 cases have been described. Miscellaneous other malformations may be associated with enlarged parietal fenestrae. Cases in which clefting has been noted are those of Irvine and Taylor (5), James (6), and Hollender (4). In the case of Hässler (3), a maternal uncle had cleft lip. Parietal foramina may be seen in *cleidocranial dysplasia* (1,2), probably in *FG syndrome* and *Rubinstein-Taybi syndrome*, and in *enlarged parietal foramina, craniofacial anomalies, mental retardation, and multiple exostoses (Potocki–Shaffer syndrome, del11p11.2p12 syndrome)*. Functional haploinsufficiency of the human homeobox gene *ALX4* causes defects in skull ossification (7a,13). Haploinsufficiency of *MSX2* also causes parietal foramina (12).

References (Enlarged parietal foramina and cleft lip and/or palate)

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Extrathoracic ectopia of the heart and cleft lip-palate

Millhouse and Joos (18) tabulated reported cases of extrathoracic ectopia of the heart and found cleft lip and/or cleft palate in 21 of 27 cases (Fig. 23–7). Our independent tally does not confirm their data; but among the 100 cases that we reviewed, there is surely a high correlation between ectopia of the heart and cleft lip–palate (4,5,9,12,14,15,16,19,20,24,26) or cleft palate (2,6,13). Many examples clearly represent the amniotic band sequence following early rupture of the chorion or yolk sac (1,3,6–8, 10,11,21,23). See *amnion rupture sequence* for detailed discussion. In one case there was cleft mandible (9). Cleft sternum, which may represent the same anomaly, has been described with cleft lip (9). Cleft of the upper sternum may be seen with facial hemangiomas and supraumbilical raphe.

Ectopia cordis may be cervical (9%); thoracic (40%); thoracoabdominal (Cantrell syndrome) (38%); or abdominal (11%). Cantrell syndrome is a midline developmental field defect of sternal clefts, anterior diaphragmatic deficiency, ectopia cordis, ventral wall deficiencies, congenital heart anomalies, and pericardial defects (14). Somewhat different values were tabulated by Shao-Tsu (22). Diagnosis can be made by ultrasound (17,25).

References (Extrathoracic ectopia of the heart and cleft lip-palate)

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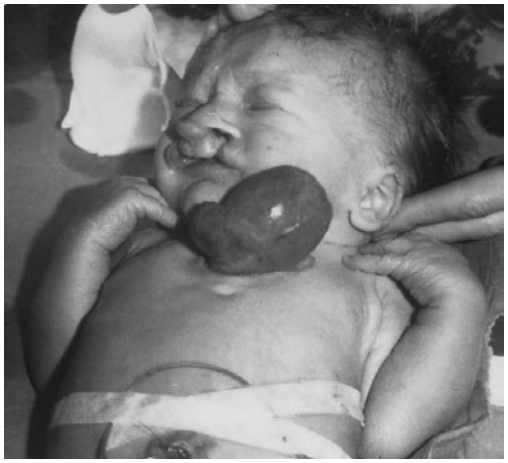
Fig. 23–7. *Extrathoracic ectopia of the heart and cleft lip-palate*. (A,B) Note bilateral cleft lip-palate and extrathoracic position of the heart. (A from F Didier et al, Z Kinderchir 14:252, 1974. B from ER Meitner, Anat Anz 107:222, 1959.)



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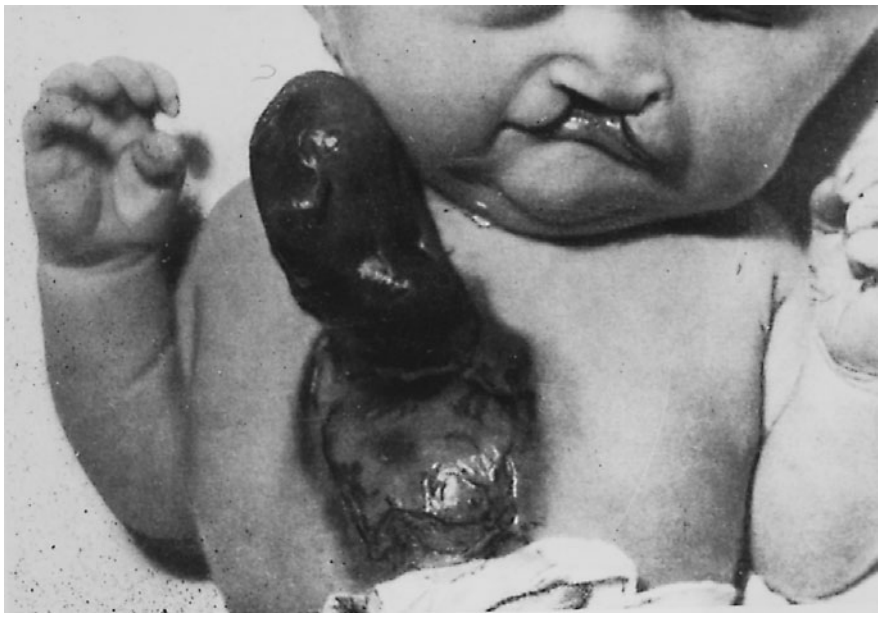

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Sprengel shoulder and cleft palate (Hodgson-Chiu syndrome)

Hodgson and Chin (1) reported apparent autosomal dominant inheritance of elevated scapula (Sprengel deformity) with cleft palate. One member had Klippel–Feil syndrome. Probably this family represents variable expression of the latter syndrome rather than being a separate entity. Another familial example is that of Monier et al (2).

References [Sprengel shoulder and cleft palate (Hodgson-Chiu syndrome)]

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Syngnathia and cleft palate

A combination of cleft palate and soft tissues or bony adhesions between the upper and lower jaws has been reported (3,9,12,14,22,26,28–31) (Fig. 23–8). Other infants with syngnathia have not had cleft palate. Presumably, the primary defect is fusion between gingivae or alveolar processes that in turn prevents the tongue from dropping and prevents closure of the palatal shelves. It may also be related to the small size of the mandible (micrognathia). In cases of firm bony fusion, the temporomandibular joint is usually ankylosed because movement is necessary during the developmental period (28). Bony union (1,13,14,26) is much rarer than fibrous union (3,9,23).

Since not all cases have been well documented, it is difficult to know how many are legitimate cases. Nearly all have been isolated examples. Gassner (12) described the occurrence in mother and child, while Sternberg et al (28) reported the combination in sibs with consanguineous parents. The surviving child also had CLP. Von Domarus and Scheunemann (32) described sibs with congenital temporomandibular ankylosis. In a few cases, there has been congenital fusion of the jaws but no associated anomalies (17–19,27). Shah (25) reviewed cases of interjaw fusion. Some examples may represent some variant of *oculo-auriculo-vertebral spectrum* (2,4,7).

Dawson et al (8) has attempted to classify syngnathia into (a) type 1-simple syngnathia and (b) type 2-complex syngnathia which they further divide into those with aglossia and those with agenesis or hypogenesis of the mandible. We suspect that this is oversimplification of a very heterogeneous group of conditions.

Syngnathia also occurs with *popliteal pterygium syndrome* (30), *Van der Woude syndrome* (30), and *glossopalatine ankylosis* (6,11,24).The reader is also referred to buccopharyngeal membrane persistence (15). Absence of the soft palate is seen in *agnathia* (5,21). Fusion between the coronoid process of the mandible and the zygoma may occur (16,20). The patient of Dobrow (10) had bilateral iris colobomas and microphthalmia in addition to syngnathia.

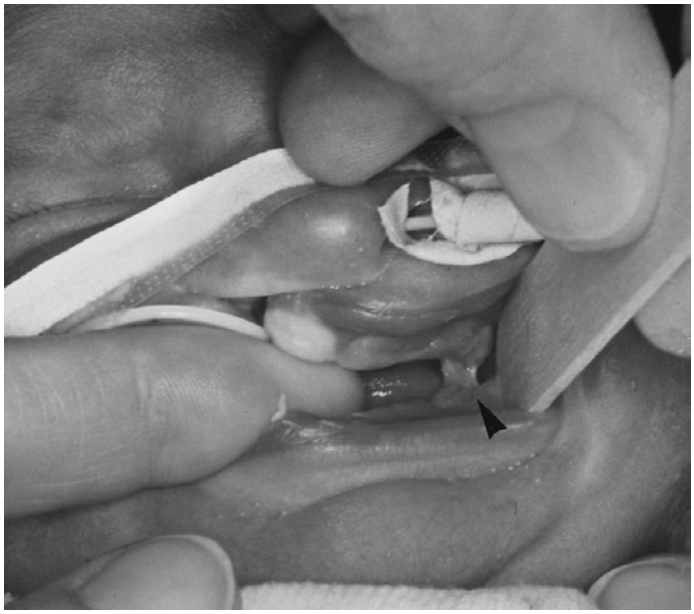

Fig. 23–8. *Syngnathia and cleft palate*. Arrow points to attachment between alveolar ridges. (From P Randall, Plast Reconstr Surg 74:686, 1984.)

References (Syngnathia and cleft palate)

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Triophthalmia and facial clefting

Tayel et al (4), in 1998, reported a Libyan male infant with dolichocephaly, porencephaly, facial asymmetry, micrognathia, cleft lip-palate, and VSD. The child had an additional eye unilaterally lateral to one of the eyes (1).

Several genes involved in eye development have been identified. The *PAX6* gene appears to play a major role. Nerve growth factor and TGFβ also play a role. Retinoic acid and its receptors in high concentration can induce duplication of eye components in animals (2,3).

References (Triophthalmia and facial clefting)

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Aplasia of the trochlea and cleft palate

Mead and Martin (1) described cleft palate in a patient who also had aplasia of the trochlea. Conceivably the association is one of chance. However, because of the rarity of aplasia of the trochlea, the finding may be significant.

Reference (Aplasia of the trochlea and cleft palate)

1. Mead CA, Martin M: Aplasia of the trochlea in an original mutation. J Bone Joint Surg Am 45:379–383, 1963.

Cleft lip-palate and supernumerary nostrils

Patients with as many as four asymmetric nostrils have been reported among those with cleft lip-palate. The extra nostrils connect to the ipsilateral nasal cavity. Presumably this results from an accessory olfactory pit or pits (4,5,8,9). Asymmetric eyelids were noted as well (9). There have been several examples of supernumerary nostrils unassociated with cleft lip and/or palate (1–3,6,7).

References (Cleft lip-palate and supernumerary nostrils)

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Cleft lip and prune belly

Matsuzaki et al (1) described a female infant with deficiency of abdominal musculature and cleft lip. In addition, she had an enlarged clitoris. Association may be adventitious.

Reference (Cleft lip and prune belly)

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Chapter 24
Syndromes with Unusual Facies: Well-Known Syndromes

Frontonasal malformation (frontonasal dysplasia, median cleft face syndrome)

Frontonasal malformation, probably first described by Hoppe (31) in 1859, consists of hypertelorism, broad nasal root, lack of nasal tip, widow's peak, and anterior cranium bifidum occultum. Associated defects may include midline clefting of nose and/or upper lip, rarely, the palate, and defects of the alae nasi (Figs. 24–1 to 24–5).

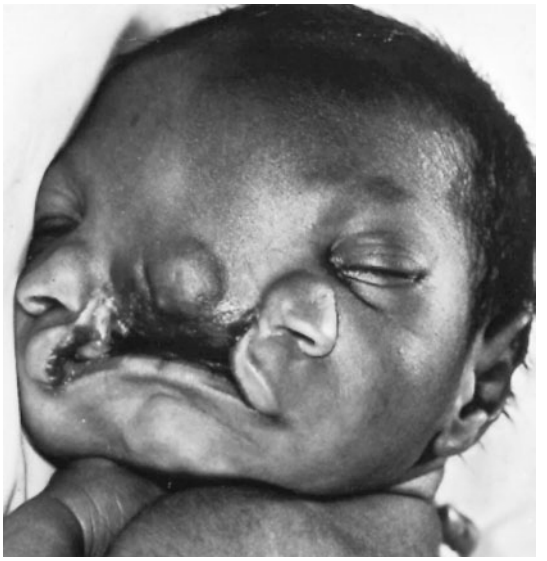
The term *median cleft face syndrome* was introduced by DeMyer (12) in 1967 to describe the disorder; Rohasco and Massa (53), in 1968, proposed *frontonasal syndrome*, and Sedano et al (56), in 1970, employed the term *frontonasal dysplasia*. Since then, the term frontonasal malformation (FNM) has been suggested (55,61) based on the premise that the observed pattern of anomalies constitutes a single developmental field defect (55). If the nasal capsule fails to develop properly, the primitive brain vesicle fills the space normally occupied by the capsule, thus producing anterior cranium bifidum occultum, a morphokinetic arrest in the positioning of the eyes, and lack of formation of the nasal tip. The widow's peak scalp-hair anomaly results from ocular hypertelorism, since the two fields of hair-growth suppression are also farther apart than usual (9,57).

Experimental models have been produced by various teratogenic agents in animals. Burck and Sadler (4) concluded that cell death in the frontonasal process midline mesenchyme and in the neural epithelium and/or increased facial width were underlying factors in diazo-oxo-norleucine-induced median cleft face in mice. Darab et al (10), studying methotrexate-induced median cleft face in mice, implicated damage to blood vessels in the frontonasal process (dilated and congested blood vessels) and to distension of the developing brain. Interestingly, the number of instances of twinning is greater in families with frontonasal malformation than in the general population (56). We have no explanation for this phenomenon.

Most cases of frontonasal malformation are sporadic (12,56), although it has been found in identical twins (A Perez Aytes et al, personal communication, 1989) and in a mother and two of her children (22). However, most reports citing familial aggregation likely represent other entities that have frontonasal malformation as a component manifestation; indeed, there are several case reports that do not represent examples of FNM (2,3,5,14–18,20,38,44,56,61,63).

Toriello (61) described a distinct subgroup associated with a severe form of frontonasal malformation. This syndrome includes epibulbar dermoids, agenesis of the corpus callosum, Dandy-Walker malformation, tibial aplasia, and bilateral polydactyly of halluces. The facies is shown in Fig. 24–2A; the halluces in Fig. 24–5. This combination in part or in full has been reported by several other authors (5,14–16,20,42,56,61,64,65). Warkany et al (65) described two half-sisters with this combination, and parental consanguinity (15) has been reported.

The *oculoauriculofrontonasal syndrome* [5,16(case 2),25,28,29,42, 43,46] includes manifestations of the oculo-auriculo-vertebral sequence, including epibulbar dermoids and preauricular tags, and FNM. *Fronto-facio-nasal dyplasia* (23,50,67) includes variable combinations of cerebral, ocular, nasal, and other defects, and may itself be heterogeneous. For example, Temple et al (60) described five children with iris coloboma, mental retardation, and other anomalies in some, whereas Reardon et al (50) described children with coloboma, marked alar deficiency, and



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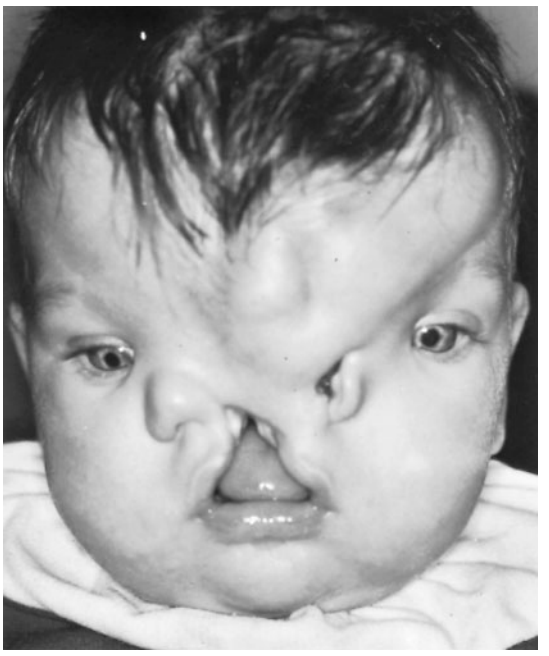
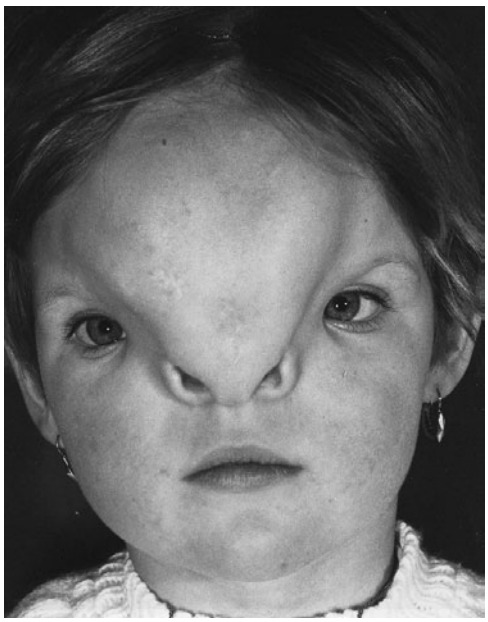


B

Fig. 24–1. *Frontonasal malformation*. (A) Most extreme example showing marked hypertelorism, separated halves, rectangular oronasal opening, absence of premaxilla, (B) Hypertelorism, frontal encephalomeningocele, separated nostrils, cleft lip-palate. (From W DeMyer, Neurology 17:961, 1967.)



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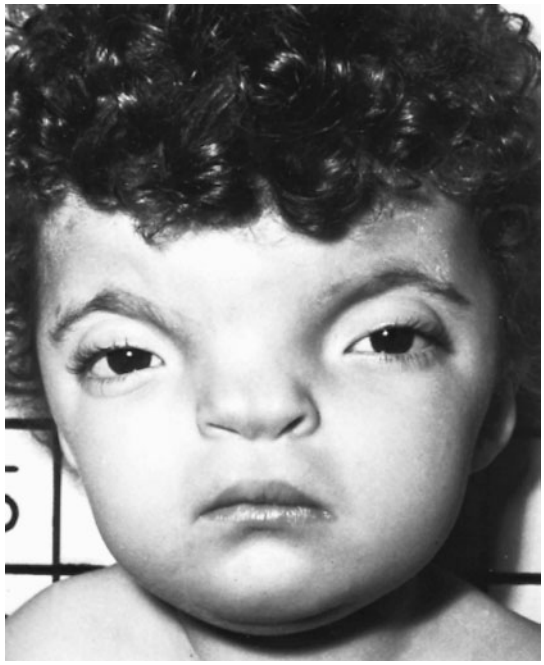

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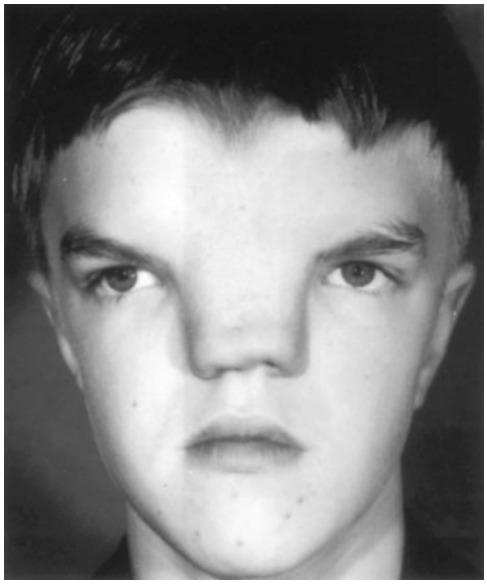
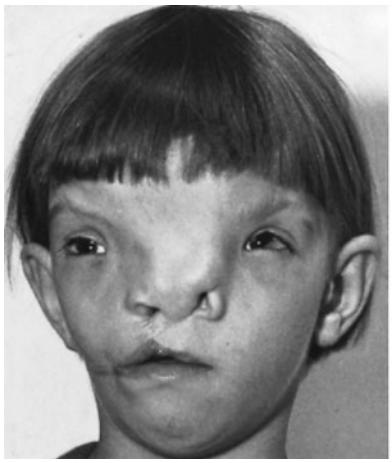


B

Fig. 24–2. *Frontonasal malformation*. (A) Note similarity to embryonal face. (B) Hypertelorism, broad nose. (C) Least severely affected example. (A,B courtesy of P Tessier, Paris, France. C courtesy of S Cocuzza and E Zoratto, Torino, Italy.)



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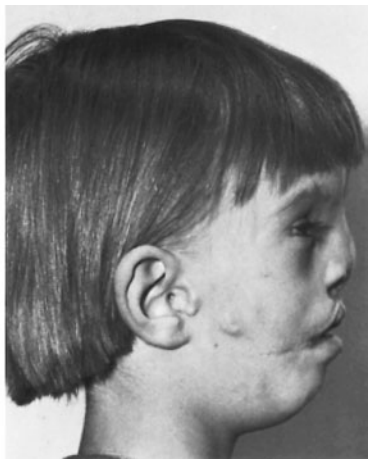
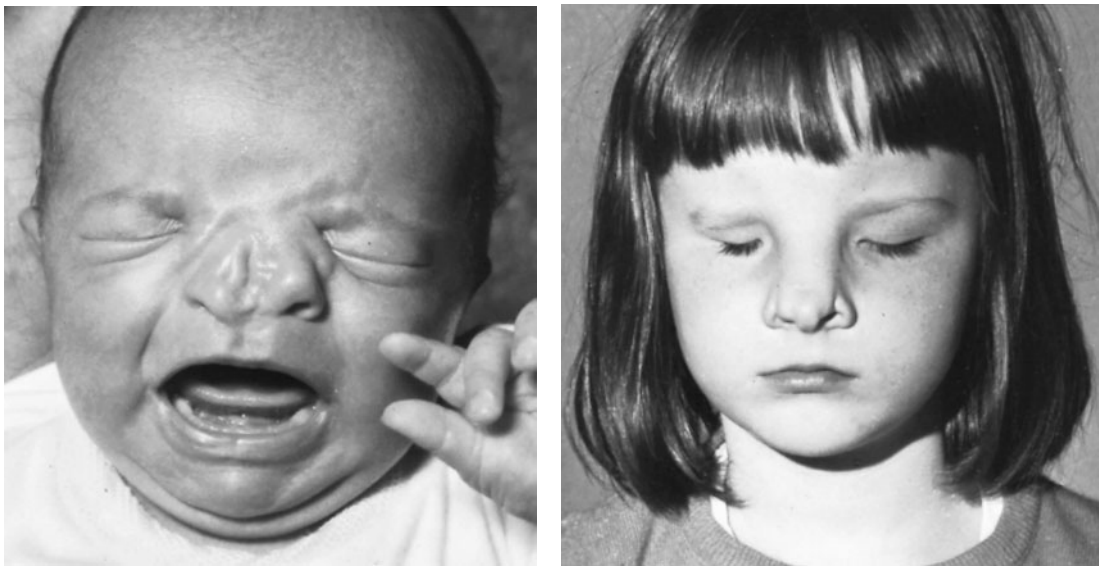


B

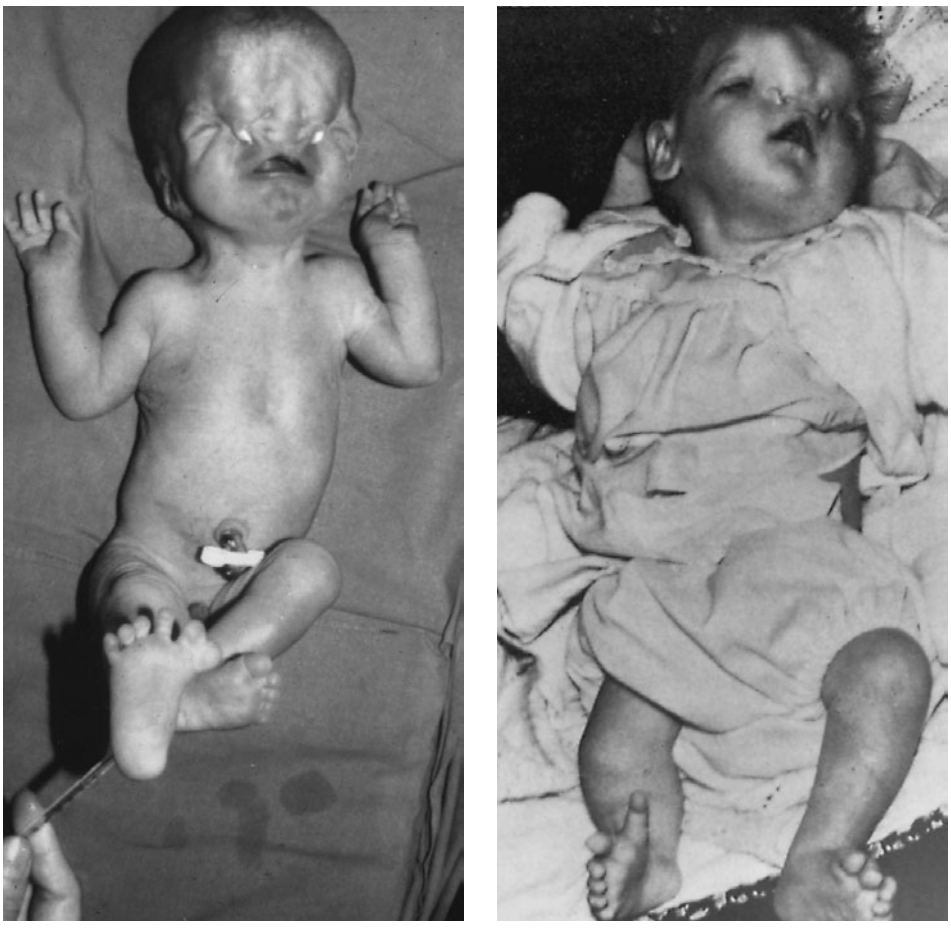
Fig. 24–3. *Frontonasal malformation, oculoauriculofrontonasal type*. (A,B) Facies similar to that in Fig. 24–2 but with coloboma of upper left eyelid and epibulbar dermoid, repaired cleft lip, repaired macrostomia, remnants of ear tags (oculo-auriculo-vertebral spectrum). (From A Fleischer-Peters, Dtsch Zahnarztl Z 24:545, 1969.)



A B

Fig. 24–4. *Frontonasal malformation*. (A) Hypertelorism, bifid nose. (B) Colobomas of nostrils, wide nasal bridge, anophthalmia on right, microphthalmia on left. When the eyes are involved, this is called *fronto-facio-nasal* type. (A from W DeMyer, Neurology 17:961, 1967.)

normal cognitive development. For a review, see Toriello et al (62). DeMoor et al (11), Meinecke and Blunck (42), and Meguid (41) described children with FNM, heart defects, and other anomalies. All cases were sporadic. Guion-Almeida and Richieri-Costa (27) and Masuno et al (40) reported children with FNM, macroblepharon, eyelid colobomas, macrostomia, ear anomalies, submucous cleft palate, mental retardation, and Dandy–Walker anomaly, which they believe represented a provisionally unique syndrome. The heterogeneity of FNM is consistent with DeMyer's (12) observation that when extracephalic anomalies occur or when hypertelorism is severe, mental deficiency appears to be increased.



A B

Fig. 24–5. *Frontonasal malformation*. (A,B) Shortening of right tibia, preaxial polydactyly. (From WC Edwards et al, Am J Ophthalmol 72:202, 1971.)

Conversely, when extracephalic anomalies are absent and hypertelorism is mild, the probability of mental deficiency is low.

There have been a few reports of chromosomal anomalies in those with FNM. Chen et al (7) described FNM in an individual with *dup(2q) syndrome*. Fryns et al (24) noted a child with FNM and an apparently balanced translocation t(15;22)(q22;q13) (although this individual may have had craniofrontonasal syndrome), and Stevens and Qumsiyeh (58) reported a complex translocation involving chromosomes 3,7, and 11. Stratton and Payne (58a) and Kirkpatrick and Pauli (36) reported deletion of 22q11.

Facies. The clinical appearance of the face has been classified on a somewhat different basis by DeMyer (12) and Sedano et al (56). Facies can be graded from mild to severe (Figs. 24–1 to 24–5), although it should be recognized that the variability seen in FNM simply constitutes a continuum of the basic developmental defect.

Eyes. Hypertelorism is a constant feature. Secondary telecanthus may be observed in severe examples. Roarty et al (51) found that patients with moderate to severe FNM had refractive errors and/or strabismus. The presence of epibulbar dermoids (9,14), congenital cataracts (56), iris colobomas (36,60), upper eyelid colobomas (16,20,57), and symblepharon has been described, but this should suggest that this could represent a multiple anomaly syndrome of which FNM is but one manifestation.

Nose. In severe cases, the nose may be flattened with widely spaced nostrils and broad nasal root. In other cases, clefting of the nose or notching or clefting of the nasal alae may be seen. When notching occurs bilaterally, the nose appears square (Fig. 24–2A). Nasal tags have also been noted (53).

Ears. Preauricular tags (4), low-set ears, absent tragus, and conductive hearing loss (55) have been reported, although here again the presence of these anomalies could suggest the presence of a syndromic cause of FNM and observed anomaly.

Central nervous system. Mental deficiency has been found occasionally (14,20,64). Although Hori (32) described two hypophyses, this case is likely an example of facial duplication.

Radiographic findings. Anterior cranium bifidum (33) and hypoplastic frontal sinuses are seen (34). Other findings include absence of corpus callosum (1,3,12,16,20,32,58,59,63,65), but in some of these cases, one of the above-described syndromes may be present. Approximately 50% of those with more severe facial phenotype, on MRI and CT examination, have dense calcification of the falx and interhemispheric lipoma (42). The latter is sometimes mistaken for callosal agenesis (46). Hydrocephaly (56), occipital encephalocele (45), early occlusive anterior and middle cerebral artery disease (RJ Gorlin and MM Cohen Jr, personal observation, 1990), as well as mild (pseudohemispheric) holoprosencephaly (54) have been documented.

Other findings. Clinodactyly (12,66), brachydactyly (RJ Gorlin and MM Cohen Jr, personal observation, 1990), parietal foramina (45), micropenis (20), cryptorchidism (12,56), tetralogy of Fallot (11,27), and other anomalies (12,52,56) have been documented. The presence of other findings should prompt a search for other manifestations indicative of an underlying syndrome.

Oral manifestations. Median cleft of the upper lip was present, especially in the more severe type, as noted above (56). Rarely, cleft lip and/or palate is observed (32,56).

Differential diagnosis. The same facial phenotype may be observed with large anterior encephalocele, hamartoma, frontal lipoma, frontal teratoma, and intracranial cyst (28,30,39). Bifid nose may occur without hypertelorism, and familial instances are known (19,66). Since epibulbar dermoids, and sometimes upper eyelid colobomas and preauricular tags, may occur in association with frontonasal malformation, differentiation from *oculo-auriculo-vertebral spectrum* should be kept in mind. *Fronto-facio-nasal dyplasia* should be considered in differential diagnosis because of clinical similarities in facial appearance (see above). This condition apparently has autosomal recessive inheritance. Keith and Macomber (35) described a case of "hypertelorism" occurring in two sisters that we cannot classify among known conditions. Fragoso et al (18) reported a patient who, in addition to frontonasal malformation, exhibited fusion of the second and third cervical vertebrae and pedal postaxial polydactyly. It was labeled frontonasal malformation in combination with Klippel-Feil anomaly. The patient was female and may represent an example of *craniofrontonasal syndrome*, although craniosynostosis was not mentioned. Various conditions recently isolated from the frontonasal malformation pool should be excluded such as autosomal dominant *Greig cephalopolysyndactyly (13), Opitz BBB/G syndrome, Sener syndrome, acro-fronto-facio-nasal dysostosis, Teebi hypertelorism syndrome, Aarskog syndrome, Waardenburg syndrome, craniofrontonasal syndrome*, and *Pai syndrome* (28). *Cerebro-fronto-facial syndrome* is discussed in Chapter 25.

Laboratory aids. Frontonasal malformation has been diagnosed prenatally (21).

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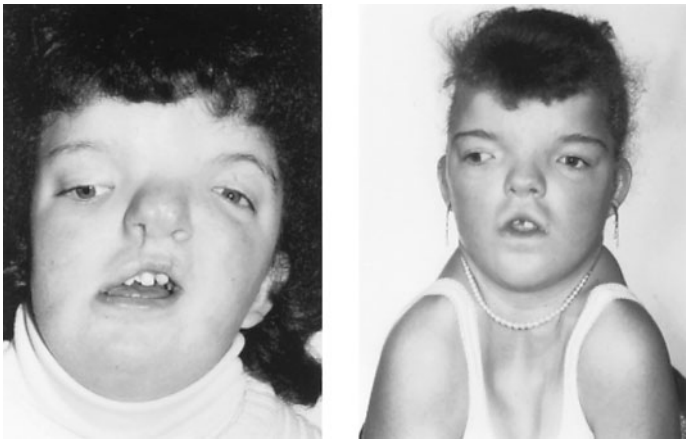
Craniofrontonasal syndrome

A subpopulation of frontonasal malformation patients was identified by Cohen in 1979 (1) as representing a heritable condition which he called *craniofrontonasal dysplasia*. An earlier series of patients was reported in 1977 by Reich et al (29). The syndrome consists of frontonasal malformation, craniosynostosis (especially including the coronal suture), and various skeletal and soft tissue abnormalities. To date over 100 cases have been identified (1–15,19,22–39,41,43). The mothers and daughters reported by McCowatt Montford (17), Ogilvie and Posel (22), and Friede (8) probably had the disorder, although craniosynostosis was not specifically mentioned. The patients with pre- and postaxial polydactyly, hypertelorism, and coronal synostosis reported by Kwee and Lindhout (16) probably have Greig cephalopolysyndactyly syndrome in which craniosynostosis can occur, albeit with low frequency. The female patient reported by Fragoso et al (7) with frontonasal dysplasia and Klippel–Feil anomaly probably had craniofrontonasal dysplasia; however, craniostenosis was not mentioned. The family with three affected males and three affected females reported by Morris et al (20) may represent some other condition. In this family, short stature, delayed bone age, shawl scrotum, and hypospadias were prominent features in affected males, and only one of three affected females had craniosynostosis. Natarajan et al (21) described affected male sibs with normal parents; the presence of multiple joint contractures and generalized hirsutism in these males suggests that they have some other condition. The reader is referred to several reviews (9,34,42).

X-linked dominant inheritance has been observed through three generations (9,15,27,32,37,38) but, uniquely, females are affected much more frequently and usually more severely than males (9,36), who usually have only hypertelorism and exotropia and are probably underascertained. The gene has been mapped to Xp22 (6,27a). However, there have been a few males with more severe manifestations than their female relatives (4,12) and a few markedly affected male examples (2,4,12). Most affected males represent new mutations. Metabolic interference analogous to the T-semilethal allele of the mouse T locus has been proposed (27,32–38).

Craniofacial features. Craniofacial features include brachycephaly, unilateral or bilateral coronal synostosis (50%), frontal bossing, hypertelorism (95%), and broad nasal bridge with broad bifid nasal tip (55%). An increased bony interorbital distance noted radiographically is essential to diagnose the "carrier male." Widow's peak, strabismus, and downslanting palpebral fissures have been frequently reported. The orbits are asymmetric in 50%. Abnormal ocular movements and/or squint are common (23). Unilateral or bilateral cleft lip has been



A B

Fig. 24–6. *Craniofrontonasal syndrome*. (A) Facial asymmetry, hypertelorism, exotropia, downslanting palpebral fissures, bifid nasal tip, and repaired bilateral cleft lip. (B) More mildly affected sister of A showing exotropia, hypertelorism, and hypermobility of shoulder girdle. (From E Grutzner and RJ Gorlin, Oral Surg Oral Med Oral Pathol 65:436, 1988.)

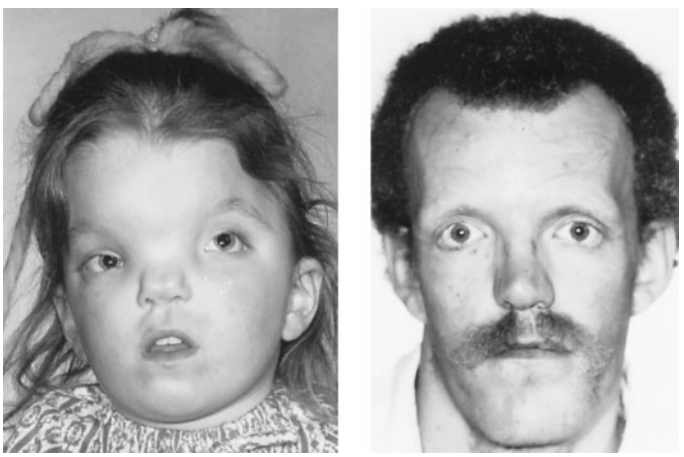
observed in a few cases (6). Other findings have included highly arched palate, malocclusion, and pterygium colli (1,5–9,15,18,20,22–27,32–38) (Figs. 24–6 and 24–7).

Limbs. Longitudinally split nails have been observed in 40% (Fig. 24–8). Other findings have included hyperextensible joints (which require supportive measures), broad great toes, partial soft tissue syndactyly, short fifth fingers, clinodactyly, gap between the first and second toes, long fingers and toes, and single transverse palmar creases (1,5–9, 15,23–27,35,38). The lower limbs are asymmetrically short in 15% (34).

Other findings. The hair is thick, wiry or curly in 30%, with this manifestation developing during childhood. There is unilateral breast hypoplasia in 50%. High and prominent scapulae, small or absent clavicles (25%), scoliosis, vertebral anomalies, pectus excavatum, axillary pterygia (10%), and other minor skeletal defects have been recorded (23,34).

Intelligence. Although normal intelligence has usually been found, mental deficiency has been noted in a few females (9,15).

Fig. 24–7. *Craniofrontonasal syndrome*. (A) Similar facies in unrelated patient. (B) Male hemizygote. Note only hypertelorism, mild downslanting palpebral fissures, and repaired cleft lip. (From E Grutzner and RJ Gorlin, Oral Surg Oral Med Oral Pathol 65:436, 1988.)



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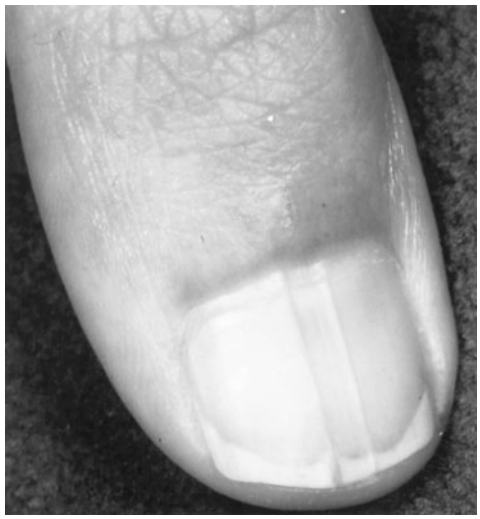

Fig. 24–8. *Craniofrontonasal syndrome*. Vertical striping of nail. (From E Grutzner and RJ Gorlin, Oral Surg Oral Med Oral Pathol 65:436, 1988.)

Differential diagnosis. *Frontonasal dysplasia, fronto-facio-nasal dysplasia, Greig cephalopolysyndactyly syndrome*, and other craniosynostosis syndromes must be excluded. *Brachycephalofrontonasal dysplasia* (*Teebi hypertelorism syndrome*) has some resemblance to craniofrontonasal dysplasia but without bifid nose, craniosynostosis, pterygium colli, rounded sloping shoulders, or nail abnormalities. Some patients have shawl scrotum (40). This may be the same disorder as that described by Morris et al (20) as their two male patients also had shawl scrotum.

References (Craniofrontonasal syndrome)

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Teebi hypertelorism syndrome (brachycephalofrontonasal dysplasia)

Teebi (4), in 1987, described an apparently new autosomal dominantly inherited syndrome with features of craniofrontal dysplasia but with normal or slightly broad nasal tip and without evidence of craniosynostosis or nail abnormalities. The face was round with prominent forehead, widow's peak, pronounced hypertelorism, mild downslanting palpebral fissures, very heavy and broad eyebrows, ptosis of lids, broad and/or depressed nasal bridge, short nose, fleshy ear lobules and/or prominent anthelix, hypoplastic maxilla, long deep philtrum, dental malocclusion, horizontal thin upper lip and/or pouty lower lip, and prominent lower jaw (Fig. 24–9). Additional cases have since been described (2,3,5,6). It may be the same as the disorder reported by Morris et al (1).

The hands are small and broad with mild interdigital webbing and clinodactyly of the fifth fingers. All of the males had a shawl scrotum. Growth and cognitive development are normal. Heart defects are an occasional manifestation (2,5,6). Differential diagnosis includes *Aarskog syndrome* and *Opitz BBB/G syndromes*, as well as *craniofrontonasal syndrome*.

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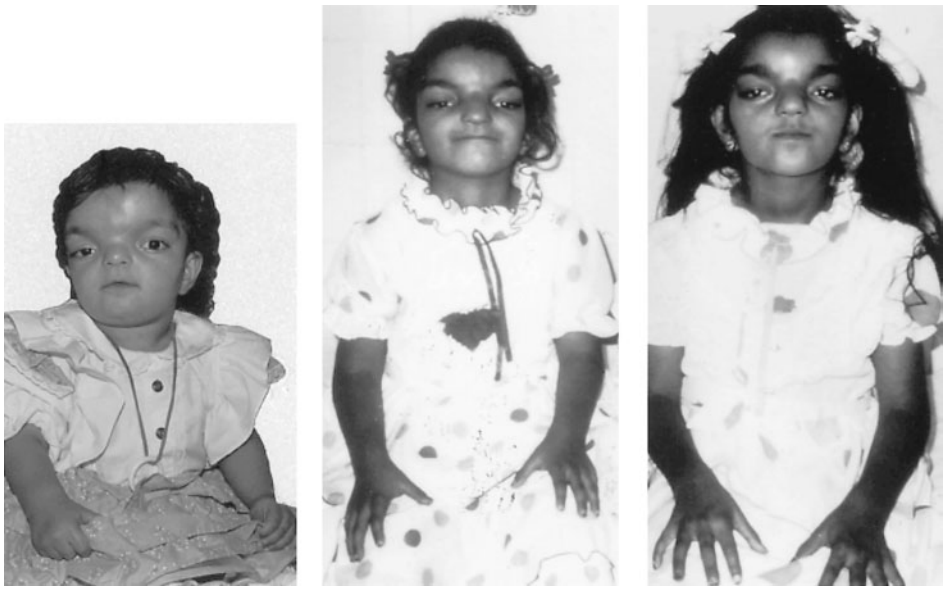
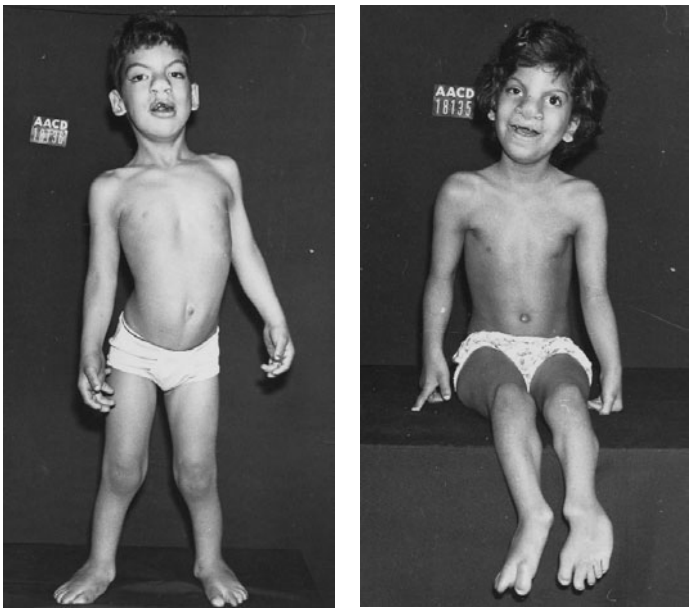


A B C

Fig. 24–9. *Teebi hypertelorism syndrome (brachycephalofrontonasal dysplasia)*. (A) Note round face with mild asymmetric, prominent forehead with widow's peak, thick eyebrows, hypertelorism, long philtrum. (B,C) Sibs of child seen in A showing similar phenotype. (From AS Teebi, Am J Med Genet 28:581, 1987.)



A B

Fig. 24–10. *Acro-fronto-facio-nasal dysostosis*. (A,B) Sibs with bilateral cleft lip-palate, severe mental retardation, and limb anomalies. (From A Richieri-Costa et al, Am J Med Genet 20:631, 1985.)

Acro-fronto-facio-nasal dysostosis

Richieri-Costa et al (2), in 1985, described two sibs born to first cousins and, in 1992, a second pair of sibs (4). In addition to bilateral cleft lip–palate, they shared severe mental retardation, hypertelorism, widow's peak, S-shaped palpebral fissures, ptosis, long eyelashes and eyebrows, broad notched nasal tip, macrostomia, anteverted pinnae, occasional postaxial polysyndactyly of hands, hypoplasia of distal phalanges of digits 1 and 5, PIP or DIP camptodactyly of some or all digits, short legs, and talipes equinovarus (Fig. 24–10). Radiographic changes included brachycephaly, vertical clivus, capitate-hamate fusion, abnormal ossification of patellae, curved or hypoplastic fibulae, brachymetacarpalia, and iliac hypoplasia (Figs. 24–10 to 24–13).

In 1989, Richieri-Costa et al (3) reported a more severe type of acro-fronto-facio-nasal dysostosis associated with microbrachycephaly, wide forehead, marked hypertelorism, broad nose with midline groove, soft tissue syndactyly of fingers 3–4, and hypospadias. Naguib (1) described an earlier example of this type. Affected sibs and parental consanguinity suggest autosomal recessive inheritance. Teebi (5) suggested the more severe form be termed the Naguib–Richieri-Costa syndrome.

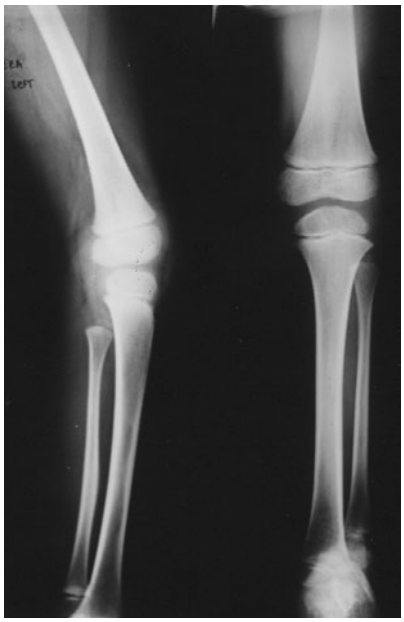


Fig. 24–12. *Acro-fronto-facio-nasal dysostosis*. Hypoplastic fibula. (From A Richieri-Costa et al, Am J Med Genet 20:631, 1985.)

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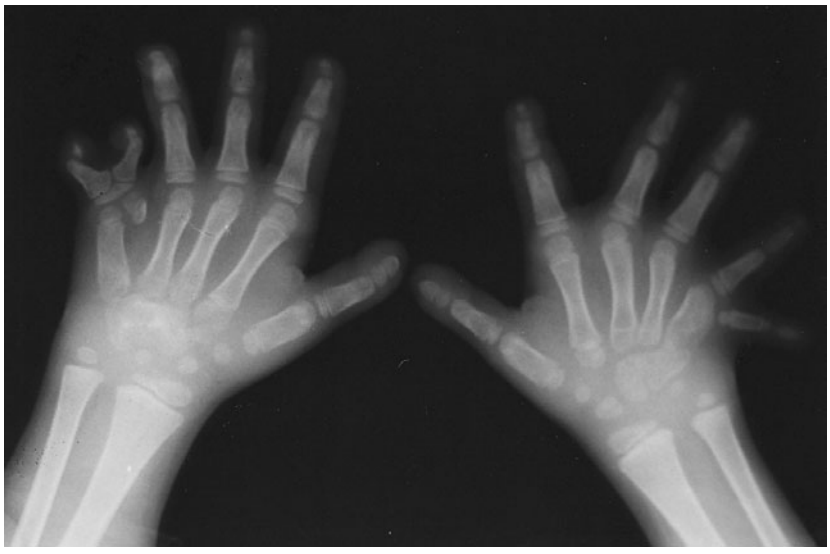

Fig. 24–11. *Acro-fronto-facio-nasal dysostosis*. Radiograph of hands showing campobrachypolysyndactyly, hamate-capitate fusion. (From A Richieri-Costa et al, Am J Med Genet 210:631, 1985.)

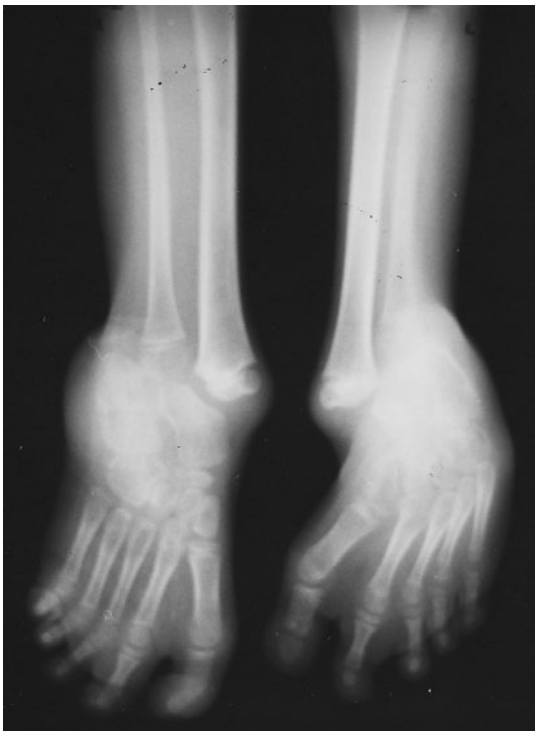

Fig. 24–13. *Acro-fronto-facio-nasal dysostosis*. Tibiotalar dislocation, abnormally modeled tarsal bones, metatarsus adductus, fibular deviation of toes 4–5, hypoplasia of distal phalanges. (From A Richieri-Costa et al, Am J Med Genet 20:631, 1985.)

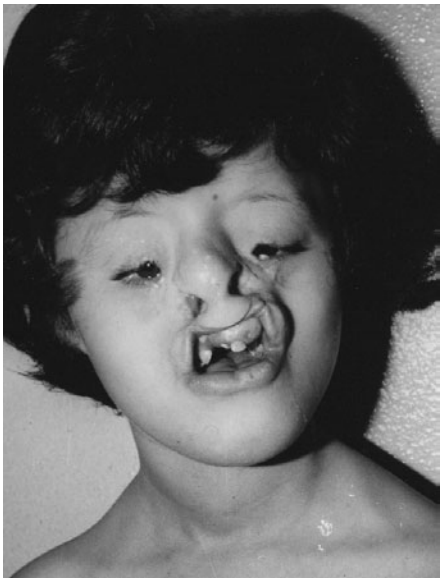

Fig. 24–14. *Fronto-facio-nasal dysplasia*. Facies of one of two sibs with bilateral facial clefts, blepharophimosis, lagophthalmos, telecanthus, S-shaped palpebral fissures, and eyelid coloboma. (From TR Gollop, Am J Med Genet 10:409, 1981.)

Fronto-facio-nasal dysplasia (cleft lip-palate, blepharophimosis, lagophthalmos, and hypertelorism) (Gollop syndrome)

Two sibs with consanguineous parents were described by Gollop (2) in 1981. The sibs had cleft lip–palate, blepharophimosis, lagophthalmos, primary telecanthus, S-shaped palpebral fissures, and eyelid colobomas (Fig. 24–14). Gollop et al (3) and others (5,8) provided additional documentation.

Inheritance is autosomal recessive. Variability of expression is wide.

The most constant features include defects of the eyes (blepharophimosis, lagophthalmos, hypertelorism, S-shaped palpebral fissures, colobomata of eyelids, absent eyelashes). The midface is hypoplastic and there is cleft lip–palate. Defects are found in the alae nasi and the nasal tip is bifid or grooved.

Less common findings include microphthalmia and iris colobomata. The corpus callosum has been absent in one of two cases.

Several examples are possible but not typical (1,4,6,7).

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Blepharonasofacial syndrome

Pashayan et al (3) and Putterman et al (4), in 1973, described autosomal dominant inheritance of a syndrome of telecanthus and lateral displacement and stenosis of lacrimal puncta, bulky nose with broad nasal bridge, masklike face, midfacial hypoplasia, longitudinal cheek furrows, and trapezoidal upper lip (Fig. 24–15). Joints were hyperextensible. All patients exhibited a positive Babinski reflex, poor coordination, torsion dystonia, mild soft-tissue syndactyly of the fingers, and mental retardation.

Allanson (1) described a mother and son with expressionless facies, telecanthus with blepharophimosis, lacrimal duct anomalies, broad nasal root, bulky nasal shape, hypoplastic alae and deficient cartilage, thickened facial skin, dysmorphic pinnae, and mild interdigital webbing. The mother had cleft palate, hoarse voice, oligodontia, and optic atrophy. Upswept frontal hair was evident in both.

Sommer et al (5), in 1983, described a mother and daughter with telecanthus, blepharophimosis, anomalous lacrimal apparatus, broad nasal root with underdeveloped alae nasi, and hypoplastic nasal root. There was sensorineural hearing loss and camptodactyly of fingers. A relationship to *Klein–Waardenburg syndrome* was raised, and a *PAX3* mutation was found (2).

Cerebro-facio-articular (Van Maldergem) syndrome must be excluded.

References (Blepharonasofacial syndrome)

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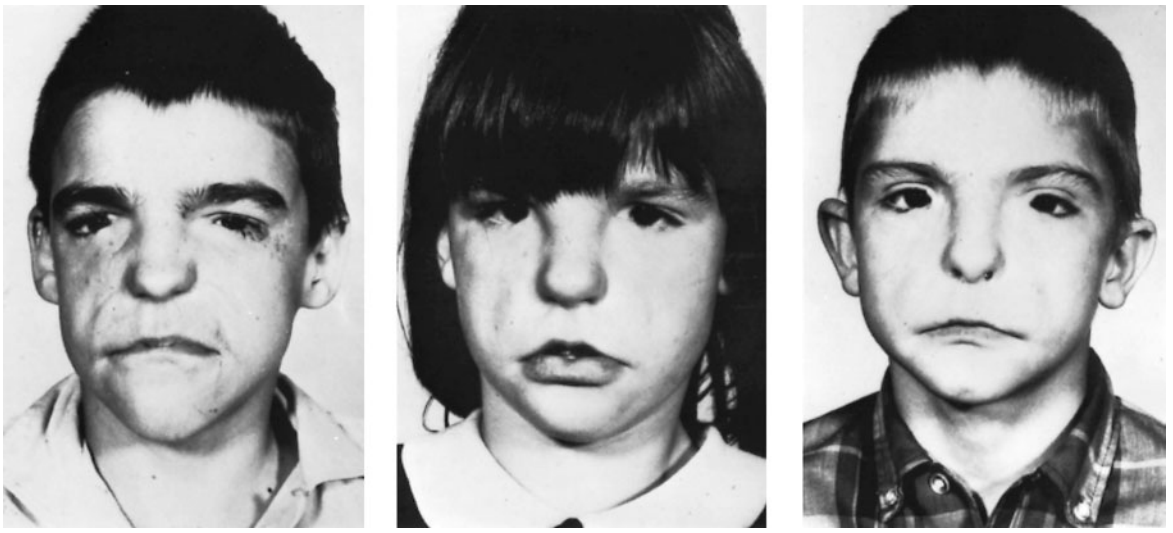


A B C

Fig. 24–15. *Blepharonasofacial syndrome*. (A–C) Facies of three mentally retarded sibs with torsion dystonia, showing telecanthus with temporal displacement of puncta, downslanting palpebral fissures. Nose is fleshy, midface hypoplastic, upper lip trapezoidal, lower lip pouty. (From H Pashayan et al, Am J Dis Child 125:389, 1973.)

X-linked mental retardation syndrome associated with α-thalassemia (ATR-X syndrome, cerebro-facio-genital syndrome)

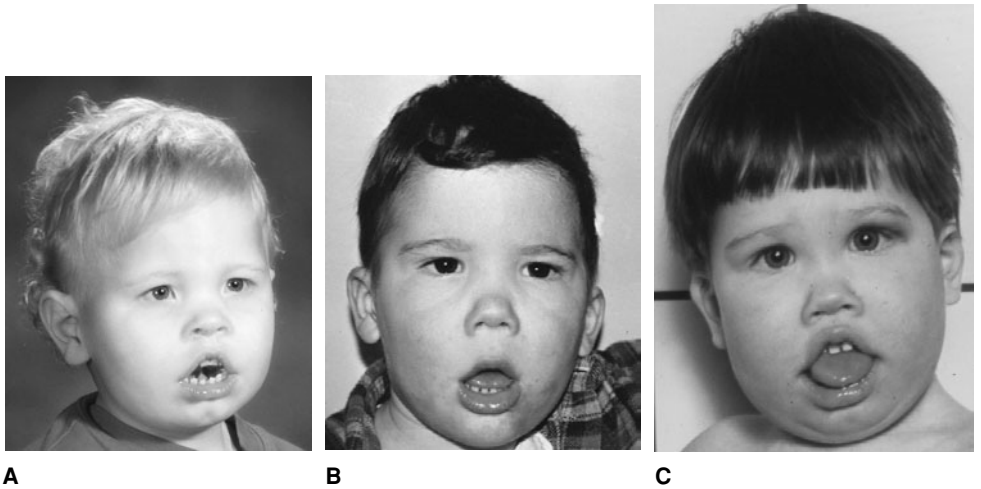
An X-linked syndrome (ATR-X) comprising severe mental retardation, characteristic facies, genital abnormalities, and mild hemoglobin H (HbH) disease was first described by Weatherall et al (30) in 1981 and further defined in the same family by Wilkie et al (34) in 1990. Since then approximately 100 cases have been reported (1–27,30,32–34). For excellent reviews, see Wilkie et al (32) and Gibbons et al (9). RE Stevenson (personal communication, 1998) suggested the name *cerebro-facio-genital syndrome* because α-thalassemia is not a constant feature.

HbH disease occurs when a greater than 50% reduction in synthesis of α globin chains of adult hemoglobin results in the accumulation of excess β globin chains. The latter form β_4 tetramers. Gibbons et al (8) and Houdayer et al (13) found that the gene maps to Xq13.3(ATR-X). The syndrome appears due to mutations in XNP which is a zinc-finger helicase-2 regulator involved in transcription (10,22,27). Skewed inactivation occurs in ATR-X so that carrier females show no expression of the condition (11,26). Mutations cause diverse changes in methylation (11a,11b,11c). Mosaicism has been noted (1a). The disorder appears to be allelic with *Juberg-Marsidi syndrome* and Carpenter–Waziri syndrome (vide infra).

The patients described by Chudley and colleagues (2,3) and Adès et al (1) have similar phenotype despite absence of HbH disease (27). There was, however, neither microcephaly nor HbH disease (Fig. 24–16C). In spite of remarkable clinical similarity, the condition does not map to Xq33.3 (26a).

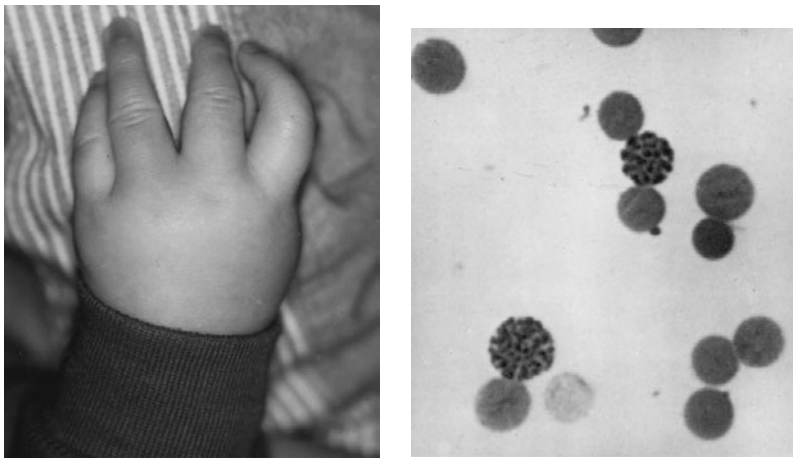
Clinical considerations. Hypotonia and feeding difficulty become apparent within the first few days of life. Birthweight is normal. All developmental milestones are subsequently delayed. Severe to profound mental retardation is a constant feature. Drooling is common. Walking is especially retarded and may not be achieved even by adulthood. Speech is absent in 90%. Even when speech is achieved, it is limited to a few words, and comprehension is poor. Self-biting and/or hitting has been noted in 50%. No more than partial bowel or bladder control is ever attained. Seizures occur in approximately 35%. Most patients (90%) are hypotonic from birth, while others develop spasticity in time. Cerebral atrophy is evident on CT scan in approximately 35%. Apneic spells are noted in 60%. Short stature is evident in 65% (11b).

Facies. Characteristic facies is marked by microcephaly, upswept frontal hairline, telecanthus (30%), epicanthic folds (85%), flat nasal bridge (70%), midface hypoplasia (85%), small triangular nose with anteverted nostrils with columella and septum above the alae (85%), and carp-shaped mouth with full drooping lip (95%) (Fig. 24–16). The tongue is often enlarged and may protrude. Malocclusion is common, and the incisors are widely spaced (70%). The pinnae are mildly dysmorphic (75%).



A B C

Fig. 24–16. *ATR-X (*A,B*). Chudley-Lowry syndrome* (C). Face marked by telecanthus, epicanthic folds, markedly flat nasal bridge, midface hypoplasia, and small triangular nose with anteverted nostrils. The columella and septum are above alae. The mouth is usually held open and the lip droops. (A courtesy of D Elliott-Pearson, Wallace, Idaho. B from D Lacombe et al, Arch Fr Pediatr 50:723, 1993. C from AE Chudley et al, Am J Med Genet 31:74, 1988.)



A B

Fig. 24–17. *ATR-X syndrome*. (A) Tapering fingers. (B) Blood stained with brilliant cresyl blue exhibits coarse hemoglobin granulations. (Courtesy of RJ Gibbons, London, England.)

Initially round, the facies tends to coarsen with age. Head circumference is less than the third centile in approximately 70% (9).

Genital anomalies. Testicular abnormalities, seen in 90%, range from small, high-lying (15%) testes to cryptorchidism (70%) to severe dysgenesis. The scrotum may be hypoplastic or shawllike (20%), and the penis small with deficient foreskin (15%). In 20%, hypospadias has been noted (5). Occasionally a male will have female or ambiguous genitalia (19,24).

Skeletal abnormalities. A wide range of relatively minor anomalies has been reported which include delayed bone age (60%), tapering digits (15%), clinodactyly (25%), brachydactyly (10%), overlapping digits (30%), syndactyly (30%), kyphoscoliosis (40%), coxa valga (35%), and talipes equinovarus (40%) (Fig. 24–17A). Short stature has been noted in approximately 50%.

Other findings. Regurgitation of food (55%), constipation (30%), and respiratory infections (40%) are relatively common. Hearing loss has been noted in a few cases.

Differential diagnosis. There is a superficial resemblance to various disorders such as *Coffin–Lowry syndrome, tetrasomy 12p, Smith-Magenis syndrome, Angelman syndrome, FG syndrome*, and *Smith-Fineman–Myers syndrome* (26a). Coarse facial appearance may bring lysosomal storage disorders to mind. There has been evidence that ATR-X syndrome is related to *Juberg–Marsidi syndrome* (25) and Carpenter–Waziri syndrome (1b). They map to the same region (Xq12–q21) and have been shown to be allelic (28).

There is another α-thalassemia/mental retardation syndrome due to contiguous deletion of 16p13.3(ATR-16). Physical anomalies are mild (tall forehead, hypertelorism, downslanting palpebral fissures, ptosis, broad flat nasal bridge, anteverted nares, macrodontia, small chin, and talipes equinovarus (6,18,30,31). Mild to moderate mental retardation has been demonstrated. Some have hypodontia, seizures, incoordination and speech delay, and some males have cryptorchidism. Nipples may be accessory or highly placed.

Laboratory findings. Hemoglobin H inclusions can be demonstrated in hemizygotes after incubation of red cells from fresh whole blood with 1% brilliant cresyl blue in isotonic saline at room temperature for 4 hours or overnight. The proportion of cells in which the coarse hemoglobin granulations are found ranges from 0.01%–40% (Fig. 24–17B). Repeated analyses may be required to demonstrate the changes (19). We were initially fooled by failure to demonstrate HbH in two families in spite of typical clinical findings. Villard et al (27), in fact, have demonstrated that one does not need α-thalassemia to manifest the ATR-X phenotype. Villard et al (29a) reported a relatively inexpensive molecular first screen approach. Detected electrophoretically, HbH has ranged from 0–6.7% and is correlated with the proportion of cells in which HbH inclusions can be found. Normal hemoglobin levels in red cell indices do not exclude the condition, nor does the inability to show HbH electrophoretically, which occurs when the proportion of HbH positive cells falls below 3% (34). In female heterozygotes one can see the rare HbH inclusions as one would expect by lyonization (8).

References [X-linked mental retardation syndrome associated with α-thalassemia (ATR-X syndrome, cerebro-facio-genital syndrome)]

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Opitz oculo-genito-laryngeal syndrome (Opitz BBB/G compound syndrome)

In 1965, Opitz et al (40) briefly reported a syndrome consisting of hypertelorism, hypospadias, and other anomalies. Four years later, Opitz et al (42), described the BBB syndrome and the G syndrome, considering them to be different disorders. The initials were those of the names of the reported families. Subsequent publications (1,12,21,30,43,57), noting similarities and differences between both disorders, proposed various names: hypertelorism-hypospadias, telecanthus-hypospadias, and Opitz syndrome for the BBB syndrome and hypospadias-dysphagia, Opitz–Frias syndrome, and Opitz G syndrome for the G syndrome. Cappa et al (6) suggested the eponym Opitz syndrome to unify both entities.

Recent molecular studies have, however, demonstrated that there is genetic heterogeneity, with one locus mapping to Xp22.3, another to Xq22 (5a) and still another mapping to 22q11.2 (48). A few patients with clinical findings consistent with Opitz BBB/G syndrome have had

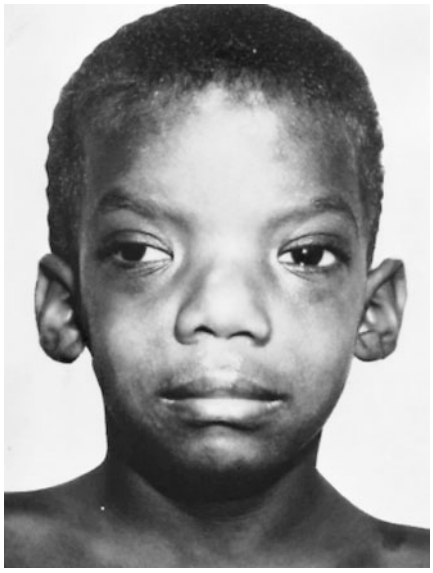


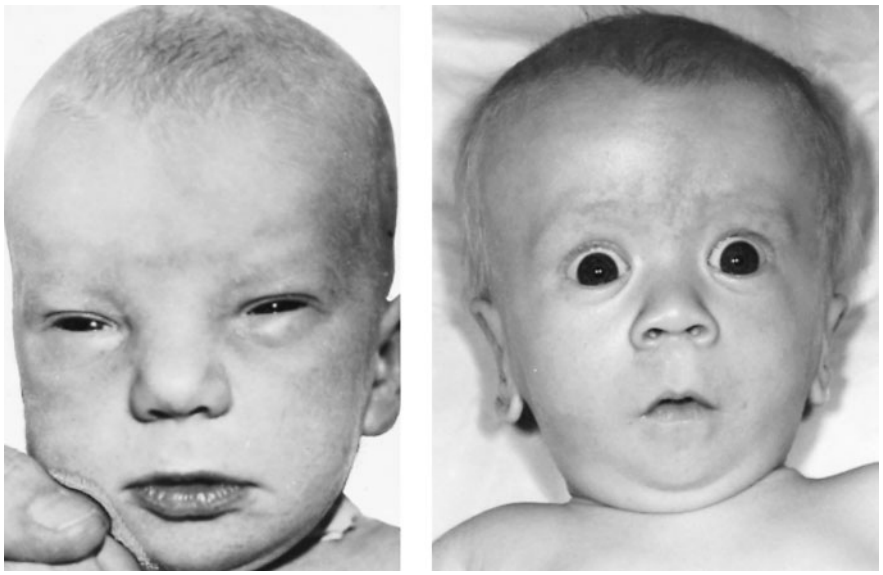
Fig. 24–18. *Opitz oculo-genito-laryngeal syndrome*. Widely-spaced eyes. [From JM Opitz et al, Birth Defects 5(2):86, 1969.]

chromosome 22q11.2 deletions (9,19,33,34). There are several examples of male-to-male transmission (7,16,17,21,54,55,60). A pericentric inversion of the X chromosome was reported by Verloes et al (58). The X-linked gene has been identified as the *MID1* gene, which is responsible for midline development (14,46). The gene product, midin, interacts with an X-chromosomal gene mapping to the linkage interval of FG syndrome (55a). Robin et al (49) concluded that posterior pharyngeal clefts and anteverted nostrils were seen in the X-linked form but not in the autosomal dominant form. Otherwise there was so much overlap that they could not be separated. Imperforate anus and dysphagia occurred more often in the X-linked form. Females with the X-linked form were not necessarily hyperteloric. Fryns et al (20a), however, suggested that there is a distinct facies in the X-linked form: prominent bossed forehead, hypertelorism, deep nasal bridge, anteverted nostrils, long philtrum, thin upper lip with downturned corners, and transverse crease below lower lip. The gene is rarely nonpenetrant (49,54).

Facies. Various degrees of hypertelorism/telecanthus are observed in 90% as well as slight upslanting or downslanting of the palpebral fissures, epicanthic folds, and strabismus (8,10,11,21,23,32,38,40,41,48,51,60), (Figs. 24–18 and 24–19). Some patients have exhibited relative entropion of the lower eyelid. The nasal bridge is flattened in the autosomal dominant form (Fig. 24–19), and the nostrils anteverted and philtrum flat and inapparent in the X-linked form (49). Usually there is mild micrognathia (13). Cephalometric analysis was carried out by Brooks et al (5). The pinnae may exhibit mild posterior rotation and occasionally abnormal modeling, primarily affecting the helix (10,13,18,35,43). Cranial asymmetry occurs in 20% (8,45) and brachycephaly, prominent forehead, open fontanels (13,18,31,36,44), prominent metopic suture, widow's peak, and low-set anterior and posterior scalp line have been observed occasionally (12,17,21,23,32). Prominence of occipital and parietal eminences can occur (12,21,41). Patients can present normal intelligence or mild to moderate mental deficiency (6,33,35,38,42,56).

Genitourinary system. Hypospadias occurs in most affected males with either genotype (49) (Fig. 24–20). The degree of hypospadias varies from a mild coronal to a scrotal type with an associated ventral urethral groove (15,23). In mild cases, the scrotum appears normal; in severe examples, the scrotum is cleft and chordee may be so severe as to draw the tip of the glans to the anterior edge of the anus (Fig. 24–21). Cryptorchidism, renal anomalies, ureteral stenosis, ureteral reflux, and inguinal hernia have been noted (6,8,12,21,23,35,38,41,42,49).

Imperforate or ectopic anus with rectourethral fistula has been reported (12,17,42,44,55) and may be associated more often with the X-linked



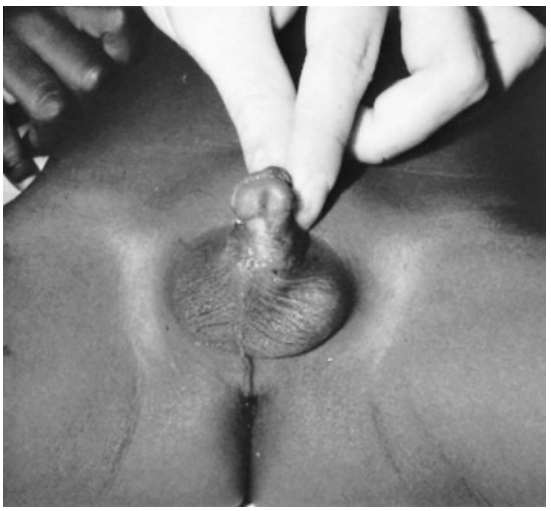
A B

Fig. 24–19. *Opitz oculo-genito-laryngeal syndrome*. (A) Hypertelorism, narrow palpebral fissures, anteverted nostrils. (B) Patient of one of the authors. [A from JM Opitz et al, Birth Defects 5(2):95, 1969.]

form (49). Affected females have normal genitalia, but splayed posterior labia majora, anteriorly placed anus, and imperforate anus have also been rarely noted (39).

Respiratory system. Minor respiratory anomalies might be present in patients. In most infants, respiration usually begins spontaneously at birth, and generally the Apgar scores are normal (12). Laryngotracheal clefting may be limited to those with the X-linked form (11,49,50), although other respiratory difficulties can occur in both types. In some infants, stridorous respiration and a hoarse cry may be noted even before the first feeding. In severe cases, the infant sucks eagerly but seems to have difficulty in swallowing, manifested by choking, coughing, and resultant cyanosis (26,36). This may be followed by respiratory distress, increase in stridor, apparent aspiration pneumonia (12), patchy atelectasis and emphysema, and, in chronic cases, bronchiectasis and anesthetic risk (4). Cinefluoroscopic studies have shown apparent neuromuscular dysfunction of the swallowing mechanism, with up to half of each mouthful entering the tracheobronchial tree with gastroesophageal reflux (10) (Fig. 24–22). It is noteworthy that cinefluoroscopic studies can miss the presence of a laryngotracheal-esophageal cleft (3). Malformation of the upper gastrointestinal tract or respiratory tract (59,60) occurs in up to 40%. Hypoplasia of vocal cords has been found at autopsy (13).

Fig. 24–20. *Opitz oculo-genito-laryngeal syndrome*. Hypospadias. [From JM Opitz et al, Birth Defects 5(2):86, 1969.]



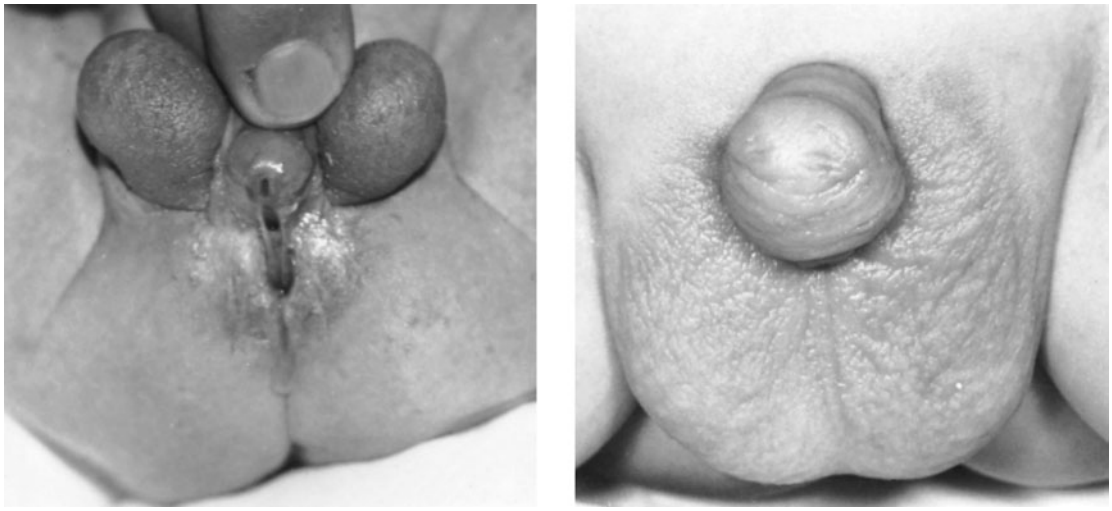
Esophageal dysmotility is present in approximately 70% (60). In one family, this was associated with complex malformations: short trachea with high carina and supraclavicular tracheal bifurcation, severe hypoplasia of a lung, epiglottis, vocal cords, and larynx, with absence of the dorsal portions of the larynx and first tracheal rings and a single cavity extending from the epiglottis and hypopharynx superiorly to the trachea and inferiorly to the esophagus (32). Hypoplasia of the epiglottis has also been noted (16,52).

Cardiovascular findings. Congenital heart defects (CA, PDA, ASD) had been estimated to occur in 20%–25% of patients (27,38,45,60), but in a recent review, Robin et al (49) found only 5% had a heart defect.

Other findings. Diastasis recti, multiple lipomas, and slight hyperextensibility of joints have been observed (8,17,41,51). Cutaneous syndactyly of toes 2, 3, and 4 has been noted (21). Distally placed axial triradii, increased number of arches, and bridged palmar creases also have been reported (21,40,54). Unlobed lungs as well as bifid renal pelvis with double ureter, Meckel diverticulum, and absence of the gallbladder and duodenal stricture have been seen (29). Fetal hydrops has been reported prenatally in a patient subsequently diagnosed as Opitz G syndrome (44). Agenesis of the corpus callosum is a relatively infrequent finding (33,37). Other brain anomalies in a few patients include cerebellar vermis hypoplasia, cortical atrophy, wide cavum septum pellucidum, and Dandy-Walker malformation (24,33). Posterior scalp defects were described in one child (20); the authors made the point that this was evidence for defective midline development. Given that the gene responsible for the X-linked form is involved in midline development, it is not surprising that a wide spectrum of midline anomalies could be found associated in low frequencies in at least the X-linked form. Platelet dysfunction has been mentioned once (28).

Oral manifestations. Cleft lip–palate and micrognathia have been observed in 25%–35% (6,8,12,21,23,35,38,41,45,49,51,53,55,56,60). Fused and supernumerary teeth and malocclusion may occur (8,35,38, 41,51,53). Additional oral manifestations include broad or bifid uvula and ankyloglossia, bifid tongue, or shortened lingual frenulum (2,13,17, 18,22). Brooks et al (5) concluded that affected males are more likely than affected females to have oral anomalies.

Differential diagnosis. Hypertelorism and hypospadias may each be observed as isolated anomalies or in association with various other malformation syndromes. Reed et al (47) erroneously reported three brothers with the *branchio-skeleto-genital syndrome* as examples of the type I syndrome. There is overlap with *FG syndrome*.



A B

Fig. 24–21. *Opitz oculo-genito-laryngeal syndrome*. (A) Cleft scrotum with anterior displacement, severe chordee deformity of hypoplastic phallus. (B) Hypospadias, chordee. [A from JM Opitz et al, Birth Defects 5(2):95, 1969.]

Laboratory aids. Cinefluoroscopic study of swallowing should be carried out to determine LTE defects. The disorder has been diagnosed prenatally by ultrasound (25). Linkage studies should be available.

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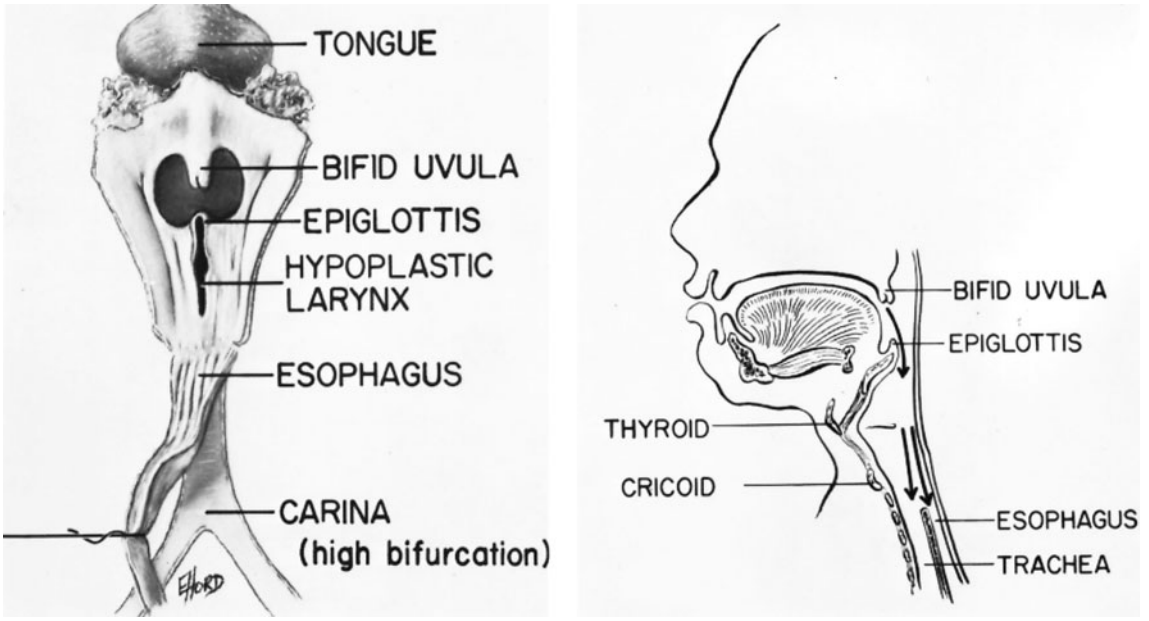

A B

Fig. 24–22. *Opitz oculo-genito-laryngeal syndrome*. (A,B) Artist's conception of defects of soft palate, larynx, and hypopharynx. Note absence of posterior wall of larynx and presence of single, large laryngopharyngeal cavity. Arrows show that solid substances are as likely to enter trachea as to enter esophagus. (From EF Gilbert et al, Z Kinderheilkd 111:290, 1972.)

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Robinow syndrome (fetal face syndrome)

Robinow et al (34), in 1969, reported a syndrome consisting primarily of characteristic facies, mesomelic brachymelia of arms, short fingers, and hypoplastic genitalia. Since then, over 80 patients have been described (1–7,9–26,28–36,39–43,45,47–55). Several cited cases are uncertain [8,27,37(case 1)].

In some families (34,42,47), the syndrome has autosomal dominant inheritance, and there is increased paternal age (33). However, affected sibs with normal parents (15,32,35,40,43,51,52) indicate an autosomal recessive type. Perhaps this is more common in Turkey (1b). Afzal et al (1,1a) and van Bokhoven et al (47a) found that the recessive form results from mutation of *ROR2 tyrosine kinase* gene located at 9q22. We assume that this is the same as in the brachydactyly B reported by Schwalbe et al (40a). Although the dominant and recessive forms have phenotypic overlap, the recessive type is more severe. Both share the typical facies, short stature, hypoplastic genitalia, and normal intelligence, but in the recessive form short stature and brachymelia appear to be more marked and there are numerous rib and vertebral anomalies and radial head dislocation (35%) (4,31). However, the ability to separate the forms has been denied by Butler and Wadlington (9), who suggested that in an isolated case a recurrence risk of 25% should be given. Robinow and Markert (33) aver that in approximately 20%, separation into dominant and recessive forms cannot be made. Robinow syndrome has been seen in identical twins (38).

Birthweight and birth length are somewhat greater in the dominant type. Death occurred before 3 years in approximately 10% with the recessive form (28,32,49,54); cause of death was pulmonary or cardiac disease.

Face. The face resembles that of a fetus at 8 weeks: disproportionately large neurocranium, dolichocephaly, bulging forehead, hypertelorism, wide palpebral fissures, S-shaped lower eyelids (which can make the eyes look exophthalmic), and short broad and upturned nose with anteverted nostrils. There is a long philtrum with a broad horizontal upper lip

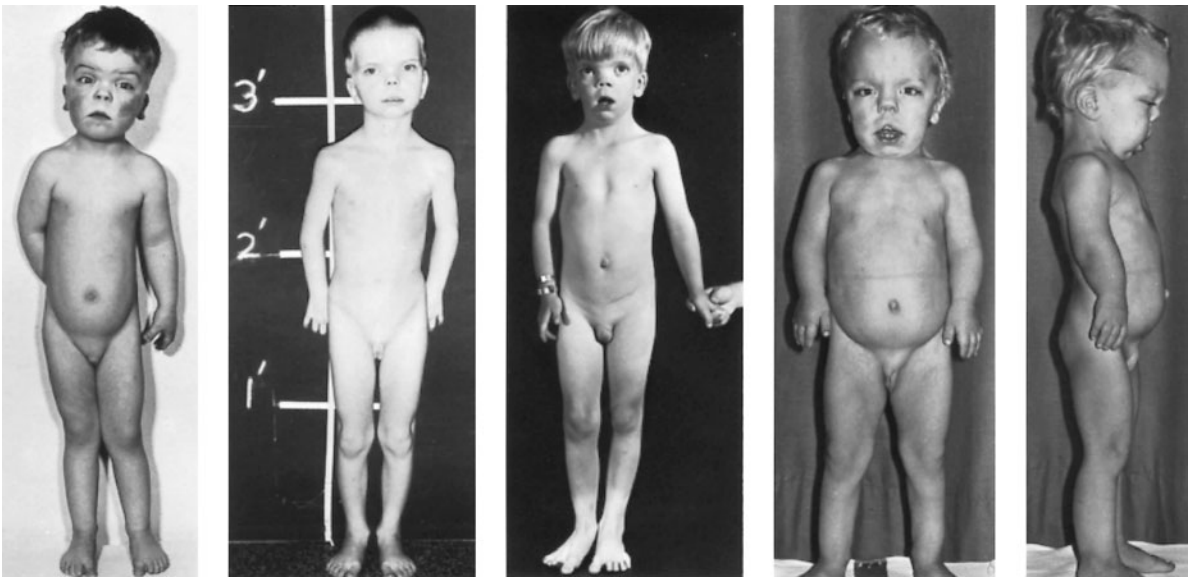


Fig. 24–23. *Robinow syndrome*. (A) Flattened facies, micropenis. (B) *Dominant form*. Short stature, mesomelia, and micropenis. (C) Compare with boy seen in A. (D,E) *Recessive form*. Note short philtrum and tented upper lip. (A from RA Pfeiffer and H Müller, Padiatr Padol 6:262, 1971. B courtesy of M Robinow, Yellow Springs, Ohio. C courtesy of HN Needleman, Boston, Massachusetts. D,E from RE Seel et al, Monatsschr Kinderheilkd 122:663, 1974.)

in the dominant form (Fig. 24–23A-C and 24–24). A short philtrum is seen in the recessive form with an inverted V-shaped or tented upper lip (Fig. 24–23D,E). In both forms, there are frequent overfolding of the helices and a small chin (Fig. 24–25). Cephalometric study has been carried out by Israel and Johnson (18).

Central nervous system. Intelligence is usually normal but developmental delay and mental retardation have been found in approximately 20%. Severe mental retardation was noted in the sibs reported by Baxovà et al (7). The macrocephaly is not associated with hydrocephaly nor is there any dramatic change in the slope of head circumference with age.

Musculoskeletal alterations. Stature is −1.5 SD in the dominant form and −4.9 SD in the recessive form. A few authors (9,42) described adults with the dominant type having normal height, although it may be possible that the diagnosis is incorrect in these cases. An alternative diagnosis could be *Teebi hypertelorism syndrome*. Kawai et al (20) reported a child with Robinow syndrome and growth hormone deficiency. However, neither photographs nor measurements were provided, thus making the diagnosis suspect. Forearm brachymelia is found to some degree in nearly all patients (21,23,42,49) making the height/span ratio excessive. Limitation of extension and supination or pronation at the elbows has been noted (21,51). Robinow and Markert (33) found radius/humerus length to be −3.6 SD in the dominant form in contrast with −10.6 SD in the recessive form.

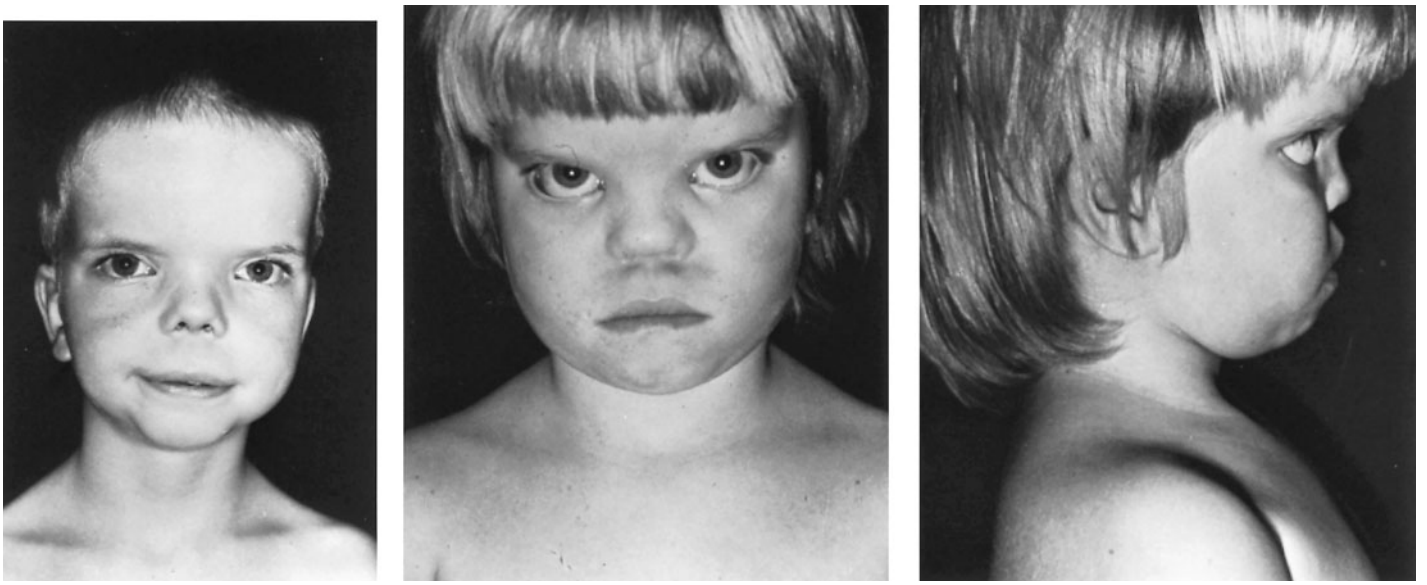


Fig. 24–24. *Robinow syndrome*. (A) Close-up of face showing fetal proportions. (B,C) Sister of boy seen in A. Note S-shaped lower eyelids, ocular hypertelorism, and midface hypoplasia. (Courtesy of M Robinow, Yellow Springs, Ohio.)

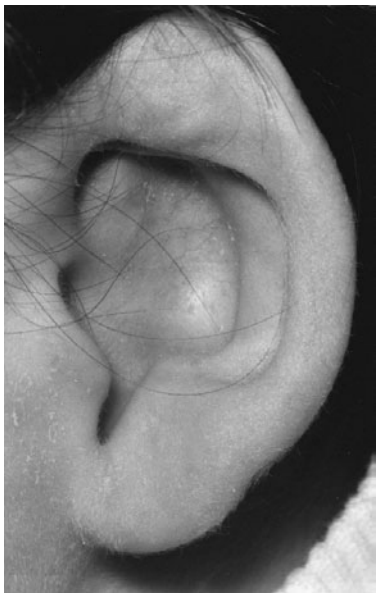
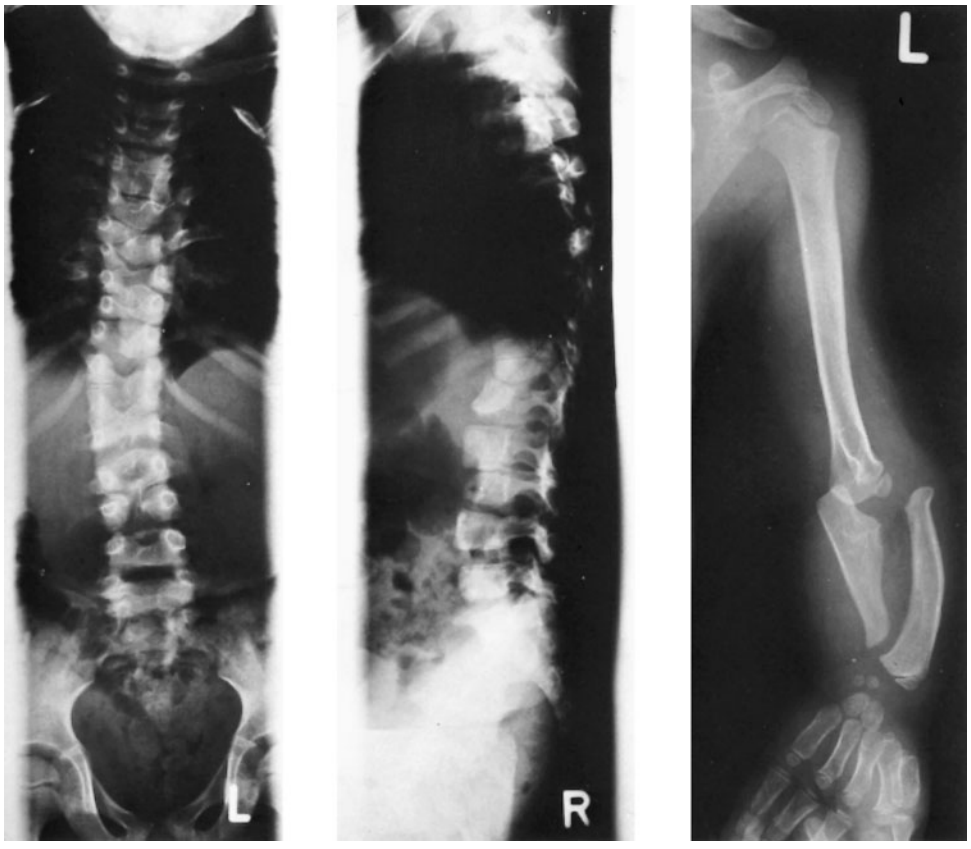


Fig. 24–25. *Robinow syndrome*. Ear with overfolded helix.

Hemivertebrae and/or fused vertebrae (65%), progressive scoliosis (50%), and displaced and/or fused and abnormal numbers of ribs (35%) are found in the recessive form (Fig. 24–26). In 10% of those with the dominant form, there is a single butterfly vertebra. Short radius and short ulna are also found. The phalanges are short, and the terminal phalanx of the thumbs and halluces may be bifid (14,17–21,29) (Fig. 24–27). Some patients have a split hand anomaly (5). Small hands with clinodactyly and brachymesophalangy of fifth fingers are noted in over 85%. An increase in bone sclerosis has been reported (21,42). Delayed bone age is evident in 35%. A characteristic metacarpophalangeal pattern profile has been demonstrated (10). Dysplastic nails occur in approximately 50% (9). Radial head dislocation is almost never seen in the dominant form but is usual in the recessive form. Inguinal hernia has been reported (42). The umbilicus may be highly placed (13).

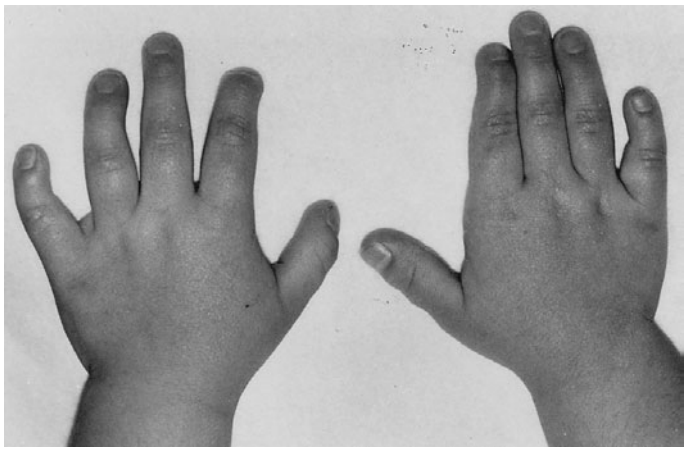
Genitourinary system. In spite of the genital malformations frequently present, sex can be properly assigned in the newborn period. Unnecessary delay in evaluating ambiguous external genitalia should be avoided since sex determination can be made by examination alone regardless of the malformation. Micropenis, a very common feature, is usually apparent at birth (34) (Fig. 24–28). Computerized tomography and magnetic resonance imaging of the genitalia has been done on three boys with Robinow syndrome (54). This demonstrated abnormal insertion of the penile crura onto the medial aspect of the ischial tuberosity. This results in a penis which appears shorter than average. Cryptorchidism has been found in 65% (9,17,34,42) and absent penis or epididymal or vasal abnormalities (12,45,46) have also been observed. Lee et al (24) evaluated testicular function and pubertal development in four males with the syndrome and found partial primary hypogonadism, normal pubertal virilization with persistence of micropenis, and normal 5a-reductase and androgen receptor activity in genital skin fibroblasts. Schönau et al (39) reported androgen receptor deficiency. The clitoris and labia minor are hypoplastic in affected females (30,34). Vaginal atresia and hematocolpos have been found (6). Inverted nipples were present in one female (25). Bilateral renal duplication and bilateral hydronephrosis have been described (47,52).

Oral manifestations. The maxillary arch is trapezoidal, and the teeth are almost always crowded. An upper lip with inverted V-shape has been described in the recessive form (7,33,34). There is gingival enlargement in 65% (9,21,23,29,34). Cleft lip and cleft palate (26,27) are found in 10% and bifid or hypoplastic uvula (21,42) in 20%. The palate is short (18). Minor clefting of the lower lip has been noted (34) as has ankyloglossia (18).



A B C

Fig. 24–26. *Robinow syndrome*. Radiographs showing keel-shaped vertebrae, hemivertebrae, and fused vertebrae. Note short, plump, and bent radius and ulna but normal humerus. (From RE Seel et al, Monatsschr Kinderheilkd 122:663, 1974.)



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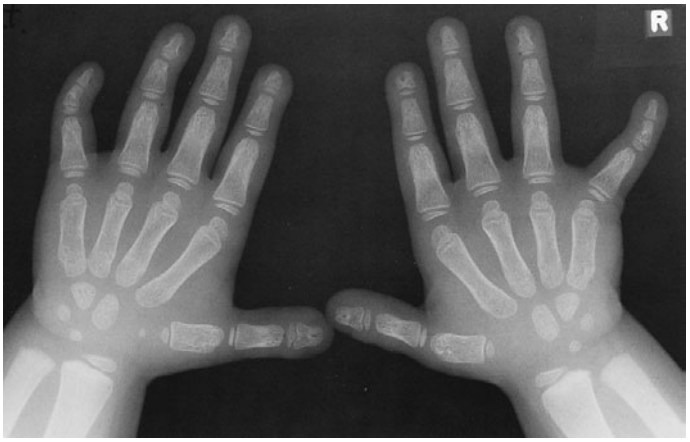


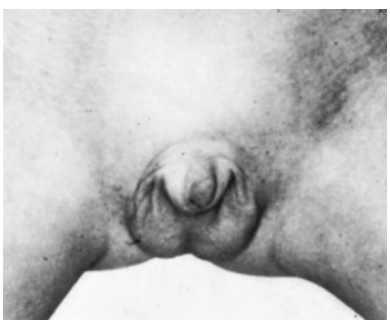
B

Fig. 24–27. *Robinow syndrome*. (A,B) Note shortened terminal phalanx of second digit and middle phalanx of fifth digit. Also note bifid terminal phalanges of thumb and right second digit.

Other. Congenital heart disease is present in 16%, with the defects causing right ventricular obstruction in over 50% of those with CHD (2,3,32,53). Guillen-Navarro et al (16) reported on a girl with developmental dysplasia of gray and white matter noted on MRI.

Differential diagnosis. The combination is so striking and characteristic that no other conditions with the possible exception of *Aarskog syndrome, acrodysostosis*, and *pseudohypoparathyroidism* with severe facial and acral involvement need be considered. Sabry et al (37) described sibs and an isolated case with a presumed diagnosis of Robinow syndrome; the sibs were thought by Van Steensel (48) to have a different condition. Baxovà et al (8a) described a child with rhizomelic dwarfism with superficial resemblance to Robinow syndrome. Turnpenny and Thwaites (46) described a girl with rhizomelia and facial anomalies, whom they believed had a Robinow-syndrome-like phenotype (46). Teebi et al (44) described a mother and daughter with facial and skeletal anomalies and noted similarities to those with Robinow syndrome. Differential diagnosis has been discussed extensively by Giedion et al (14).

Fig. 24–28. *Robinow syndrome*. Micropenis. (Courtesy of M Robinow, Yellow Springs, Ohio.)



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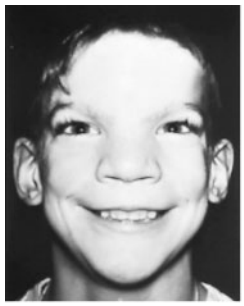
Greig cephalopolysyndactyly syndrome

The combination of frontal bossing, scaphocephaly, hypertelorism, broad thumbs and halluces, pre- and postaxial polydactyly of hands and feet, and variable syndactyly of fingers and toes was probably first described by Greig (12) in 1926. Over 50 patients have been described subsequently (1,2,4–11,13–26,31) under a variety of terms, including frontodigital syndrome (20), Hootnick-Holmes syndrome (13), and unacceptable ones: Noack-type acrocephalopolysyndactyly (8), frontonasal dysplasia (19), median cleft face syndrome (14), and acrofacial dysostosis (16). Greig cephalopolysyndactyly syndrome is the most commonly used designation and appears to be most appropriate. Just using the designation cephalopolysyndactyly is too nonspecific. Furthermore, the term "Greig syndrome," used in the past to refer to hypertelorism, describes a symptom complex known to be etiologically and pathogenetically heterogeneous. Hence, the term "Greig syndrome" bears no relationship to Greig cephalopolysyndactyly syndrome and should be abandoned.

Autosomal dominant inheritance with markedly variable expressivity has been demonstrated in several families. Several families were reported with translocations or deletions involving 7p13 (17,23,28,33). Subsequently, the responsible gene has been mapped to 7p13 (3,30,32), and has been identified as the *GLI3* gene, which is a zinc finger transcription factor and homologous to *Cubitus interruptus* in the fruit fly (15,29,32). Haploinsufficiency as well as point mutations of this gene causes Greig cephalopolysyndactyly, postaxial polydactyly type A, and PIV syndrome (polydactyly, imperforate anus, and vertebral anomalies). An animal model has been suggested (34). Deletions that encompass neighboring genes cause a syndrome indistinguishable from *acrocallosal syndrome* (LG Biesecker, personal communication, 2000).

Facies. Approximately 50% manifest frontal bossing, increased head circumference, and broad forehead. Broad nasal bridge is seen in 85% (Fig. 24–29A). In children, the sutures may be broad and close late. The facies is not always striking. Hypertelorism is less common than the

Fig. 24–29. *Greig cephalopolysyndactyly syndrome*. (A) Note broad forehead, broad nasal bridge, and apparent hypertelorism. (B) Deviated and duplicated thumbs with 2–4 soft tissue syndactyly. Postaxial digit removed earlier. (C) Preaxial duplication or triplication and syndactyly.(From D Hootnick and LB Holmes, Clin Genet 3:128, 1972.)



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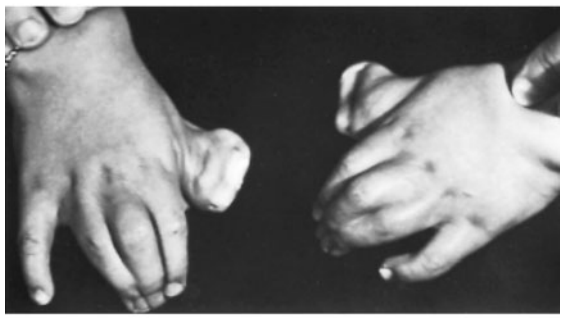

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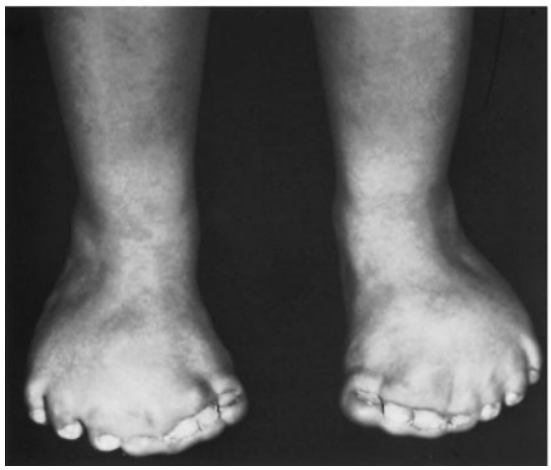

C

literature would suggest (1,5,6,21). Craniosynostosis has been reported on occasion (13,19). The patient of Töllner et al (27), in spite of having cleft lip–palate, may have the syndrome.

Extremities. Broad thumbs (60%) and broad halluces (40%) are rather frequent. Soft tissue syndactyly of fingers (70%) and toes (95%) is variable in degree. Although postaxial polydactyly of the hands is common (65%), postaxial polydactyly of the feet is relatively infrequent (10%). Preaxial polysyndactyly of the thumbs varies from broad terminal phalanx (common) to bifid distal phalanx to complete duplication (rare) (26). Preaxial duplication of the thumbs always seems associated with bifid hallux (Fig. 24–29B). In the feet, the most common anomaly is preaxial polydactyly (75%). In some patients who clinically do not appear to have polydactyly, radiographs will demonstrate duplication of phalanges (1). Syndactyly, nearly a constant feature in the feet, may be present in the absence of polydactyly (Fig. 24–29C). It is unilateral in 40%. The halluces and thumbs may be medially deviated. Radiographic changes in the halluces are bifid terminal phalanges (30%) and duplication of both phalanges (55%). The first metacarpal is duplicated in approximately 15%. Bony fusion of the third to fifth distal phalanges of the hands has been reported (7,8,28). Bone age has been somewhat advanced (21,27,28). Characteristic dermatoglyphic changes have been reported. Several digital triradii are missing. Whorl patterns are present on the thumbs with the loops extending beyond the end of the thumb (14). A t′ axial triradius is often seen.

Muscular system. Inguinal and, rarely, umbilical hernia have been noted.

Central nervous system. Intelligence is normal with rare exception (8,13). Agenesis of the corpus callosum (13) and hydrocephaly (2,13) have been reported.

Differential diagnosis. The *acrocallosal syndrome* markedly overlaps with Greig cephalopolysyndactyly syndrome but differs in that agenesis of the corpus callosum and severe mental retardation are rare in Greig cephalosyndactyly syndrome. Furthermore, the latter clearly has autosomal dominant inheritance. *Acrocallosal syndrome* probably has autosomal recessive inheritance. *Craniofrontonasal syndrome* has a somewhat similar facies. The *OFD syndromes* (cleft palate, tongue hamartoma, polysyndactyly) have similar hands and feet. *Pallister-Hall syndrome* also has some phenotypic overlap with Greig cephalopolysyndactyly syndrome but is clinically distinct.

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Acrocallosal syndrome

The acrocallosal syndrome, first reported by Schinzel (24) in 1979, is characterized by post- and/or preaxial polydactyly and syndactyly of fingers or toes, severe mental retardation, agenesis or hypoplasia of the corpus callosum, and growth retardation. Schinzel et al (25-28), in a series of papers, developed and expanded the phenotype. Over 30 cases have been reported (1-4,10,13,15-29). A good survey is that of Casamassima et al (3). The patient reported by Guion-Almeida and Richieri-Costa (10a) does not have the syndrome.

There has been no sex predilection. The disorder has been described in siblings and in cousins (2,4,5,10,26,27). All other cases have been sporadic. Parental consanguinity has been demonstrated (6,21,22,29,33), thus autosomal recessive inheritance has been suggested. Bonatz et al (1) described a child with a diagnosis of acrocallosal syndrome whose father had Greig syndrome. Sporadic *GLI3* deletions encompassing neighboring regions of 7p13 cause a phenotype indistinguishable from acrocallosal syndrome (LG Biesecker, personal communication, 2000). Perhaps the child in the report of Bonatz (1) had a severe form of Greig syndrome. Pfeiffer et al (20) described a child with inverted tandem duplicated 12p11.2-13.3, who they believed had acrocallosal syndrome. They suggested a common cause of the phenotypes of acrocallosal syndrome,

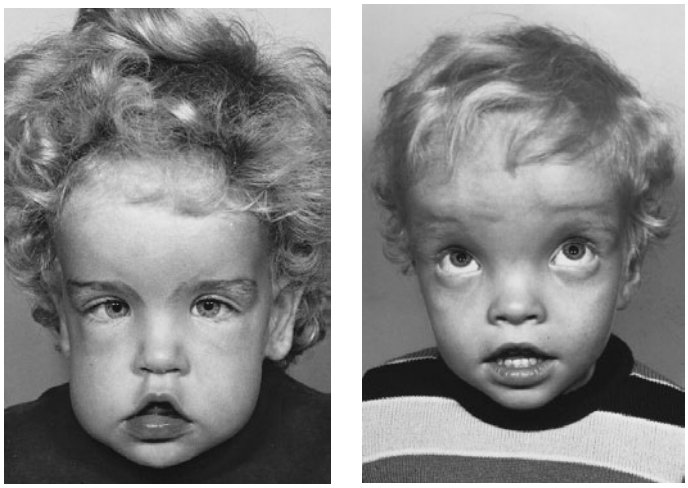

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Fig. 24–30. *Acrocallosal syndrome*. (A,B) Unrelated patients exhibiting large head, prominent forehead, broad nasal bridge. (From A Schinzel and N Schmidt, Am J Med Genet 6:241, 1980.)

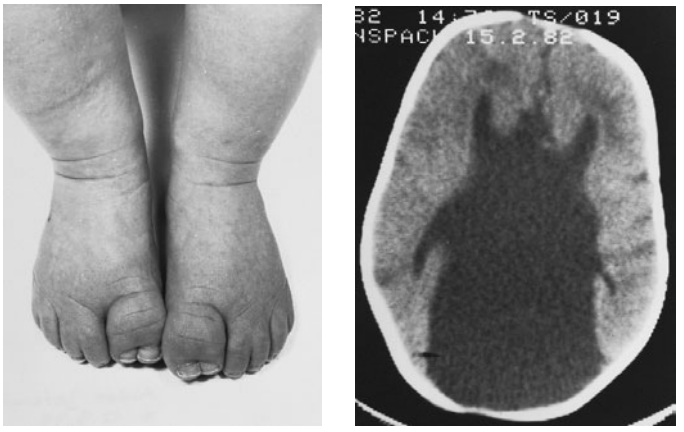
duplication 12p, and Pallister-Killian (tetrasomy 12p mosaicism) syndrome.

Craniofacial findings. Macrocephaly with bulging and high broad forehead, prominent occiput, large fontanel, hypertelorism, downslanting palpebral fissures, ptosis, epicanthal folds, convergent strabismus, hypoplastic midface, posteriorly rotated and somewhat dysmorphic pinnae, short nose, and protruding lips constitute the facies (Fig. 24–30). Cleft lip and palate has been found in approximately 15%.

Growth. Birthweight and length are usually normal; high birthweight has been reported in some patients (4,5,13,18,19). However, postnatal growth retardation, even in some of the infants with high birthweight, is fairly common (3,5,13,15,18,23,24,26–28,33).

Musculoskeletal findings. Duplicated halluces (65%), postaxial polydactyly of toes (40%), fully formed postaxial polydactyly of fingers (70%), bifid terminal phalanges of thumbs (20%), inguinal (55%) or umbilical (20%) hernia, and epigastric (15%) hernia have been found. Partial syndactyly of the toes occurred in approximately 65% (Fig. 24–31A).

Fig. 24–31. *Acrocallosal syndrome*. (A) Duplication, syndactyly, and fusion of nails, and halluces. (B) Agenesis of corpus callosum. (A from A Schinzel and N Schmidt, Am J Med Genet 6:241, 1980. B from A Schinzel and U Kaufmann, Clin Genet 30:399, 1986.)



A B

Central nervous system. Severe mental retardation is an almost constant finding, although there have been reports of children with a clinical diagnosis of acrocallosal syndrome who have had normal cognitive development (8,9,11). Since the child in the report of Guzzetta et al (11) also had trigonocephaly, it could be argued that this is a distinct, yet pathogenetically related condition. Total or partial agenesis of the corpus callosum are constant findings (Fig. 24–31B). Approximately 75% exhibit seizures. Congenital cysts of the brain (including interhemispheric, arachnoid, and supratentorial) (21,25–27,30), Dandy-Walker anomaly (18), and central diffuse cerebral cortical atrophy (10,13,22) have been demonstrated. Three children with anencephaly have been described (4,6,17).

Other findings. Miscellaneous findings include: cryptorchidism (20%) (29), micropenis and hypospadias (10,22), diaphragmatic eventration (4), sensorineural hearing loss (4), broad nasal bridge, and prominent occiput.

Differential diagnosis. Greig cephalopolysyndactyly syndrome overlaps considerably, but in that disorder there are few reports of agenesis of the corpus callosum or mental retardation (14). Moreover, postaxial manual digits are only minimally found. In contrast to acrocallosal syndrome, inheritance is clearly autosomal dominant. Agenesis of the corpus callosum is a field defect and is found in a host of chromosomal and single gene disorders listed extensively by Temtamy and Meguid (29). Among these are the *FG syndrome, Aicardi syndrome, Neu-Laxova syndrome, cerebro-oculo-facial-skeletal syndrome, Opitz BBB/G syndrome, hydrolethalus syndrome* and several of the *oral-facial-digital syndromes*. It should be noted that there is a severe form of frontonasal malformation in which duplication of halluces and agenesis of the corpus callosum are found. This has been called *Toriello syndrome*.

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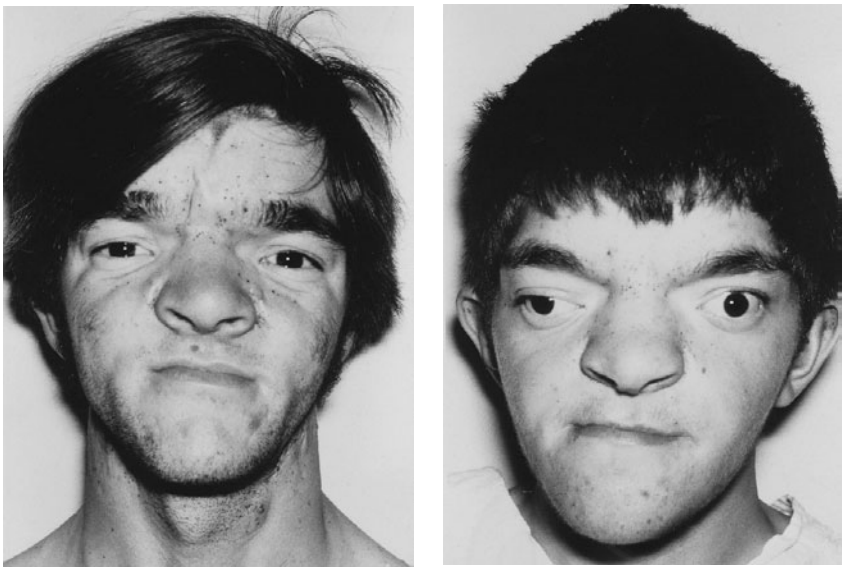

A B

Fig. 24–32. *Branchio-skeleto-genital syndrome*. (A,B) Two affected sibs with hypertelorism, exotropia, midfacial hypoplasia, extensive acne, and relative mandibular prognathism. (From MH Reed et al, J Can Assoc Radiol 26:240, 1975.)

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Branchio-skeleto-genital syndrome (Elsahy-Waters syndrome)

Elsahy and Waters (1) described three male sibs who exhibited seizures, moderate mental retardation (IQ 45–60), pectus excavatum, and penoscrotal hypospadias. Family 1, in the article by Reed et al (2), also had the syndrome. The detailed account of the oral and dental findings presented by Wedgwood et al (4) represent the same family reported by Elsahy and Waters (1). A very doubtful example was reported by Shafai et al (3).

The facies was characterized by brachycephaly, frontal bossing, marked midfacial hypoplasia, hypertelorism, divergent strabismus, nystagmus, and mild ptosis. The nasal bridge was broad with a wide nasal tip and flared alae. There was relative mandibular prognathism and facial acne (Fig. 24–32).

Radiographic study showed brachycephaly, mild microcephaly, extensive development of the mastoids, hypertelorism, short cranial base, bony projections above the external occipital protuberance (2), and fusion of the second and third cervical vertebrae in two brothers. Schmorl nodules were evident in the vertebral bodies (Fig. 24–33).

Hypospadias involving the glans, penile shaft, and proximal scrotum were present in all three sibs but to various degrees (Fig. 24–34).

Oral manifestations included multiple dentigerous cysts, cleft uvula or cleft soft palate, and teeth having dysplastic dentin with partial obliteration of pulp chambers resembling that seen in radicular dentin dysplasia (5) (Fig. 24–35). The dental anomalies were also described by Wedgwood et al (4).

References [Branchio-skeleto-genital syndrome (Elsahy-Waters syndrome)]

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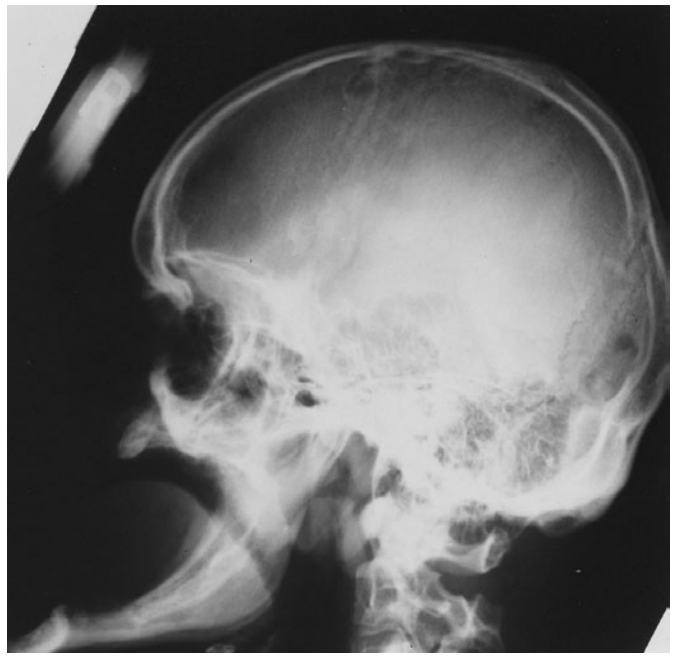
Fig. 24–33. *Branchio-skeleto-genital syndrome*. Note maxillary hypoplasia, mastoid hyperpneumatization, and bony excrescences at occipital protuberance. (From MH Reed et al, J Can Assoc Radiol 26:240, 1975.)



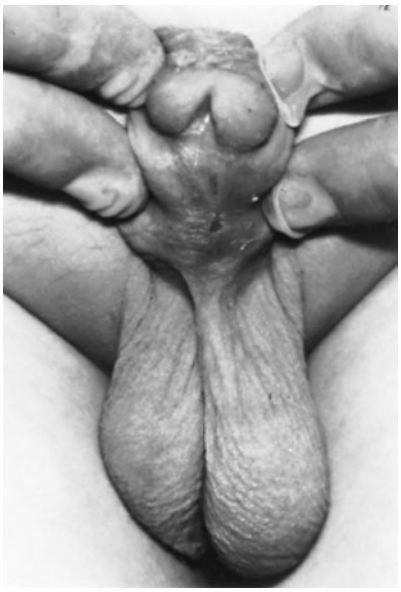
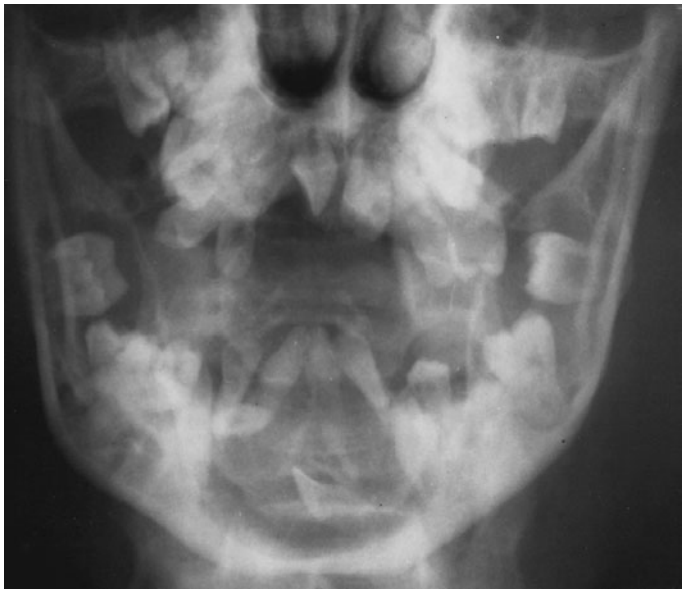


Fig. 24–34. *Branchio-skeleto-genital syndrome*. Penoscrotal hypospadias. (From NI Elsahy and WR Waters, Plast Reconstr Surg 48:542, 1971.)

Fig. 24–35. *Branchio-skeleto-genital syndrome*. (A,B) Dentigerous cysts. (From MH Reed et al, J Can Assoc Radiol 26:240, 1975.)



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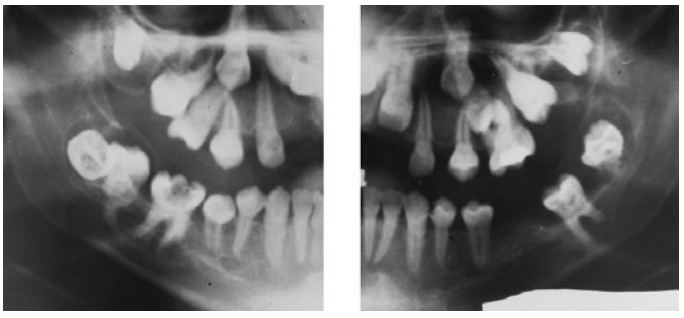

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Nasopalpebral lipoma-coloboma syndrome (Penchaszadeh syndrome)

Penchaszadeh et al (2), in 1982, reported an apparently unique autosomal dominantly inherited syndrome in eight members of a Venezuelan kindred. A Turkish family of seven affected members was described by Akarsu and Sayli (1) and Sevin et al (3).

The facies is striking. It is characterized by congenital symmetrical round to ovoid lipomas of the upper eyelids. More extensive, less circumscribed lipomas of the nasopalpebral regions may cover the root of the nose and extend symmetrically toward the inner canthi that are laterally displaced, covering the medial part of the irides. There are bilateral symmetrical colobomas of both upper and lower eyelids at the junction of the inner and middle third of the lids. The eyelashes are long and curly lateral to the lid defect but absent medially. The upper and, less often, lower lacrimal puncta are malpositioned or occasionally absent with resultant epiphora. Divergent strabismus is marked in all patients. The conjunctivae are hyperemic and several patients have corneal opacities, probably secondary to exposure (Fig. 24–36).

Broad forehead, widow's peak, medial outflaring of the eyebrows, and short philtrum add to the unusual appearance. Midface hypoplasia which was present in the Venezuelan family was not present in the Turkish family. Radiographic studies reveal normal bony interorbital distances (3).

References [Nasopalpebral lipoma-coloboma syndrome (Penchaszadeh syndrome)]

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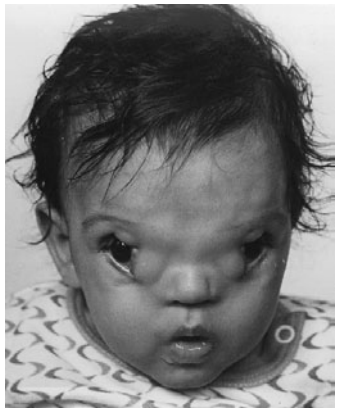
Fig. 24–36. *Nasopalpebral lipoma-coloboma syndrome*. (A,B) Facies showing symmetric round to ovoid lipomas of upper eyelids and nasopalpebral regions, lateral displacement of inner canthi, colobomas of upper and lower eyelids. Also note widow's peak. (Courtesy of VB Penchaszadeh, New York, New York.)



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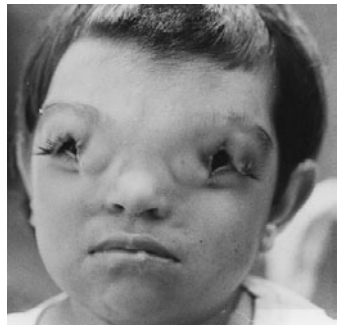

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Noonan syndrome

Noonan syndrome is characterized by short stature, various congenital heart defects, broad or webbed neck, chest deformity, hypertelorism with characteristic facial appearance and, in some cases, mild mental deficiency. Described by Noonan and Ehmke (102) in 1963, the syndrome was first reported by Kobylinski in 1883 (83). Over 400 cases have been recorded and a number of excellent reviews are available (4,28,34, 39,46,94,101,102,104,105,109,125,140a). Birth prevalence is estimated to be between 1/1000 and 1/2500 (97).

Etiology and pathogenesis. Although most of the early cases appear to be sporadic, recent surveys indicate transmission from parent to child in 30%–75% (4,28,94,97,105,109,128). Autosomal dominant inheritance with highly variable expression is evident (141). Improved recognition of the adult phenotype may further reduce the frequency of sporadic cases. Maternal transmission of the gene is three times more common than paternal transmission, most likely because of associated cryptorchidism and reduced male fertility (4,34). The gene has been mapped to 12q24 (85), although it has not yet been isolated (22,76). There is evidence of a recessive form (140b).

Several pathogenetic hypotheses have been proposed. Sanchez-Cascos (122) noted that the abnormalities of the head, neck, and heart that occur in Noonan syndrome could be produced by altered embryonic branchial arch structures. Another hypothesis implicates lymphedema. Intrauterine cystic hygroma resulting in pterygium colli and disruption of tissue migration and organ placement could possibly explain hypertelorism, downslanting palpebral fissures, low-set posteriorly angulated ears, prominent trapezius, widely spaced nipples, cryptorchidism, and abnormal dermatoglyphics. Clark (32) proposed that lymphatic obstruction might reduce right-sided cardiac blood flow and cause pulmonic stenosis.

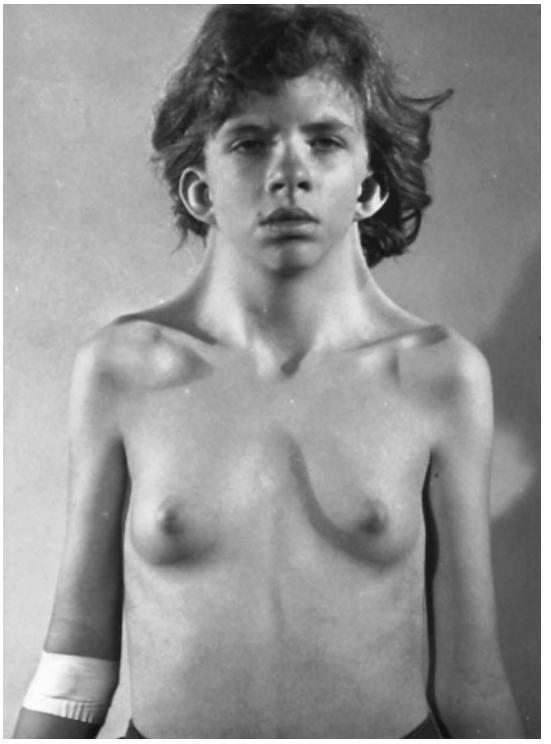


Fig. 24–37. *Noonan syndrome*. Pterygium colli and prominent ears. Note normal breast development.

Craniofacial features. Facial characteristics change with age (5,125). In the newborn, features include tall forehead, hypertelorism (75%), downslanting palpebral fissures (40%–95%), epicanthal folds, depressed nasal root with upturned nasal tip, deeply grooved philtrum with high, wide peaks of the vermilion border (95%), highly arched palate (45%), micrognathia (25%), low-set and posteriorly angulated ears with thick helices (90%), and excessive nuchal skin with low posterior hairline (55%). During infancy, the head is relatively large with a turricephalic configuration. Hypertelorism, prominent eyes, and thick hooded eyelids are characteristic. The nasal bridge is low and the nose has a wide base with bulbous tip. During childhood, the face may appear coarse or myopathic. Facial contour becomes more triangular with age. During adolescence and young adulthood, the eyes become less prominent, and the nose has a thin, high bridge and a wide base. The neck appears longer with accentuated webbing or prominent trapezius (90%). In older adults, the nasolabial folds are prominent, the anterior hairline is high, and the skin appears wrinkled and transparent (4,5,7) (Figs. 24–37 and 24–38). An extensive photoanthropometric study of the face has been reported (127).

Features present regardless of age include blue-green irides, halo iris, arched eyebrows, and low-set posteriorly angulated ears with thick helices (4,27,125). The hair may be wispy during infancy and curly or woolly in older childhood and adolescence. Loose anagen hair has been described in two children (139). Malocclusion occurs in 35% (4,5). Allanson (5) discussed the changing facies of Noonan syndrome with age.

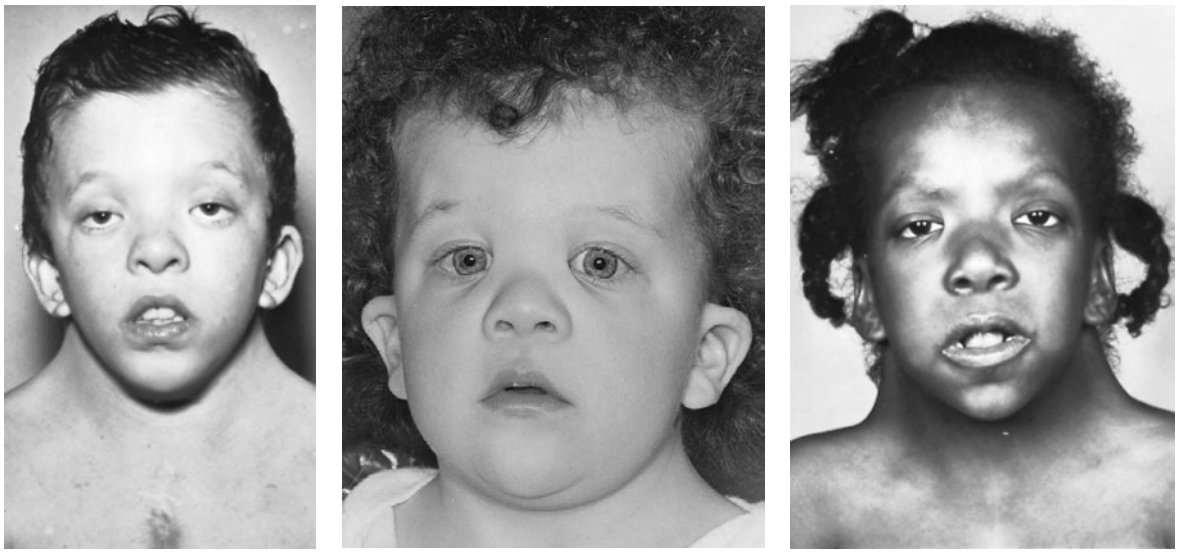
Ocular anomalies. Ocular anomalies are fairly common. One study of 58 patients (86) reported strabismus in 48%, refractive errors in 61%, amblyopia in 33%, and nystagmus in 9%. Anterior segment changes (prominent corneal nerves, anterior stromal dystrophy, cataracts, and panuveitis) were found in 63% (84). Coloboma (9,84) and spontaneous corneal rupture (9,11) are rare complications; however, some of those with coloboma may have a distinct condition.

Cardiovascular anomalies. Congenital heart defects occur in approximately 65%. The most common anomaly is dysplastic and/or stenotic pulmonary valve (50%) (76). In addition, some degree of hypertrophic cardiomyopathy, both obstructive and nonobstructive, occurs in 20%–33% (23,24,75,100,103). Other common cardiac anomalies include atrial septal or ventricular septal defects and tetralogy of Fallot. Less common defects are atrioventricular septal defect, aortic stenosis, coarctation of the aorta (42,44,66,153), bicuspid aortic valve (23), double chambered right ventricle (108), mitral valve anomalies (89), Ebstein anomaly, total anomalous pulmonary venous return, restrictive cardiomyopathy (145), and dilated cardiomyopathy (129,152). ECG commonly demonstrates a wide QRS complex, left axis deviation, giant Q waves, and the left precordial leads have a negative pattern (122).

Growth and skeletal findings. Polyhydramnios occurs in 33% (125). Average birth length is 47 cm and birthweight is usually normal (40%) but may be increased by subcutaneous edema. Childhood growth tends to parallel the third percentile (60%), usually with normal growth velocity. The growth spurt during puberty is frequently reduced or absent (136). Delay in osseous maturation has been recorded in approximately 20%. Growth hormone levels have been normal with a slight rise in somatomedin in some patients (48). Growth curves specifically for Noonan syndrome are available (115,148). Average adult height in males is 162.5 cm and in females is 152.7 cm (115). Recent studies have described the use of growth hormone in children with Noonan syndrome (3,43,137) with promising results.

Characteristic are pectus carinatum superiorly and pectus excavatum inferiorly (70%–95%) due to precocious closure of sternal sutures. The thorax is broad. During childhood, the upper chest appears to lengthen; the nipples appear low set, and axillary webbing, which persists into adulthood, is present. Common features include rounded shoulders, cubitus valgus (50%), clinobrachydactyly and blunt fingertips (30%), and vertebral and sternal anomalies (25%). Other described skeletal anomalies include talipes equinovarus (12%), joint contractures (4%), radioulnar synostosis (2%). Joint hyperextensibility occurs in 30% (125).

Abdominal organ anomalies. Renal anomalies are fairly common, and include dilation of renal pelvis (most common), duplex systems (60),



A B C

Fig. 24–38. *Noonan syndrome*. (A–C) Similar facies showing ptosis, widespread eyes, pterygium colli, and dysmorphic pinnae. [C from F Char et al, Birth Defects 8(5):110, 1972.]

minor rotational anomalies, distal ureteric stenosis, and renal hypoplasia/aplasia. Splenomegaly is common (53%), as is hepatomegaly (26%). Other reported abdominal anomalies include choledochal cyst and midgut rotation (60).

Central nervous system. Failure to thrive in infancy occurs in 40%. Feeding difficulties occur in 77% (124a,125), and range from mild characterized by poor suck to severe characterized by the necessity for tube feeding. Other abnormalities include psychomotor delay (25%), learning disability with specific visual-constructional problems and verbal-performance discrepancy (36,95,122a) (15%), and language delay (20%), which may be secondary to perceptual motor disabilities, articulation abnormalities (70%), or recurrent convulsions (125). The hearing loss is usually a mild conductive loss (40%–50%) secondary to recurrent otitis media, but congenital conductive, sensorineural (3%), or mixed hearing loss has also been described (38). Qui et al (114) found progressive high tone loss in 50% of 20 individuals with Noonan syndrome. Naficy et al (98) described temporal bone anomalies in patients with Noonan syndrome. Mild mental retardation, found more often in males (115), may occur in up to 35%. However, IQ has ranged from 64 to 127 (4,94,95,105,109,125).

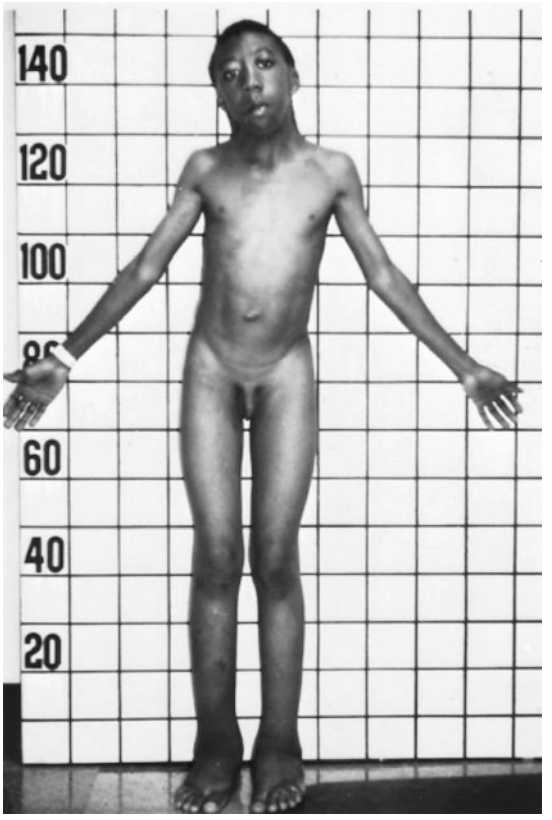
Cerebrovascular anomalies have been described in a few (14,65,69, 70,118,122,135). Hydrocephalus is not often reported in Noonan syndrome (68), although two Noonan-phenotype affected individuals in the same family were described by Henn et al (67). Fryns (56) noted that in their experience 5% (3/62) of patients had hydrocephalus, which was causally heterogeneous.

Genitourinary system. In males, pubertal development varies from normal virilization with subsequent fertility to delay but normal pubertal development to inadequate sexual development associated with early cryptorchidism (60%) and later deficiency in spermatogenesis (49). Most females are fertile, and puberty may be either normal or delayed (4,49).

Skin. A number of skin manifestations have been reported including café-au-lait spots (10%), pigmented nevi (25%), and lentigines (2%) (39) (also see Differential diagnosis). Keratosis pilaris atrophicans faciei has been noted in several instances (110). RJG has seen several children with multiple subcutaneous granular cell schwannomas. This has been discussed under *LEOPARD syndrome*. Other examples have been reported (86a,120a).

Lymphatics. Hypoplasia or aplasia of the lymphatic channels (20%) may result in generalized lymphedema, peripheral lymphedema, pulmonary lymphangiectasia, chylothorax, intestinal lymphangiectasia, hydrops fetalis, and cystic hygroma (1,17,61,121,149) (Fig. 24–39). A rare complication is lymphangioma (21,52).

Fig. 24–39. *Noonan syndrome*. Note lymphangiectatic edema of feet and ankles. (Courtesy of RL Summitt, Memphis, Tennessee.)



Hematologic abnormalities. Bleeding abnormalities (126,150) are found in 50%–65% and include (most commonly) factor XI deficiency (40,82,90,126), factor XII deficiency (50,90), factor VIII deficiency (126,130), von Willebrand disease, and platelet dysfunction, which may be associated with trimethylaminuria (73,147) or acyclooxygenase deficiency (55). Low frequency abnormalities such as congenital bone marrow hypoplasia (53), congenital hypoplastic anemia (84), and pancytopenia (120) have been reported. A low frequency association with myeloproliferative disorders has been noted. These include acute lymphoblastic anemia (10,77,111) and chronic myelomonocytic leukemia (12,57). The exact frequency of hematologic malignancy in Noonan syndrome is unknown but considered low.

Malignant hyperthermia. Malignant hyperthermia has been reported in a number of cases (74,81,117,132). Some authors have designated this as King syndrome, but we feel separate nosologic status is unnecessary as long as the possibility of malignant hyperthermia is recognized. However, some examples of King symptoms are associated with congenital myopathies (30).

Behavior phenotype. A behavioral profile for Noonan syndrome was suggested by Wood et al (151). Over 50% in this study were stubborn, clumsy, affected by mood disorders and faddy eating. Although autism has been reported in a few individuals (59), the association is not common.

Other findings. Various low frequency abnormalities have included autoimmune thyroiditis (29,143), pheochromocytoma (18), malignant schwannoma (78),vaginal rhabdomyosarcoma (80), neuroblastoma (37,87,88a), lateral meningocele (72), xanthomas of the skin and oral mucous membranes, polydactyly (62), Moyamoya disease (58), and constrictive pericarditis (107). Several have found central giant cell lesions of the jaws consistent with cherubism (1a,20,30,47,71,134,144; L Kaplan, personal communication, 1987; C Hall, personal communication, 1988).

Differential diagnosis. Differential diagnosis includes *Turner syndrome, Aarskog syndrome* (51), *Gorlin syndrome* (35,54,63), *Williams syndrome* (25,36), *Baraitser-Winter syndrome* (16,142), *fetal alcohol syndrome* (64,131), and *primidone embryopathy* (96). There is also overlap with several cardiocutaneous syndromes including *LEOPARD syndrome*, Watson syndrome (6,57) [which has been shown to probably be allelic with the NF1 gene on chromosome 17 (5)], and, especially, neurofibromatosis (8,72,93,94,106,112,113). Opitz and Weaver (106) enumerated four possible interpretations of the Noonan-neurofibromatosis association: (a) chance concurrence of Noonan syndrome and neurofibromatosis, (b) neurofibromatosis/Noonan syndrome as an unusual variant of Noonan syndrome, (c) neurofibromatosis/Noonan syndrome as an unusual type of neurofibromatosis, and (d) neurofibromatosis/Noonan syndrome as a newly recognized entity (5). Carey (26) and Meinecke (92) reviewed the evidence that cases of NF–Noonan syndrome (NF–NS) have been shown to have the phenotype based on all four of these mechanisms. Colley et al (33) described a family in which the genes for NF and NS were co-segregating independently. Khalifa and Graham (79) surely were describing Noonan syndrome. Ahlbon et al (2) described a family with NS and café-au-lait spots in which there was no linkage to NF1, supporting hypothesis (a); Stern et al (133) and Colley et al (33) also described families in which the manifestations of Noonan occasionally occurred in individuals with NF thus supporting hypothesis (c). Finally, Bahuau et al (13) described a novel nonsense mutation of the NF gene in a family with NF–NS. A similar relationship exists for Noonan syndrome-LEOPARD syndrome-cherubism-polyarticular pigmented villonodular synovitis. We suspect that this represents a contiguous gene syndrome. Cherubism may occur as an autosomal dominant disorder, in combination with neurofibromatosis or in the *Ramon syndrome* with juvenile rheumatoid arthritis (polyarticular pigmented villonodular synovitis). The gene for cherubism has been mapped to 4p16.3 (88b,137a). *Noonanoid syndrome* has giant cell granulomas (20,140).

Cardio-facio-cutaneous syndrome includes mental deficiency, growth retardation, cardiac anomalies, a Noonanoid facial appearance, and abnormalities of the hair and skin. Facial features were coarse. Sparse hair broke easily, leaving patches of alopecia, and skin abnormalities varied from follicular hyperkeratosis to an ichthyosis hystrixlike picture (116). As indicated elsewhere, there is good evidence to suggest that cardio-facio-cutaneous syndrome maps to the same region as Noonan syndrome (55,86,88,99). Possibly the children reported by Baraitser and Patton (15) have the same syndrome. Maximilian et al (91) described three sibs with a Noonan-like phenotype but with the additional manifestation of mental retardation. The parents were normal. Tonoki et al (138) described a boy with a phenotype vaguely reminiscent of Noonan syndrome and deletion 12q12-q13.12. Wilson et al (146) described a child with a Noonan syndrome phenotype, DiGeorge anomaly and deletion 22q11; others have not found this deletion in patients with Noonan syndrome (43,119). However, chromosome studies with particular attention paid to the 22q11 region may be worthwhile in a child with suspected Noonan syndrome and unusual manifestations. A unique patient with polycystic brain disease and Noonanoid appearance is called *Sener syndrome* (124). Fryns and Aftimos (56a) and others (40a) reported patients with webbed neck, unusual facies, inverted nipples, and pachygyria of frontal lobes. This condition is now called *cerebro-fronto-facial syndrome*.

Laboratory aids. If posterior cervical cystic hygromas are present on ultrasound and polyhydramnios and normal karyotype are present, a tentative diagnosis of Noonan syndrome is indicated (19). Those fetuses with nonseptate cystic hygroma with regression prior to mid second trimester have a more favorable prognosis than those with later regression (45).

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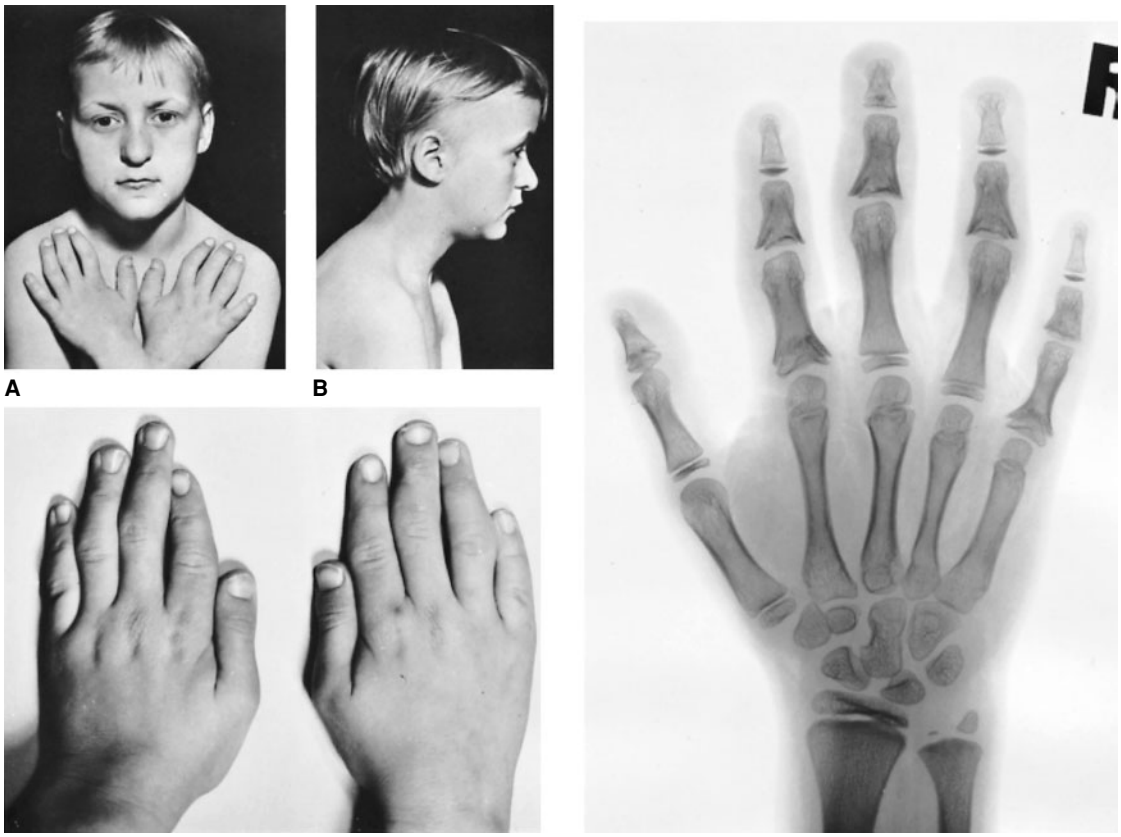

Fig. 24–40. *Trichorhinophalangeal syndrome, type I.* (A,B) Pear-shaped nose, frontal bossing with high lateral hairline, fingers deviated at proximal interphalangeal joints. (C) Hands showing deviation of fingers at proximal interphalangeal joints. (D) Cone-shaped epiphyses (type 12) and eburnated epiphyses. (A, B, and D from A Giedion, Fortschr Roentgenstr 110:507, 1969. C from A Giedion, Helv Paediatr Acta 21:475, 1966.)

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Trichorhinophalangeal syndrome, type I

The disorder was described initially by Klingmüller (49) in 1956, although it was mentioned even earlier (85). The name trichorhinophalangeal syndrome was first applied by Giedion (26,27). The condition is characterized by cone-shaped epiphyses, sparse fine hair, bulbous nose with lack of alar flare, and variable growth retardation. The majority of reported kindreds are consistent with autosomal dominant inheritance (2,4,16,18,19,21,22,24,25,29,30,32,33,39,53–57,63,69,74,88–90). Monozygotic twins have been reported (66). A few affected sibs with normal parents (42,45,86) may represent gonadal mosaicism. Translocation involving 8q24 has been found (61,77). The parental origin of the deletion is probably not significant (65). TRP syndrome, type I, is due to a deletion of band 8q24.11 or a point mutation. The gene is a zinc finger transcription factor (62a). The more severe type II (Langer–Giedion) syndrome is due to a larger deletion which also includes the EXT1 gene for multiple exostoses (9,40). Type III refers to those with a phenotype like type II but without exostoses or mental retardation (43,46,57,64,67,81). In contrast to TRP I, growth retardation and brachydactyly are more severe. On radiographic exam, the metacarpals had bulbous ends. Patients with this condition who have been karyotyped did not have a detectable deletion of chromosome 9 (43,65). We view type III as a severe form of type I, probably due to a different mutation, and not worthy of separation.

Facies. The nose is pear-shaped (51,53–55,59,60,68) and the alae are retropositioned. The philtrum is elongated (41,70) and the lips are thin (32,59). There may be a small protuberance below the lower lip (32,42,68,70). Cephalometric analysis (42,58) has documented a shortened posterior facial height associated with short mandibular ramus and reduced and superiorly deflected posterior cranial base. The lower border of the mandible is more steeply inclined, and the gonial angle is more obtuse than normal. Ears are often large and outstanding (12,16,19, 32,51,76, 87,89) (Fig. 24–40A,B).

Hair and nails. Scalp hair may be sparse from birth (38,69,89) and is especially scant in the frontotemporal areas, simulating male pattern baldness. Its texture is fine and brittle, and growth is slow (7,41,68,71,85). Scalp hair is more like vellus than terminal hair. In some patients, hair falls out during the mid-second decade of life (3,41,47,85); male (30) and female (84) patients may become almost totally bald prematurely. Electron microscopy has shown an elliptical rather than cross-sectional pattern, although the authors were not certain whether this finding was typical for trichorhinophalangeal syndrome (6). Lalevic-Vasic et al (53) also described an oval pattern, as well as folded cuticle cells and clear rhexis. Eyebrows are thick medially and sparse laterally (18,30,32,46, 48–50,67–70). Eyelashes and pubic and axillary hair may be scant (25,47). Nails may be thin (26,38,89). Koilonychia (32,69,70) and leukonychia (32,69,70,85) have been described. The diameter of the hair shaft is markedly decreased (72) and there may be abnormalities of the cuticle cells (72). Van Neste and Dumortier (86) reported that hair diameter was thinner than normal, but that the cuticular pattern was normal;

they also reported that hair follicles had a relatively hypoplastic papilla when inserted into a well-developed hair matrix.

Musculoskeletal system. Height is below the third centile in 40% and seldom above the twenty-fifth centile (26, 30, 42, 71, 86). Bone age is often several years behind chronologic age.

Characteristically, there is swelling of the proximal interphalangeal joints, resulting in clinobrachydactyly (70,89) (Fig. 24–40C). Burgess (10) suggests that ulnar deviation of the index and middle fingers at the PIP and radial deviation of the fourth and fifth fingers at the PIP are characteristic of trichorhinophalangeal syndrome. The distal phalanges in both thumbs and halluces are usually short (38,69,70). Toes as well as fingers may be abbreviated. Pes planus has been noted in several cases (26,48). Limitation of movement and bone pain can occur in the hips (26, 30,41,47,50,51,68) and hands (51,67,83). Joint hypermobility at the elbows (12) and fingers (38,52,67) has been noted. On occasion, severe arthritic involvement has been found (BD Hall, personal communication, 1984).

Radiographically, the mandibular condyles may be flattened (59). Cone-shaped epiphyses (type 12) are most frequently present in the middle and less often the proximal phalanges of the second, third, and fourth fingers (28,70) and there are eburnated epiphyses of the distal phalanges in fingers 2, 4, and 5 (Fig. 24–40D). The fifth fingers as well as both phalanges of the thumbs may be similarly affected. Metacarpals, especially the fourth and fifth, are shortened (19) in approximately 50% (30). Multiple cone-shaped epiphyses may also be noted in the toes (10,54). Scoliosis and lordosis have been described by several authors (10,16,26,32,38,42). The scapulae are often winged (63). Up to 50% have Legg-Perthes-like changes in the hips (4,12,15,16,25,41,62,63,67,70,83), although in contrast to Perthes disease, there is more severe joint involvement, increased age of presentation, and increased number with hinge abduction and pain in adolescence. Degenerative arthritis can also occur in the spine, hips, knees, elbows, and sacroiliac joints (12). The ulnae may be short. Schlessinger and Poznanski (80) documented flattened distal femoral epiphyses. Pectus carinatum has been found in 40% (12,16). Knee and wrist dislocations can occur (73). Basilar impression and syringomyelia occurred in one patient (17). Pattern profile analysis of the hands without typical cone deformity in clinically normal individuals at risk for the syndrome has been reported (16). Findings suggested that these individuals indeed had the disorder, and that the condition has wide variation in expression; however, none had affected children. Frias et al (20) described a woman who had no clinical signs of the disorder, yet her mother was affected; her son had marked changes in the capital femoral epiphyses but normal radiographs of the hands. Metacarpophalangeal pattern profiles resemble those of TRP type II (14,78).

Other findings. Frequent upper respiratory tract infections have been described (26,38,49,67,79) but are not well documented. Melanocytic nevi may occur (7,75). Giedion et al (30) and others (42,56) suggested possible increased frequency of congenital heart defects and renal disorders. Renal disease was present in the patient described by Yanez (91). Floppy mitral valve has been described by several authors (21,30,45). Polycystic ovaries are an occasional manifestation (7). Intelligence is normal (18,31,35,41,42,52,60,71), although mild mental retardation or learning disability has been described (32,63). Severe mental retardation was found by Yamamoto et al (90) and Hamers et al (34) in patients with significant interstitial deletions around 8q24.12.

Oral manifestations. Malocclusion (19,68) and supernumerary teeth (26,38,52,67,76,85) have been documented.

Differential diagnosis. Cruz and Francés (13) described a mother and daughter with abnormalities similar to those observed in the trichorhinophalangeal syndrome but without characteristic nasal alterations. The disorder described by Bellini and Bardara (3) represents a different entity, with cone-shaped epiphyses (not type 12) and involvement of the epiphyses of both knees.

Cone-shaped epiphyses in the hand may occur as an isolated finding in approximately 1% of children in southwest Ohio and in almost 9% in Guatemala (37). They may be associated with a plethora of disorders, among which are *de Lange syndrome*, *cleidocranial dysplasia*, asphyxiating thoracic dystrophy, *Ellis–van Creveld syndrome, cartilage-hair hypoplasia* and *pseudohypoparathyroidism*. Herman et al (36) described a family with facial features of trichorhinophalangeal syndrome but with the radiographic features of metachondromatosis.

Absence of exostoses should distinguish this disorder from *trichorhinophalangeal syndrome, type II* (Table 24–1). However, Jorgenson et al (44) discussed the great variation that may exist in both of these conditions and emphasized that there may be phenotypic overlap between the two syndromes. This presumably reflects the extent of chromosome deletion. Autosomal dominant cartilaginous exostoses exists without unusual facies, hair abnormalities, or cone epiphyses.

Short stature, sparse hair, and short fingers may also be observed in *cartilage-hair hypoplasia*. Carrington et al (11) described a girl with TRP initially diagnosed as having ectodermal dysplasia. H. Toriello (personal communication, 1998) has seen similar patients.

Table 24–1. Comparison of features in TRP I and TRP II and additional features of TRP II

Features	TRP I	TRP II
Features in common		
Recurrent respiratory infections	+	+
Sparse scalp hair	+	+
Large, laterally protruding ears	+	+
Bulbous nose with tented alae	+	+
Prominent elongated philtrum	+	+
Thin upper lip	+	+
Apparent mandibular micrognathia	+	+
Clinobrachydactyly	+	±
Cone-shaped epiphyses (Type 12) of the hands	+	+
Winged scapulae	+	+
Short stature	+	+
Additional features of the Langer–Giedion syndrome		
Multiple exostoses	−	+
Redundant and/or loose skin in infancy and early childhood	−	+
Laxity or hypermobility at joints	−	+
Microcephaly	−	+
Mental retardation	−	+
Significantly delayed onset of speech	−	+
Skin nevi	−	+

(Modified after BD Hall et al, Birth Defects 10(12): 147, 1974.)

Laboratory aids. Using high resolution G-banding, a number of investigators (8,9,23,31,34) have found a microdeletion of 8q23q24, while others (5,24,64) did not. Sánchez et al (77) described a boy with presumed trichorhinophalangeal syndrome, type I, who was severely mentally retarded and who, by age 9, had no exostoses; his karyotype showed a complex, apparently balanced translocation involving break points in bands 3q13, 8p22, 8q13, 11p12, and 11q21.

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Trichorhinophalangeal syndrome, type II (Langer-Giedion syndrome)

Langer (28) and Giedion (19), in 1969, first described this disorder with multiple exostoses and many features of trichorhinophalangeal (TRP) syndrome, type I. In the same year, Gorlin et al (20) reported an example among a group of TRP I cases. The condition was thus termed the "Langer-Giedion syndrome" by Hall et al (23). However, an earlier description was made by Alé and Caló (1). Most examples have been sporadic. However, father-to-son transmission and mother-to-daughter transmission have been documented (27, L Kinross, personal communication, 1999), and it has been seen in monozygotic twins (23,26). Over 30 cases published prior to 1983 have been reviewed in detail by Langer et al (29). Approximately 100 examples have been published to date.

Cases with del(8)(q24.11–q24.13) have been reported by a number of authors (3,4,6–8,14,15,17,24,29,34,37,40,41,43,45,46) while others have found normal karyotypes (19,21,29,41). Molecular study, however, shows loss of genetic material in those with "normal karyotypes" (32). Bühler et al (6–8) have concluded that TRP types I and II differ only in the size of the deletion, TRP type I having the smaller. TRP II is a contiguous gene deletion (31,32), which includes the *EXT1* gene for multiple exostoses (8,24,31,32). Genetic heterogeneity has been suggested (9). There is a no sex predilection (L Kinross, personal communication, 1999).

Craniofacial findings. The craniofacial appearance has some resemblance to that in *trichorhinophalangeal syndrome, type I*, but the nose tends to be less bulbous and the philtral area more prominent. Scalp hair is sparse, The forehead is prominent. Mild microcephaly has been a feature in approximately 60% (18,29,44,45). The eyebrows are broad and the eyes deeply set. Exotropia or exophoria has been documented in approximately 40% (23,29) (Fig. 24–41A–D). The pinnae are large and outstanding. The philtrum is long and the vermilion of the upper lips is thin.

Central nervous system. Mild to moderate mental retardation has been noted in 75% (20,23,27,29,41,45). Severe mental retardation has rarely been reported (17,18,44). Approximately 25% are normal or in the dull normal range (22,29), and some have attention deficit disorder. Delayed onset of speech (20,23,45) and, less often, moderate hearing deficit, both sensorineural and conductive, have been noted, although the frequencies affected, age of onset, and degree of severity have not been well documented (23,27,29,42). Seizures and hypotonia are more common than in the general population.

Skeletal system. In addition to skeletal abnormalities similar to those found in trichorhinophalangeal syndrome, type, I, multiple exostoses are found in 98% and are characteristic (5,17,43) (Figs. 24–41E,F and 24–42). They are usually present by the third or fourth year of life, although they may be found as early as birth. The exostoses increase in size and number until skeletal maturity. They occur in the long and short tubular bones of the limbs, primarily at the metaphyses (16,18,23,25) but may also be seen in the ribs, scapulae, and vertebrae. They may cause pain or functional problem due to pressure or interference. Cone-shaped epiphyses (Giedion, type 12) are seen in 92% in both the proximal and middle phalanges of the second to fifth fingers and in both proximal and distal phalanges of the thumb. Approximately 40% have one or more shortened metacarpal bones. The ribs may be narrowed posteriorly (6,17,20,27), and the scapulae may be winged (17). Growth retardation, postnatal in onset (2,23,29), is a constant finding, and seems to antedate multiple exostoses. Laxity or hypermobility of joints, including pes planus and calcaneovalgus foot deformities, has been observed in 65% (23,27,29). The metacarpal phalangeal pattern profile differs mildly from that of type I (11). Fractures, due to osteoporosis, have been noted in 30%. Tibial hemimelia has been described (39).

Skin and hair. During infancy and early childhood, the skin is loose or redundant in 75% (16,17,23,29). Multiple nevi are found on the face and extremities in over 50% (23,29,43). Scalp hair is sparse, but the eyebrows are full (29). Brittle nails are found in 70% (29).

Other findings. Recurrent respiratory tract and middle ear infections during infancy and childhood are found in 60% (20,23,29,43). Feeding problems during infancy and early childhood are noted in over 90% (29). This seems related to uncoordinated swallowing causing choking. Some have cyclic vomiting and/or reflux. Fryns (13) and Partington et al (34) reported hydrometrocolpos and hematometra in females. Ureteral reflux has also been documented (29,34,43,45). Miscellaneous findings have been meticulously documented by Langer et al (29). More recently, prune belly and persistent cloaca have been found (36).

Oral manifestations. Micrognathia and retrognathia (20,29) have been reported and the mandibular angle may be more obtuse than normal (23); however, measurements have not been made to confirm these subjective observations. Supernumerary central incisors (17) as well as congenitally missing teeth (17) have been noted. Malocclusion is common. Submucous cleft palate has been reported (33).

Differential diagnosis. The differential diagnosis includes *trichorhinophalangeal syndrome, type I*, although given that both TRP I and II are caused by deletions of 8q24–11, it may be argued that distinction between the two is no longer valid (see Table 24–1). Cone-shaped epiphyses occur in the general population as an isolated finding. They may also be associated with *de Lange syndrome, cleidocranial dysplasia, asphyxiating thoracic dystrophy, Ellis–van Creveld syndrome, cartilage-hair hypoplasia*, and *pseudohypoparathyroidism*. Multiple cartilaginous exostoses in the absence of other abnormalities constitute a well-established autosomal dominant entity. Three loci are involved: 8q24.1, 11p11–p13, and 19p (35).

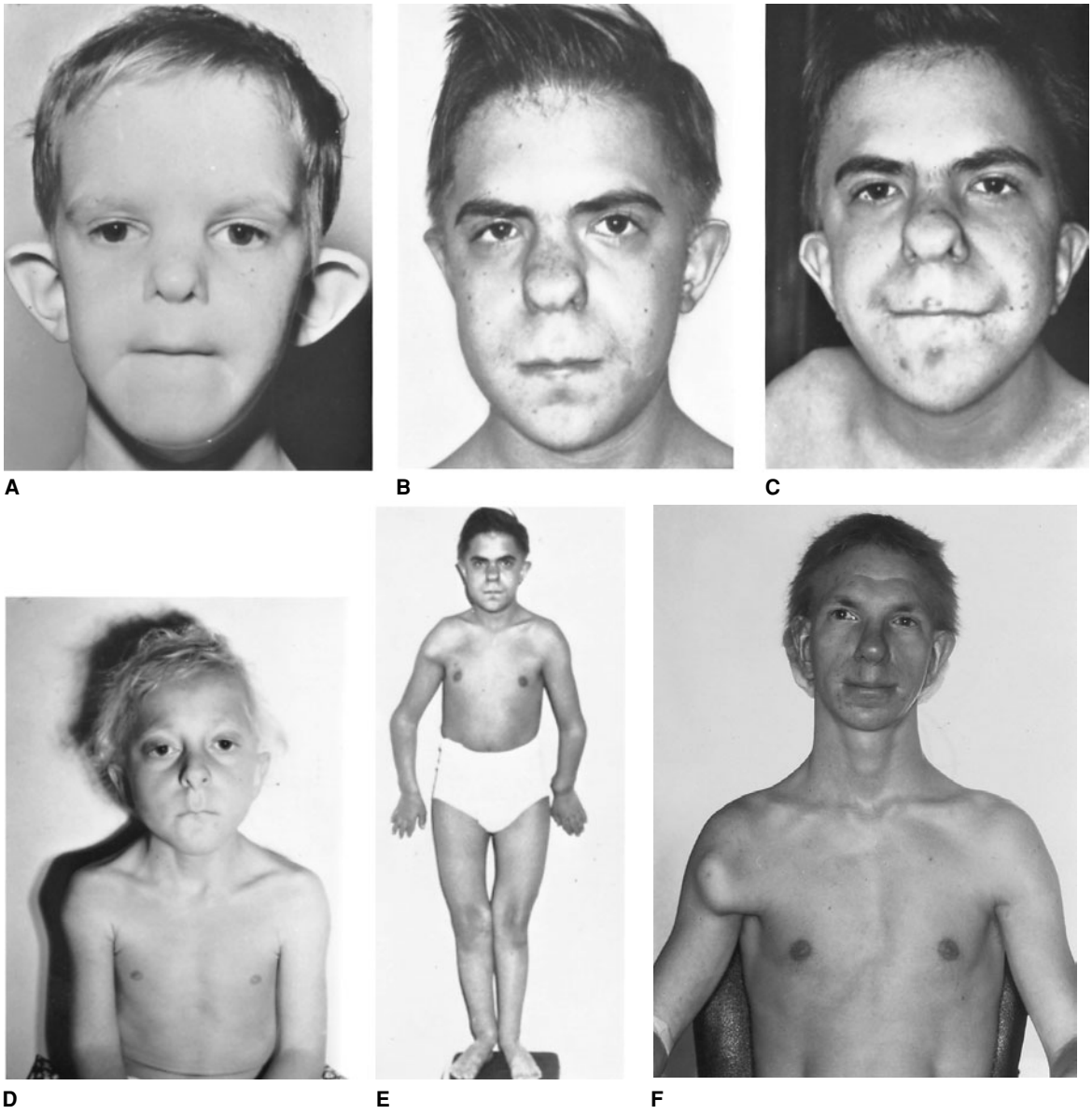

Fig. 24–41. *Trichorhinophalangeal syndrome*, *type II*. (A–D) Compare facies of four children with the disorder. All have mild microcephaly, outstanding ears. (E,F) Multiple exostoses become evident by the fourth year of life. [A–C,E from BD Hall et al, Birth Defects 10(12):147, 1974. D from RJ Gorlin et al, Am J Dis Child 118:595, 1969.]

Shabtai et al (38) reported a mother and two sons with features of trichorhinophalangeal syndrome, type II. They lacked mental retardation, microcephaly, and cone-shaped epiphyses but had a paracentric inversion of chromosome 8, inv8(q11.23;q21.1).

Deletions in 8q have been reported in patients without the trichorhinophalangeal syndrome, type II phenotype (10). At age 5 1/2 years the patient reported by Dallapiccola et al (10) still had no exostoses (12).

Lü et al (30) described an error in maternal gametogenesis in deletion of 8q23–24.1.

Laboratory aids. Karyotype analysis should be carried out to demonstrate the del(8)(q24.11–q24.13) abnormality.

References [Trichorhinophalangeal syndrome, type II (Langer-Giedion syndrome)]

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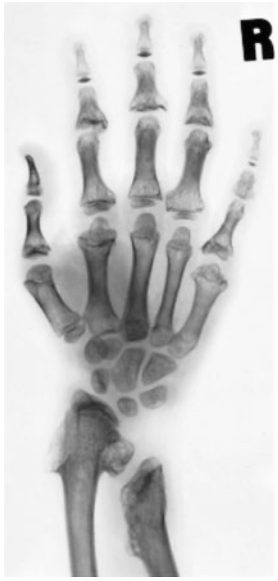

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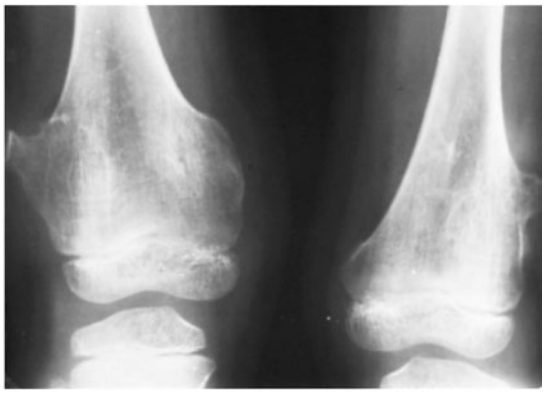

B

Fig. 24–42. *Trichorhinophalangeal syndrome, type II*. (A,B) Multiple exostoses, cone-shaped epiphyses. (A from A Giedion, Fortschr Roentgenstr 110:507, 1969. B from RJ Gorlin et al, Am J Dis Child 118:595, 1969.)

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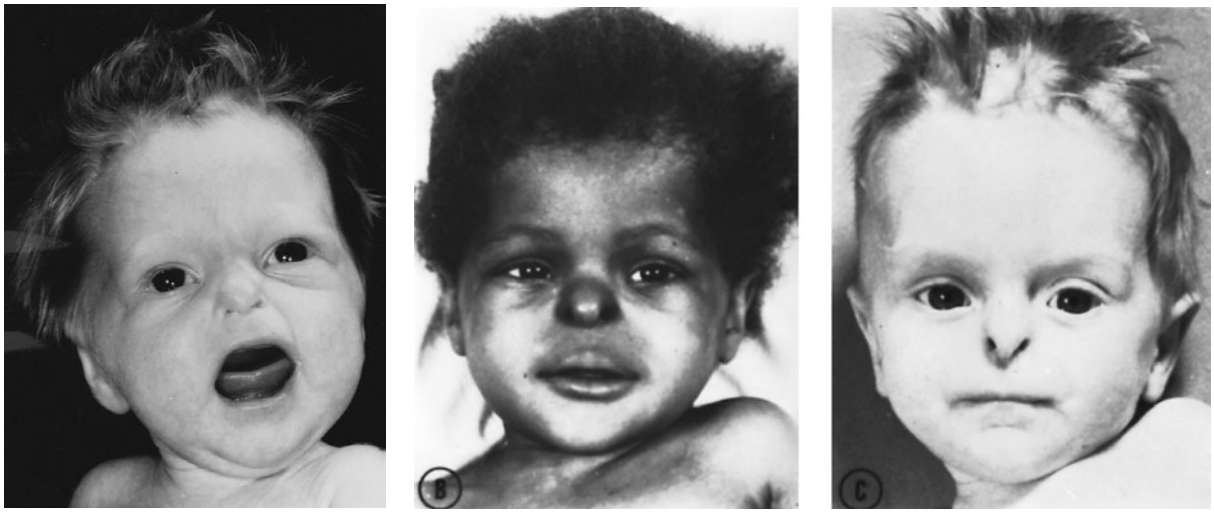
Johanson-Blizzard syndrome

Johanson and Blizzard (12), in 1971, reported three unrelated children with characteristic facies, severe mental and somatic retardation, sensorineural hearing loss, and malabsorption due to pancreatic insufficiency. The patients described in 1967 by Morris and Fischer (19) and Townes (29), in 1972, clearly had the same disorder. Approximately 30 patients have been reported (11,14). We have classified a case as probable (15) and another as an unlikely (8) example. Parental consanguinity (3,16,26,27) and affected sibs (5,10,17,24) have been reported, indicating autosomal recessive inheritance.



A B C

Fig. 24–43. *Johanson–Blizzard syndrome*. (A–C) Children exhibiting similar facies characterized by hypoplasia of nasal alae. They also have hypotonia, genital anomalies, and trypsinogen deficiency. (A from M Baraitser and SV Hodgson, J Med Genet 19:302, 1981. B and C from A Johanson and R Blizzard, J Pediatr 79:982, 1971.)

Birthweight has been low in approximately one-third of the cases (18). There is failure to thrive; somatic retardation is usually severe. At least 70% remain well below the third centile for height, weight, and head circumference with true microcephaly in 35%. Generalized edema (anasarca) due to protein loss is evident from birth. Death often occurs in childhood with malabsorption being the primary cause (31).

Facies. Aplastic nasal alae producing a beaklike nose is the most striking and constant feature of the syndrome. Aplasia of lacrimal puncta or cutaneolacrimal fistula is often noted (5,19,26). The anterior fontanel is open (19). Midline skin dimples and/or defects are noted in 90% over the anterior and posterior fontanels (7,11,12,18,26). The scalp hair is often blond, sparse, dry, and coarse. The hair in the frontal area has a marked upsweep and there is extension of the lateral hairline onto the forehead (Fig. 24–43).

A radiocephalometric study has been carried out on two patients (20). While microcephaly has been present in 35%, this was not borne out in patients studied by Motohashi et al (20) or by Sismanis et al (27). Facial, skeletal, and cranial base measurements were reduced, especially the length of the maxilla. CT of the temporal bone demonstrated cystic dilatation of the cochlea and vestibulum (2), although this is not a consistent finding (27).

Musculoskeletal. Severe hypotonia with hyperextensibility of joints is noted in 80% (12,18,19,26). Pitting edema of the hands and feet due to protein loss may be striking (19,23). Bone age is delayed in approximately 80% (20,27,29).

Genitourinary and gastrointestinal. Single urogenital orifice with infantile ovaries and double or septate vagina, clitoromegaly, micropenis, cryptorchidism, or urethrovaginal fistulae are noted in 30% and imperforate or anteriorly placed anus in approximately 50% (3,5,7,10,12,15–17, 27,30). Kristjansson et al (14) have suggested that some examples of genital hypoplasia are secondary to hypopituitarism. Pancreatic insufficiency, failure to thrive, and malabsorption have been constant features (18). Juvenile onset diabetes mellitus may be a not uncommon complication (21,31).

Central nervous system. Bilateral sensorineural hearing loss has been noted in approximately 60% (5,7,11,14,17,18,26). Speech is rudimentary both from hearing loss and psychomotor retardation. Approximately 60% of patients are mentally retarded (IQ 35–50), but intelligence may be normal (17,24) or only mildly delayed (5,11,20,29). The presence of hypothyroidism is independent of the presence of MR (6). Swanenburg-DeVeye et al (28) described a child with high intelligence. There is also some evidence that females have a better prognosis (25).

Thyroid. Hypothyroidism has been found in approximately 30% (7,11,17,18,32). The reader is also referred to several possible examples of hypothyroidism (4,5,12,22).

Skin. Nipples and areolae may be hypoplastic.

Heart. ASD, VSD, and situs inversus have been reported in 15% of the cases (10,11).

Oral manifestations. There is severe microdontia in both dentitions and, not uncommonly, the permanent dentition may be entirely absent except for the first permanent molars (32). The roots of the deciduous teeth are short, irregular, and deformed. The crowns of the few secondary teeth are frequently reduced in form, incisors being conical, maxillary molars having only three cusps. The tooth pulps are large. Permanent first molars are somewhat taurodont (22,24).

Pathology. Pancreatic changes include dramatic fatty replacement with a paucity of acini but without concomitant hypoglycemia (7,18). Jones et al (13) evaluated the nature of the pancreatic dysfunction and found reduction of secretion of trypsin, colipase, and lipase and postulated that there was primary acinar cell failure with preserved ductal function. The brain exhibits abnormal gyral formation and cortical neuronal disorganization (3,4).

Differential diagnosis. Johanson-Blizzard syndrome shares proteolytic deficiency features with other disorders: cystic fibrosis, Schwachman syndrome, *cartilage-hair hypoplasia*, trypsinogen deficiency disease, Donlan syndrome, and intestinal enterokinase deficiency. Their differentiation and the use of electrophoretic studies of pancreatic enzymes have been discussed at length by Townes (29).

While the signs and symptoms manifested by the sisters described by Reichart et al (24) are similar to those of Johanson–Blizzard syndrome, they probably represent another disorder. Guzman and Carranza (9) reported sibs, one with Donlan syndrome and one with Johanson-Blizzard syndrome and suggested these conditions are variable expression of the same entity.

Several other syndromes are characterized by varying degrees of hypoplasia of nasal alae: *trichorhinophalangeal syndrome*, *oculodentoosseous dysplasia*, *craniocarpotarsal dysplasia*, and *Roberts*

syndrome. Aplasia cutis congenita usually occurs as an isolated finding but may be seen with trisomy 13, focal dermal hypoplasia, Sakati syndrome, etc. Aplasia cutis congenita of the scalp is associated with a plethora of disorders.

Laboratory aids. Iron deficiency, low hemoglobin, fat, foul, bulky stools, hypocalcemia, and low total serum proteins are evident in early infancy (32). There is a combined proteolytic, lipolytic, and amylolytic defect manifested by complete absence of trypsin, chymotrypsin, amylase, carboxypeptidase, and lipase activities. Activation studies have proven negative. Fat and nitrogen balance studies confirm the enzyme deficiencies.

References (Johanson-Blizzard syndrome)

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Binder anomaly (maxillonasal dysplasia)

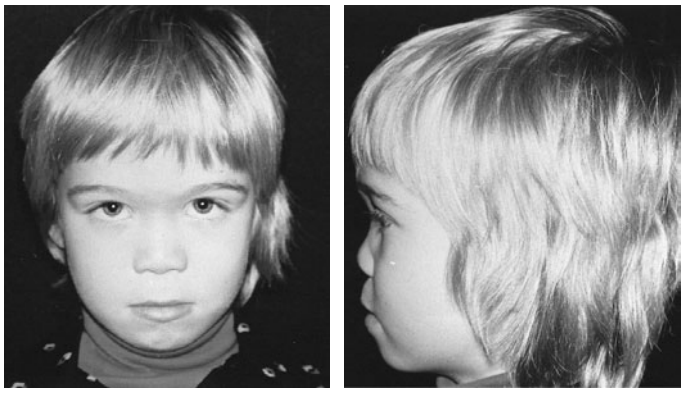
In 1962, Binder (3) reported a condition which he called maxillonasal dysostosis. He thought the condition was a form of arhinencephaly, which it is not. Noyes (22) reported an example as early as 1939 and Zuckerkandl (44), in 1882, described a similar malformation. The condition has also been called facies scaphoidea and congenitally flat nose syndrome (12).

Fifty patients were reported by Holmström (12) and well over 200 examples have been described, including several large series of cases or reviews (2,5–21,23–27,30,31–35,40–44). We believe the condition is rather common. We do not regard it as a true syndrome, agreeing with Toriello (41) that it is a nonspecific abnormality of the nasomaxillary complex, possibly related in many cases to prenatal deficiency of vitamin K (15,16). Several cases that we have seen, when sufficiently studied, were identified as being examples of chondrodysplasia punctata. The basic significance of Binder anomaly is as a surgical entity, not as a genetic, nosologic, or syndrome entity. It is neither a dysplasia nor a syndrome. Although most cases involve only the nasomaxillary complex, a variety of other anomalies have been recorded including, especially, cervical vertebral anomalies, but also various other skeletal defects, cardiac anomalies, orofacial clefting, strabismus, mental retardation, and other abnormalities (5,9,12,23,41). Many of these cases likely have a syndrome of which Binder anomaly is a component manifestation. Others have mild chondrodysplasia punctata (5,21,28,38) or, possibly, Warfarin embryopathy.

Almost all cases are sporadic (26). Affected parent and child have been noted thrice (12,21,26) and affected sibs have been observed on four occasions (12). Consanguinity has been recorded in a few instances (5,40). Holmström (12) suggested that 16% of his sample exhibited "hereditary factors." We interpret reported familial examples to result from complex genetic factors (oligofactorial inheritance) similar to those involved in producing malocclusion. Although Binder anomaly is believed to be common, it is often unrecognized in some ethnic groups, such as the Japanese (39).

Facies. The nasofrontal angle is absent and the nose is hypoplastic with flattened alae and nasal tip (Figs. 24–44 and 24–45). The profile does not change with time (37). There is a palpable depression in the anterior nasal floor and localized maxillary hypoplasia in the alar base region (12). The nostrils are half-moon shaped when viewed from below (Fig. 24–45A). The nasal mucosa has been described as atrophic, but the sense of smell is normal (3). The philtral crests may be bow shaped, rising vertically to the columella without convergence.

Radiographically, aplasia or hypoplasia of the anterior nasal spine, thinness of the labial plate of alveolar bone over the upper incisors, and an increase in the nasomaxillary angle have been observed (5,8,13,17,19,26) (Fig. 24–46). The frontal sinuses are often hypoplastic or absent (3,5). Cephalometric studies have shown increased gonial angle and proclination of the incisors (5,8,24). There are decreased anterior cranial base measurements and a smaller maxilla vertically and anteroposteriorly, although Eliasson et al (7) have suggested that less than half have maxillary retrognathia. The cervical spine is anomalous in 40%–60% (29). The atlas and axis are most frequently involved. Various anomalies include short posterior arch, block vertebrae, separate odontoid, spina bifida occulta,



A B

Fig. 24–44. *Binder anomaly*. (A,B) Typical facies, frontal and lateral views. (Courtesy of M Olow-Nordenram, Linköping, Sweden.)

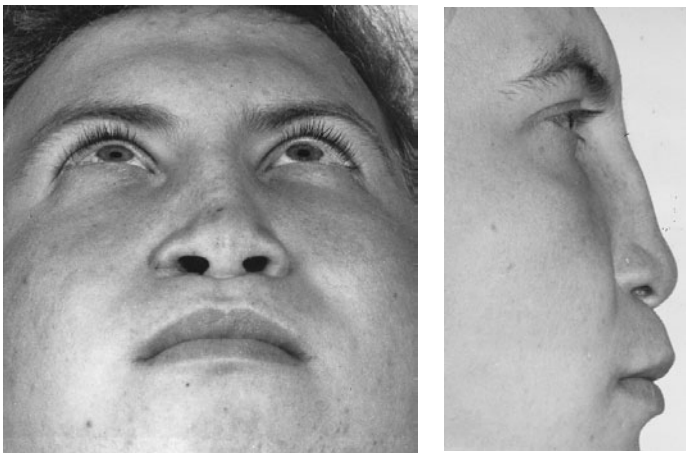
and persistence of chorda dorsalis (15%) either isolated or in various combinations. Calcifications extending from the anterior arch of the atlas have been noted as well as mild scoliosis and/or kyphosis (5,23).

Other findings. Strabismus has been found occasionally as well as mild mental retardation (5,8,14), but they probably have no statistical significance. Nonspecific congenital heart defects have been found in 5% (12,14). Hearing loss occurs in approximately 5% (8,14). George et al (9) described a girl with arteriovenous malformation of the toes. Bütow et al (4) described a boy (Case 12) with growth hormone deficiency, deafness, glaucoma, and Binder phenotype, a probable example of a Stickler-like syndrome. Minor finger anomalies have been reported (29).

Oral manifestations. The upper lip has a convex contour with poorly developed philtrum. The premaxillary area is hypoplastic, with flattening of the maxillary base and sagittal shortening of the dental arch. The mandible is of normal width, but the gonial angle is increased and the chin is flattened (5,8,24). Because of maxillary shortening, all patients have a relative mandibular prognathism with reverse overbite (class III malocclusion) (Fig. 24–47). Rarely there is cleft lip (5,12) or cleft palate (8,12,14).

Differential diagnosis. Although the facies may appear "arhinencephaloid," no brain abnormalities have been observed in this condition.

Fig. 24–45. *Binder anomaly*. (A,B) Flattened nose with depressed subnasal or alar base area and hypoplasia of premaxillary area of upper jaw. Upper lip has convex contour; nostrils are half-moon shaped. (Courtesy of H Holmstrom, Göteborg, Sweden.)



A B

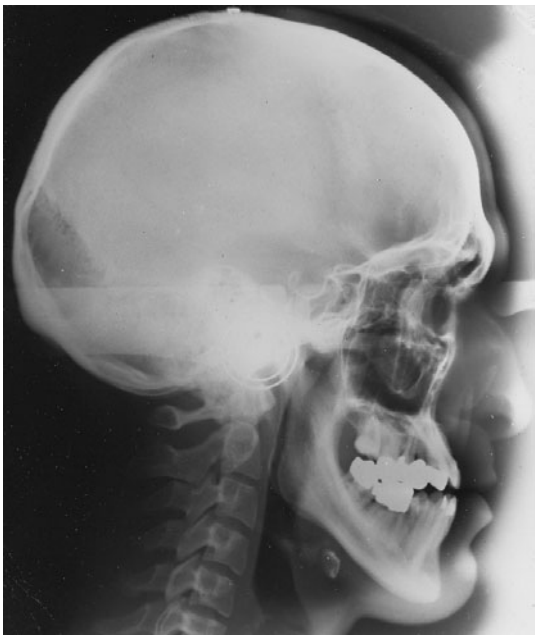


Fig. 24–46. *Binder anomaly*. Radiograph showing aplasia of anterior spine, thinness of labial plate of alveolar bone over upper incisors, and increase in naxomaxillary angle. (Courtesy of M Olow-Nordenram, Linköping, Sweden.)

The sense of smell is completely normal. Absent frontal sinuses and relative mandibular prognathism can be associated with a host of conditions and may be seen in otherwise normal individuals. Nasal hypoplasia occurs in *pseudohypoparathyroidism, acrodysostosis, Stickler syndrome, Marshall syndrome, OSMED*, and *Warfarin* or *phenytoin embryopathy*. Toriello (personal communication, 1998) recently saw a patient with a "Binder face" but with other anomalies consistent with *Keutel syndrome*. It is possible that the Binder anomaly and Keutel syndrome are allelic (21a).

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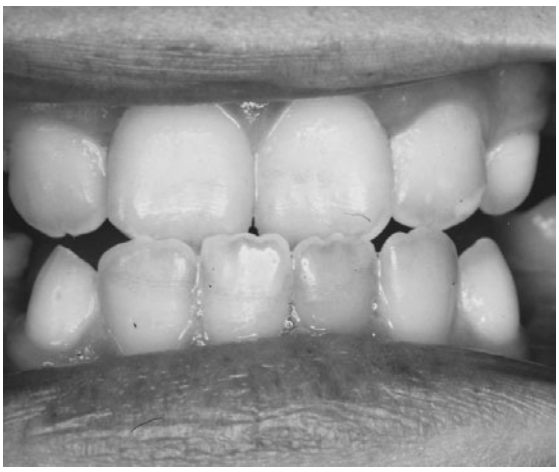
Fig. 24–47. *Binder anomaly*. Relative mandibular prognathism with reverse overbite. (Courtesy of I Jackson, Rochester, Minnesota.)



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Lenz microphthalmia syndrome

In 1955, Lenz (13) described a syndrome consisting of microphthalmia, skeletal anomalies of the hands and clavicles, renal anomalies, genital abnormalities, and defects of the dentition. Several other kindreds have been reported (2–9,12,15,18). Four cases in a family described by Hoefnagel et al (10) possibly represent the same syndrome. We are less certain about the family reported by Cuendet (4) and that of James et al (11).

X-linked recessive transmission seems apparent. Minor malformations have been noted in heterozygous carriers in some instances (9,13). Krishnamurthy (12) described fairly significant manifestations (microphthalmia, strabismus, coloboma, and skeletal anomalies) in two sisters, therefore suggesting manifestations in carrier females could be severe. Female carriers have also been noted to have an increased abortion rate, suggesting that many cases may only appear to be sporadic (5,13). Linkage studies have shown that the gene is located in the Xq27–q28 region (6a).

Facies. The forehead is high. Unilateral or bilateral eye defects ranging from colobomatous (usually) microphthalmia to clinical anophthalmia have been observed (2–13,15). Upward slanting of palpebral fissures may be present (9). Microcornea (9), strabismus (13), nystagmus (8,9), epicanthal folds (8), and blepharoptosis (2,5,7,8,10,21) as well as other defects have been reported in over 80%. Krishnamurthy et al (12) described pathologic findings in an enucleated eye from one affected boy. The ears are asymmetric, dysplastic, hypoplastic, or protuberant in 80% (2–13,15,21) (Fig. 24–48). Micrognathia has also been noted (9). Craniosynostosis occurred in one patient (6).

Central nervous system. Mental retardation and microcephaly have been reported in over 90% (2–9,15,18,21). MRI evaluation has demonstrated agenesis of the corpus callosum and dilatation of the ventral horns (17).

Musculoskeletal system. Camptodactyly of the fifth fingers (9,13, 18), clinodactyly of the second fingers (9), hypoplastic thumb (21), duplication of the thumb (13,21), symphalangism of the thumb (12), cutaneous syndactyly of the third and fourth toes, clinodactyly of toes (20), wide gap between first and second toes, pseudoclubbing of the toes, flat foot, calcaneovalgus deformity (9,15), and varus deformity (10) have been observed in approximately 60%.

Short stature (1–5,7,8,12–15), cylindrical thorax with sloping shoulders and clavicular defects (5,9,12,13,15,18), kyphosis (5), low scapulae, notching of the vertebral bodies, mild cubitus valgus, limited extension in both hip joints, and mild genua valga with internally rotated knees and prominent fibulae (9) have been reported (Figs. 24–49 24–50).

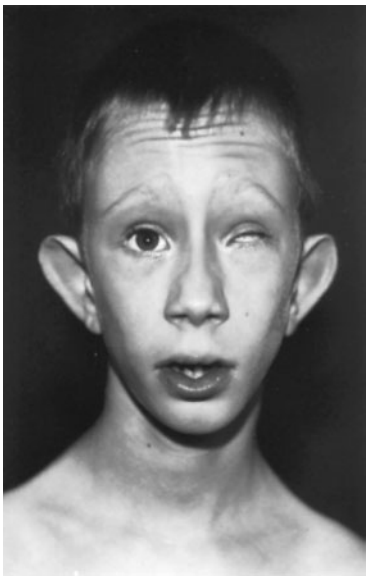


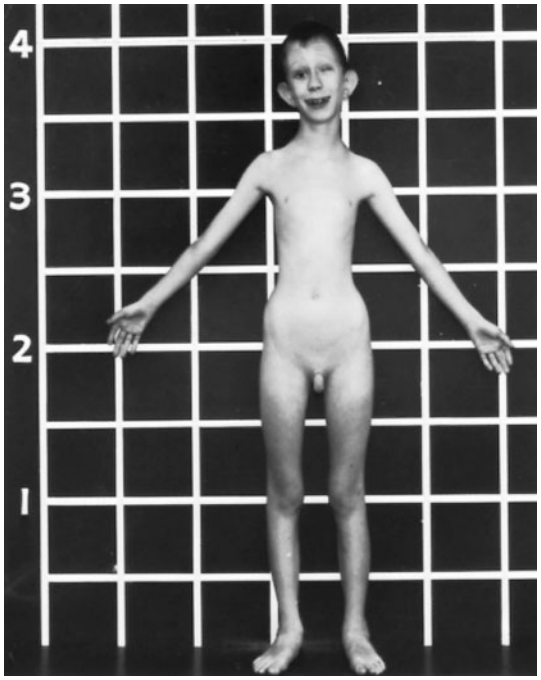
Fig. 24–48. *Lenz microphthalmia syndrome*. Eye defects range from microphthalmia to clinical anophthalmia and may be unilateral or bilateral. Note outstanding ears. [From J Herrmann and JM Opitz, Birth Defects 5(2):138, 1969.]

Genitourinary system. Unilateral renal agenesis (13), bilateral renal agenesis (10), renal dysgenesis, hydroureters (9), cryptorchidism (9,13,15,18), and hypospadias (5) were described in approximately 50%.

Other findings. Congenital heart defect (13), atresia of the ileum (10), umbilical hernia, unusual dermatoglyphics (9), defective speech (9,10), and hirsutism of lower back (5,9,18) have been noted.

Oral manifestations. Highly arched palate, cleft palate (2,4,7,9), crooked anterior teeth (9,13), and agenesis of the permanent maxillary lateral incisors (9,18,19) have been reported in approximately 65%.

Fig. 24–49. *Lenz microphthalmia syndrome*. Patients are short with cylindric thorax and internally rotated knees. [From J Herrmann and JM Opitz, Birth Defects 5(2):138, 1969.]



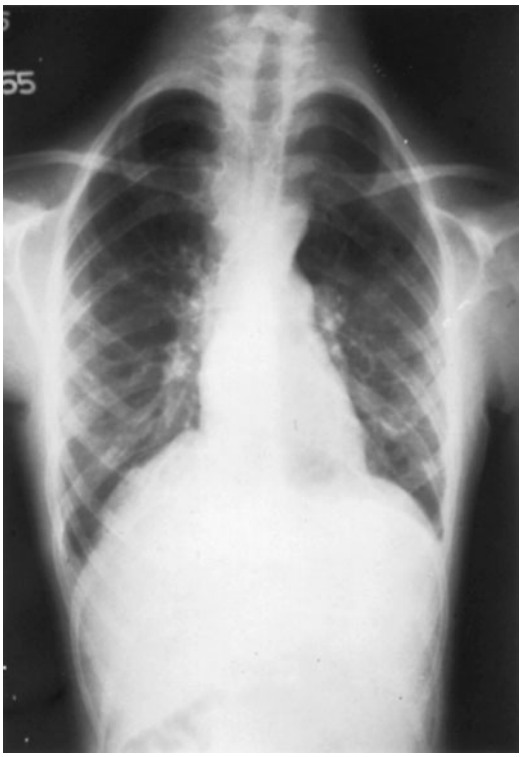


Fig. 24–50. *Lenz microphthalmia syndrome*. Radiograph showing cylindric thorax, sloping shoulders, and clavicular defects. (From JM Opitz, Birth Defects 5(2):138, 1969.)

Differential diagnosis. Isolated bilateral anophthalmia is inherited as an autosomal recessive trait. Microphthalmia may be inherited as an autosomal dominant, autosomal recessive, or X-linked recessive trait. Microphthalmia may also occur as an integral part of several different disorders (14). There is some overlap with the *Nance-Horan syndrome* (22) and an X-linked syndrome consisting of microcephaly, microphthalmia, corneal opacities, hypospadias, cryptorchidism, and dental anomalies (20). Similar changes are also seen in *dup(10q) syndrome*.

Laboratory aids. Ultrasound studies are indicated in affected individuals.

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Cryptophthalmos syndrome (Fraser syndrome)

The cryptophthalmos syndrome is characterized by cryptophthalmos, syndactyly, abnormal genitalia, and other variable defects such as nasal colobomas, malformed ears, cleft lip–palate, renal agenesis, and mental deficiency. The syndrome was first described by Zehender (67), in 1872, although it has been suggested that Pliny the Elder may have reported it in the first century AD (21). Over 150 cases have been described (1–5,7–11,12–38,43–45,47,49–57,59–63,66,67). The most extensive review is that of Thomas et al (55). Several other reviews are also available (18,21,27,30,35,44,47,51,53). Histopathologic documentation of the ocular manifestations is especially well reviewed by François (18), and detailed postmortem studies have been reported (4,38,45,47,55).

The syndrome has autosomal recessive inheritance. Among 86 cases, 48 were familial and 38 were sporadic. Consanguinity has been reported in 6 of 42 families in which published pedigree data are available (55). Winter (65) and Darling and Gossier (12) suggested that Fraser syndrome could be homologous to one of the mouse bleb mutants. Because the syndrome is variably expressed, including some infants without cryptophthalmos (6,33,43) and some cases of isolated cryptophthalmos occurring as a separate entity, Thomas et al (55) proposed diagnostic criteria of the syndrome (Table 24–2). Cases were diagnosed on the basis of at least two major criteria and one minor criterion or on the basis of one major criterion and at least four minor criteria. The frequencies of individual syndrome manifestations are listed in Table 24–3. Gattuso et al (21) surveyed 68 cases. Figures differ somewhat from those of Thomas et al (55).

Approximately 50% survive for a year or more, 25% are stillborn, and 20% die within the first year of life with most deaths occurring within the first week of life. Death is usually associated with renal agenesis and laryngeal stenosis (4,21).

Craniofacial features. The face is asymmetric in approximately 10% (21). The eyebrows may be completely or partially missing (66). The globes can be seen and felt beneath the skin covering, which extends from the forehead over the eyes. Cryptophthalmos is found in 85%, and in approximately 72% of these there is bilateral involvement (55) (Fig. 24–51A–D). With unilateral cryptophthalmos, the opposite eye may exhibit upper lid coloboma, microphthalmia, epibulbar dermoid, or supernumerary eyebrows (55,63). The conjunctival sac is partially or completely obliterated, and lashes, meibomian glands, and lacrimal glands are absent. The cornea is differentiated from the sclera. The lens may be absent, hypoplastic, or calcified and displaced. Orbicularis and levator palpebrae muscles are, however, normal (68). Exposure to strong light may induce reflex wrinkling of the skin because of contraction of the orbicularis muscles (21). Surgical correction of the lid defect has been described (5,13,54,63); however, prognosis for vision is considered poor (21), although ERG and flash-VEP studies done in one child were normal (28). Rarely there is Potter facies (21). Pankau et al (46) reported a child with normal eyelids but anophthalmia. The diagnosis of Fraser syndrome may be questionable.

The hairline is bizarre in at least 25%, extending over the entire temple area and tapering to a point on the skin of the forehead overlying the eyes.

Nasal abnormalities are seen in approximately 85%. Most frequently the nose is broad with a low nasal bridge. Colobomas of the alae nasi, either unilateral or bilateral, may be observed, and midline grooving of the nasal tip has been noted (2,24,25,53,55,57,60,68). Choanal atresia is an occasional finding (19,28,49,66).

Cleft lip and/or cleft palate and ankyloglossia have been found in approximately 10% (21). Malocclusion and, on occasion, hypoplastic teeth have been reported (2,18,25,30,51,68). Laryngeal atresia or hypoplasia, as well as laryngeal cysts, laryngomalacia, or subglottic diverticulum occur in approximately 80% (2,32,49,55,60), and lung hyperplasia has been documented (36,52).

Table 24–2. Diagnostic criteria for the cryptophthalmos syndrome

Major
Cryptophthalmos
Syndactyly
Abnormal genitalia
Sibling with cryptophthalmos syndrome
Minor
Congenital malformation of nose
Congenital malformation of ears
Congenital malformation of larynx
Cleft lip and/or palate
Skeletal defects
Umbilical hernia
Renal agenesis
Mental Retardation

(From IT Thomas et al, Am J Med Genet 25:85, 1986.)

Table 24–3. Frequency of individual manifestations in cryptophthalmos syndrome

Features	Percent	(Sample size)
Craniofacial		
Cryptophthalmos	85	(93)
Abnormal nose	84	(62)
Abnormal ears	83	(64)
Cleft lip–palate	9	(65)
Abnormal larynx	81	(27)
Limbs		
Syndactyly	78	(78)
Urogenital		
Abnormal genitalia	80	(71)
Renal agenesis	84	(37)
Performance		
Mental deficiency	81	(21)
Other		
Skeletal defects	70	(33)
Umbilical hernia	28	(60)

(From IT Thomas et al, Am J Med Genet 25:85, 1986.)

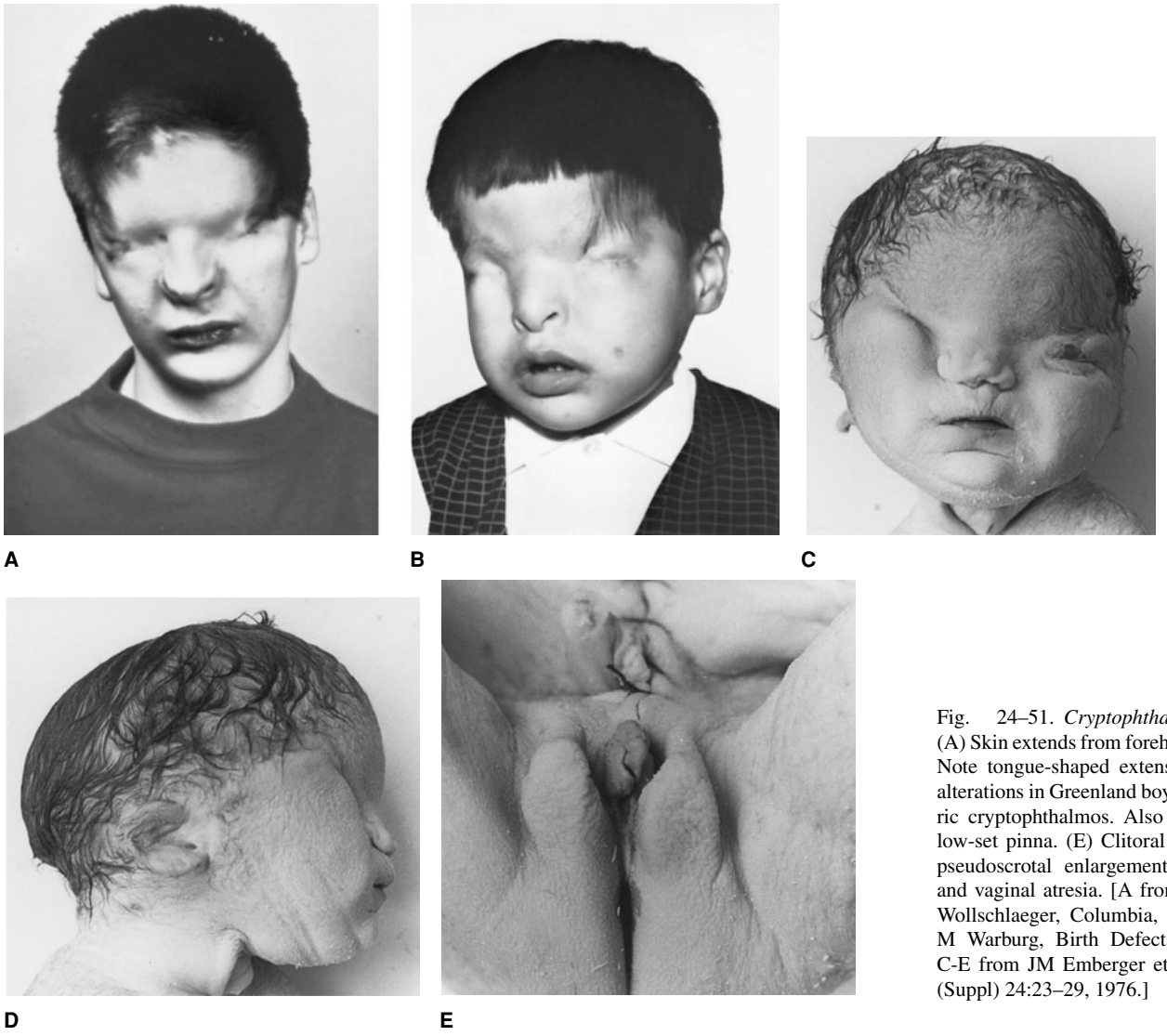

Fig. 24–51. *Cryptophthalmos syndrome*. (A) Skin extends from forehead covering eyes. Note tongue-shaped extensions. (B) Similar alterations in Greenland boy. (C,D) Asymmetric cryptophthalmos. Also note dysmorphic, low-set pinna. (E) Clitoral enlargement with pseudoscrotal enlargement of labia majora and vaginal atresia. [A from CH Ide and PB Wollschlaeger, Columbia, Missouri. B from M Warburg, Birth Defects 7(3):136, 1971. C-E from JM Emberger et al, J Genet Hum (Suppl) 24:23–29, 1976.]

The ears are abnormal in approximately 85% (32). They may be malformed and/or low set (30%), small (10%), or with fusion of the superior margin of the helix to the scalp (6%) with stenotic external ear canals (6%–15%) or with some combination of these (21,24,30,44,55,60) (Fig. 24–51D). Conductive hearing deficit is common and malformed ossicles have been noted (21,30).

Urogenital anomalies. Abnormal genitalia found in approximately 80% include cryptorchidism (7%), hypospadias, chordee, hypoplastic penis (20%), large clitoris (20%), large labia majora, vaginal atresia (15%), bicornuate or rudimentary uterus (20%), and ambiguous external genitalia (5,10,15,21,30,31,37,38,44,55,56,59,61,68) (Fig. 24–51E).

Endocrine studies in one girl with primary amenorrhea were normal (9). Greenberg et al (23) reported gonadal dysgenesis and gonadoblastoma. Renal agenesis occurs in 85% and may be either unilateral (37%) or bilateral (47%) (2,3,11,15,17,18,30,37,38,43,44,55). Abnormalities of the ureter and/or bladder are found in 10%–15% (21). Anterior urethral structure has also been documented (1).

Extremities. Marked soft-tissue syndactyly has been observed in 60%–75% (21,30,53,54,62,67,68). In most cases, both fingers and toes are involved, although in some instances, either fingers or toes alone may be affected (Fig. 24–52).

Central nervous system. Mental deficiency is observed in approximately 80% of those patients whose intelligence has been documented. Malformations of the central nervous system occur in approximately 20% and may include encephalocele (10%) or occasional anomalies such as Dandy–Walker cyst or absent left ventricle. Some patients have calcification of the falx cerebri (18,22,29,30,37,53,55,67,68).

Other abnormalities. Skeletal defects occurring in approximately 70% include small orbits, skull asymmetry, abnormal facial bones and sinuses, deformed optic foramen, absent sphenoid wing, parietal lucent defects, and diastasis of the symphysis pubis (29,30,38,44,55,59,60,67). Other low frequency skeletal anomalies have been summarized by Thomas et al (55).

Omphalocele or umbilical hernia has been noted in 10% (21,67). Low insertion of the umbilicus has been described, and may not be rare (57). Congenital heart defects have been recorded in approximately 5%. Anal anomalies, thymic aplasia or hypoplasia, intestinal hypoplasia, intestinal malrotation, and other less commonly occurring anomalies are listed elsewhere (21,32,55,66).

Differential diagnosis. Isolated cryptophthalmos may be either unilateral or bilateral and may, on occasion, have midline nasal grooving. Approximately two-thirds of these cases are sporadic, one-third occurring as an autosomal dominant trait (48,55). Brownstein et al (6) reported a patient with bilateral corneal and lenticular opacities, malformed nose, anomalous ears, bilateral renal agenesis, and cryptorchidism. Mena (42) described siblings with fused eyelids, subglottic stenosis, digital anomalies (but not syndactyly), and ovarian cysts. Marles et al (39) described unilateral upper eyelid coloboma, abnormal anterior hairline, and anal anomalies. Turner (58) and Winter et al (64) described a syndrome

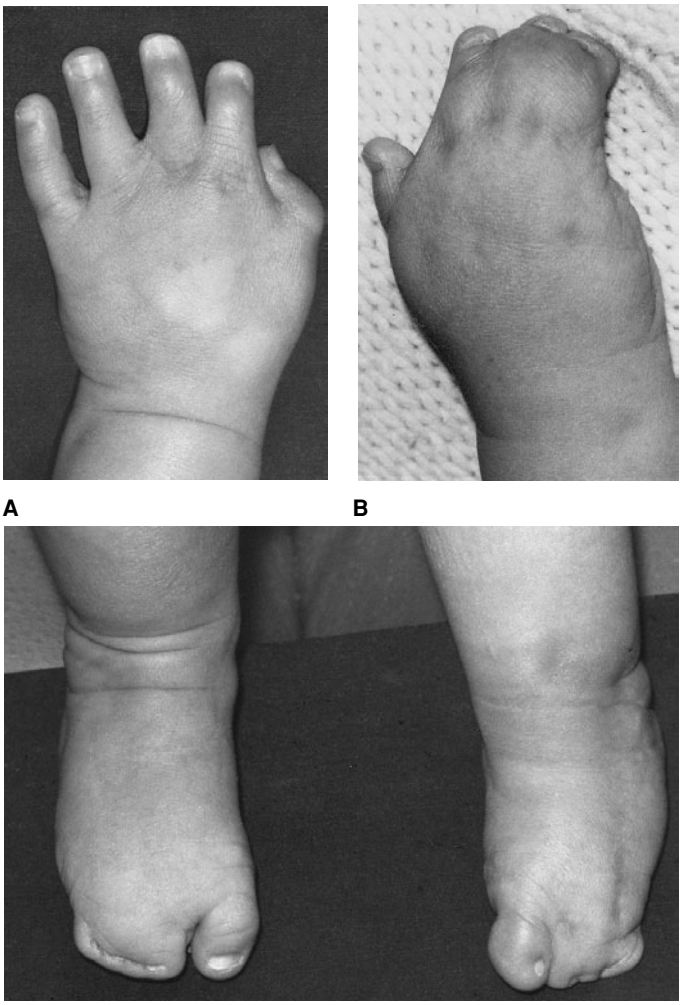

Fig. 24–52. *Cryptophthalmos syndrome*. (A,B) Varying degrees of syndactyly. Note similarity of changes in B to Apert syndrome. (C) Marked syndactyly of toes, somewhat resembling that seen in Apert syndrome. [From N Dinno et al, Birth Defects 12(6):109, 1976.]

characterized by renal agenesis, genital abnormalities, anomalous ears with stenotic ear canals, ossicle defects, and, in some instances, an abnormal nose with grooving of the nasal tip. Martínez-Frías et al (40) described a child with sclerocornea, syndactyly, and ambiguous genitalia. In their review of mouse bleb mutants, Darling and Gossier (12) suggested that there may be several nonallelic genes which could lead to a similar phenotype. This may be the explanation for some of the above-mentioned conditions. The cryptophthalmos syndrome should easily be distinguished from *ablepharon-macrostomia syndrome* (41).

Laboratory aids. Prenatal diagnosis has been made using fetoscopy and ultrasound (4,16,21,50).

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Nasal alar colobomas, mirror hands and feet, and talipes (Laurin-Sandrow syndrome)

In 1964, Laurin et al (7) first described mirror image duplication of the ulna and fibula with absence of the tibia and radius, talipes equinovarus, and dislocated knees. No mention was made of unusual facies, but examination of the photograph shows a distinctly unusual nose. Sandrow et al (12), in 1970, documented a father and daughter with mirror hands and feet and unusual face. Several other examples have confirmed the syndrome (2,3,4a,6,8,9). There have been other cases (1,11) in which the nose appears normal. The mandibular condyle is enlarged (4a).

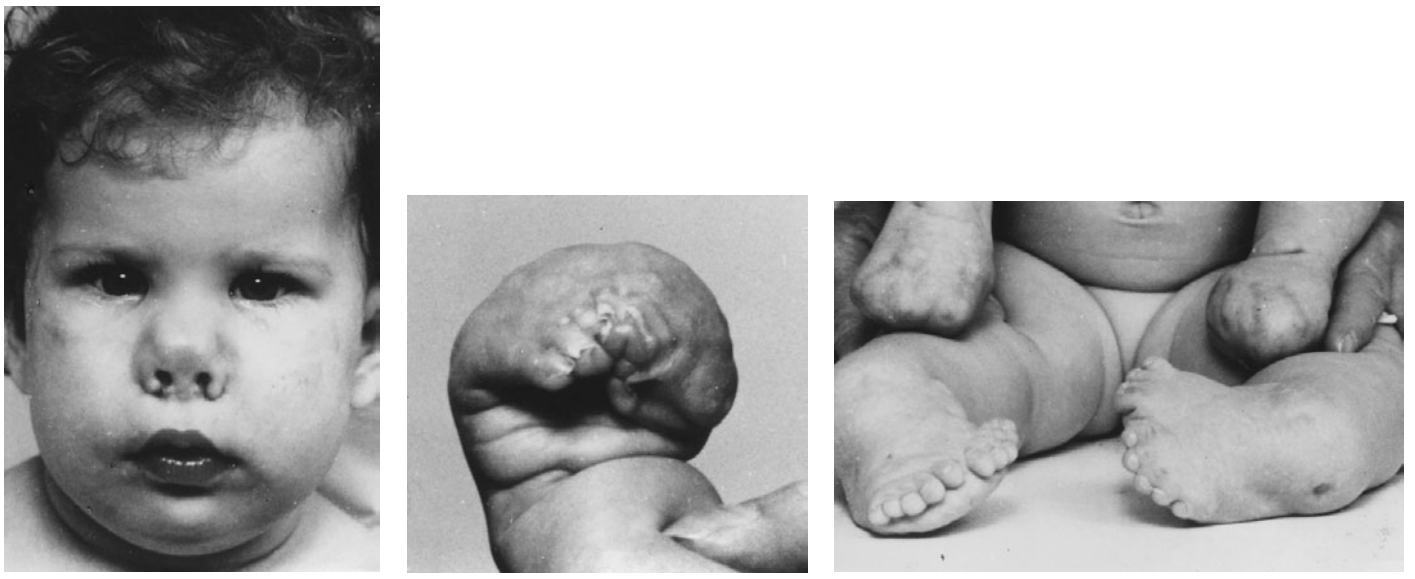
The occurrence of syndrome in parent (milder) and child in several cases (1,8,12) indicates autosomal dominant inheritance with variable expression. All other examples have been sporadic. A gene for mirror image polydactyly has been mapped to 14q13 (10).

The face is distinctively characterized by upturned nose, hypoplasia of the nasal alae with coloboma, and short grooved columella (Fig. 24–53A).

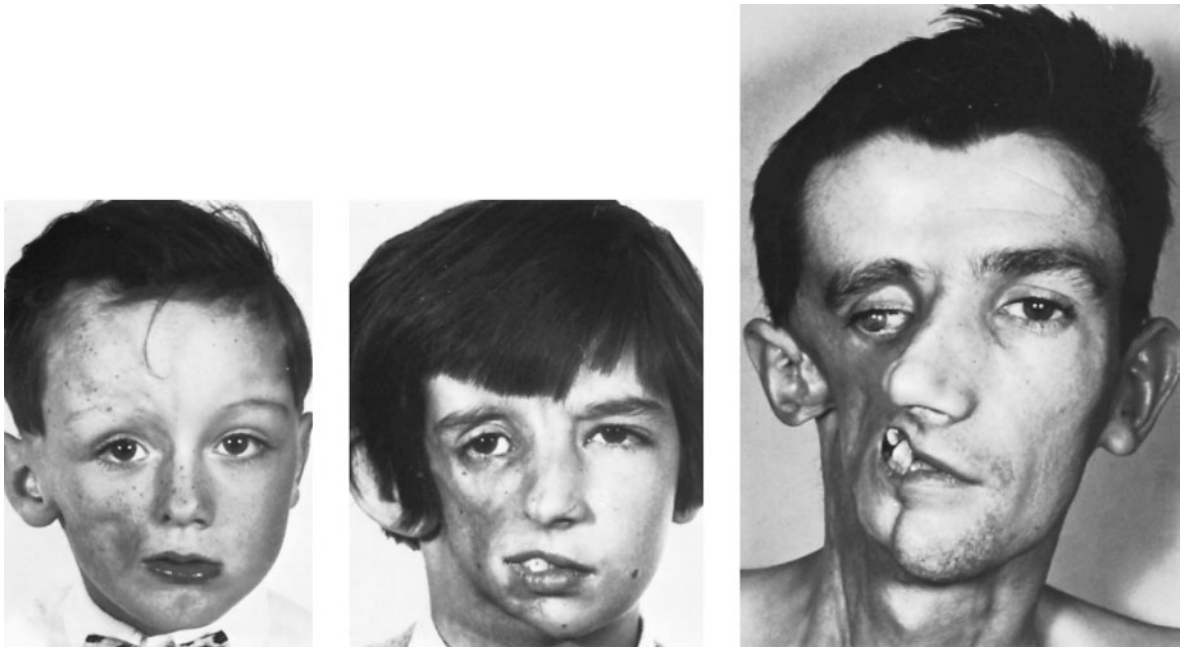
The arms and legs exhibit absent or hypoplastic radius and tibia (which may not be symmetrical) and duplication (dimelia) of the ulna and fibula. Supernumerary digits with complete syndactyly are arranged in mirror form (mirror hands and feet). The hands have mitten or rosebud form. The feet may show a median fused wide hallux. Duplication of carpal and tarsal bones in combination with talipes equinovarus and dislocated knees are usually noted (Fig. 24–53B,C).

Mirror imaging seems to depend on the gene, *Sonic Hedgehog*, which induces and regulates FGF4 in the apical ectodermal ridge, creating a positive feedback loop between the apical ectodermal ridge and the zone of proliferating activity in the limb bud. Possibly the inductive interactions of these factors indicate expression of a homeobox D gene or bone morphogenetic protein 2 or 4. Probing discussions of various possibilities are those of Hersh et al (3) and Kim et al (5). Mirror imaging can accomplished experimentally by implanting the zone of proliferating activity beneath the apical ectodermal ridge. Retinoic acid will do the same thing. We suspect that there are examples of the syndrome that have been classified as Werner syndrome 2 (4).

Fig. 24–53. *Nasal alar colobomas, mirror hands and feet, and talipes*. (A) Unusual facies marked by short nose, hypoplasia of nasal alae, and defective columella. (B) Mirror duplication of hands and extensive syndactyly leads to rosebud appearance. (C) Similar mirror duplication in feet. Note deep skin dimple, and talipes equinovarus. (Courtesy of HH Steele, Philadelphia, Pennsylvania.)



A B C



A B C

Fig. 24–54. *Romberg syndrome*. (A–C) Increased severity of disorder in patients illustrated from left to right. (A,B, from D Glass, Br J Oral Surg 1:194, 1963. C courtesy of P Cernea, Paris, France.)

References [Nasal alar colobomas, mirror hands and feet, and talipes (Laurin–Sandrow syndrome)]

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Romberg syndrome (progressive hemifacial atrophy)

Romberg syndrome consists of slowly progressive atrophy of the soft tissues of essentially half the face accompanied most frequently by contralateral Jacksonian epilepsy, trigeminal neuralgia, and changes in the eyes and hair. Romberg (52) is usually credited for delineation of the disorder, but Parry (47) discussed the disorders as early as 1825. The condition has been called progressive facial hemiatrophy (1,3,4,6,16,18, 28,32,35,37,39,40,43,46,49,56,61,70,71,72), hemifacial atrophy (6,14, 17,19,20,26,29,38,41,48,64), and Parry-Romberg syndrome (12,25,27, 30,34,55). Comprehensive surveys have been carried out by a number of authors (3,6,11,15,34–36,39,42,50,63,68,69). Over 1000 examples have been reported (48). Surgical aspects are particularly well covered by Rees (50) and Saccomanno et al (55). Classification is discussed by Roddi et al (51).

Nearly all cases have been sporadic, but several familial instances have been recorded (22,29,69). Familial aspects have been particularly well reviewed by Lewkonia and Lowry (34); however, discordant monozygotic twins have also been described (31) casting doubt on a single autosomal dominant gene as the cause. Theories of pathogenesis have been numerous (3,69), most emphasis being placed on alterations in the peripheral trophic sympathetic system (24,70). Up to a third of affected individuals have had a history of prior trauma or surgery (13,28,37). Moss and Crikelair (40) carried out unilateral cervical sympathectomy in rats and produced a condition that resembled hemifacial atrophy in the human. Studies have also investigated the role of autoantibodies or antibodies to infectious agents with mixed results (1,2,18,25). The presence of multiple aneurysms in one child suggested a neural crest migration disorder to the authors (56), although this hypothesis has been disputed (9). Thus it is likely that this condition is heterogeneous, with a genetic cause in some, but attributable to environmental factors such as trauma, infection, or autoimmunity as other causes (31). Pensler et al (48) opined etiology in chronic cell-mediated vascular injury.

Face, skin, and hair. In advanced cases, the face is quite distinct (Fig. 24–54). The ear may become misshapen and smaller than normal or, because of lack of supporting tissues, may project from the head (26). Basilar kyphosis, an alteration in the basal skull angle, has been described (14). An extensive cephalometric study was carried out by Berkman (6). Early facial change, usually appearing during the first decade (average-9 years) (Fig. 24–54), involves the paramedian area of the face and slowly spreads, resulting in atrophy of underlying muscle, bone, and cartilage. First to be involved is usually the area covered by the temporal or buccinator muscles. The process extends to involve the brow, angle of the mouth, neck, or even half the body (3,69) (Fig. 24–55). There is a marked predilection for left-sided involvement of the face. The overlying skin often becomes darkly pigmented. The condition slowly progresses for several years (about 9 years) and then usually becomes stationary for life (14,26,57). In those with skeletal involvement, onset is at an earlier age (5 years vs. 15 years).

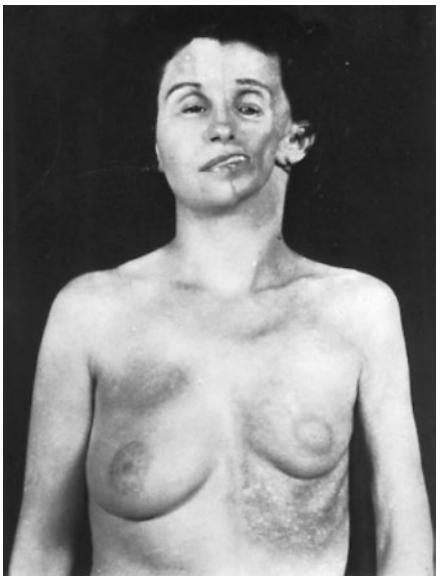

Fig. 24–55. *Romberg syndrome*. Involvement of half of body. (From AJ Barsky et al, Principles and Practice of Surgery, 2nd ed. McGraw-Hill, New York, 1964.)

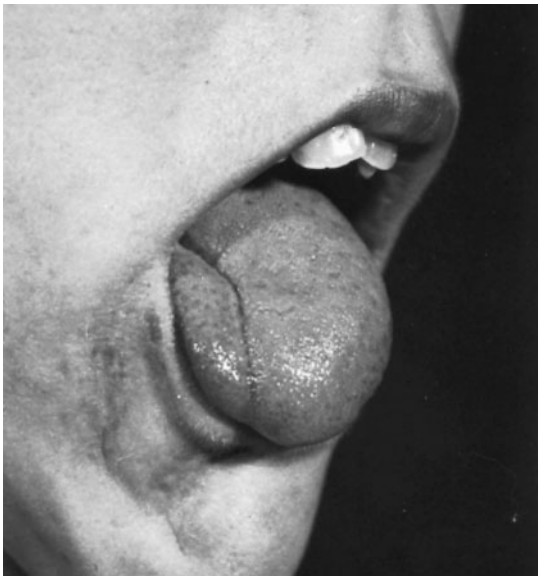

Fig. 24–56. *Romberg syndrome*. Atrophy of right side of tongue.

There has been a long-standing debate about the relationship between progressive hemifacial atrophy and scleroderma, several authors stoutly defending the position that the coup-de-sabre form of scleroderma is only a special type of progressive hemifacial atrophy (3,33,65,68,70). Others indicate that the two conditions may occur simultaneously (44). Lewkonia and Lowry (34) suggested that progressive hemifacial atrophy be considered an anatomically limited form of linear scleroderma without extensive limb or trunk involvement, although some patients diagnosed with Romberg syndrome had multiple sites of localized scleroderma on the body, or atrophy or neural involvement of the arm, chest, and/or back (30,48). There is therefore some support for the hypothesis that these conditions form a spectrum (38). It should be pointed out that, in some instances, the skin is spared while only fat and subcutaneous tissue disappears. Occasionally, vitiligo accompanies the disorder (13,58).

Changes in the hair may precede those of the skin (3,70,71). The scalp on the affected side may exhibit circumscribed but complete alopecia limited to the paramedian area, eyelashes, and median portion of the eyebrows (70). Poliosis, or blanching of the hair, has also been noted (69).

Ocular manifestations. Ocular manifestations are particularly well documented by Muchnick et al (41) and occur in 35%. Loss of periorbital fat results in enophthalmos in 80% (45,68) or, rarely, upper eyelid retraction (23) in those with involvement of the first trigeminal division. Underlying bone may disappear causing the outer canthus to be displaced downward. Muscular paralysis has been noted by several authors (20,22), as well as lagophthalmos and ptosis (3,20,70). Horner syndrome, heterochromia iridis, upper eyelid coloboma, and dilated and fixed pupil have also been reported. More rarely, posterior segment involvement can occur, and includes uveal coloboma, chorioretinal atrophy, and retinal pigmentary changes (43). Common inflammatory processes involving the eyes include neuroparalytic keratitis, iritis, iridocyclitis, choroiditis, papillitis, and cataract (22,24,69). In some instances, ocular findings may affect the eye on the contralateral side (22). Duane anomaly was described in one child (60). Vision may be mildly impaired or blindness can occur (39).

Oral manifestations. Atrophy of half of the upper lip and tongue are characteristic (46) (Fig. 24–56). Maxillary teeth on the involved side are exposed. Spontaneous fracture on the affected side of the mandible has also been noted (7,20,65,71). Other dental anomalies include delayed tooth eruption, abnormal root morphology, and, in rare cases, root resorption (19).

Radiographically, the body and ramus of the mandible are shorter on the involved side, and delayed development of the mandibular angle may be observed, resulting in malocclusion. Teeth on the affected side occasionally are delayed in eruption or have atrophic roots (21,26,53,54,62).

Central nervous system. The most common neurologic finding is epilepsy, often of the sensory Jacksonian type, which frequently appears late (3,4,9,17,49,69,71). However, trigeminal neuralgia and/or facial paresthesia may appear early, preceding other neurologic changes. Migraine has also been an occasional finding (17,69,71,72). MRI imaging has demonstrated intracranial calcifications, cerebral atrophy, porencephaly, and agenesis of the right caudate nucleus (10,12,16, 21,27,32,38,66,67) especially in those with neurologic signs or symptoms. Abnormalities of cerebral vasculature were found in one patient (72), and cerebral aneurysms were described in two (56,64).

Differential diagnosis. Asymmetric facial deformities have a diversity of manifestations and causes and these have been discussed by Souyris et al (62). Congenital facial hypoplasia can be diagnosed by its presence at birth and diminution of tooth size on the affected side following eruption (5,8,54). Scleroderma (60), fat necrosis, and *oculo-auriculo-vertebral spectrum* should also be considered.

References [Romberg syndrome (progressive hemifacial atrophy)]

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Leprechaunism (Donohue) and pseudoleprechaunism (Patterson-David) syndromes

Although the first description of this condition is attributed to Donohue (13) in 1948, Baumeister (4) suggests that Janssen and deLange first described this as familial congenital hypertrichosis totalis. The syndrome consists of failure to thrive, unusual facies, facial hirsutism, sexual precocity, retarded bone age, and insulin resistance with glucose intolerance and hyperinsulinemia. The term "leprechaunism" was introduced by Donohue and Uchida (14) in 1954.

The disorder has autosomal recessive inheritance, but there has been a 2:1 female predilection (6). Affected sibs (12,39,40) and increased (30%) parental consanguinity (6,8,11,12,14,27,39,41) have been noted. Approximately 50 examples have been reported (6,17).

The basic defect is a mutation in the insulin receptor gene which maps to 19p13.2–13.3. (2,25,26,30,36,38). Human insulin receptor is

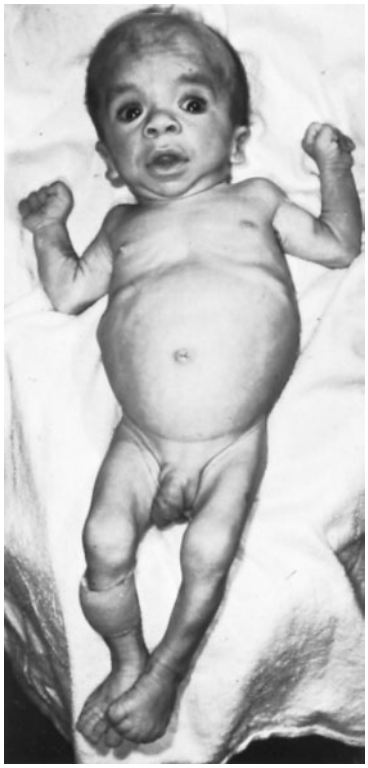

Fig. 24–57. *Leprechaunism*. Note hirsutism, large hands, feet, and penis.

composed of two extracellular alpha subunits which bind insulin and two beta subunits which span the plasma membrane (18,22). The receptor is encoded by a single gene. A great variety of mutations have been identified, with single base pair changes, deletions, and alternative splicing of mRNA. It is theorized that insulin receptor defects may also impair the function of other receptors, thus accounting for the varied aspects of the phenotype. Wertheimer et al (47) showed that homozygous deletion of the insulin receptor gene results in leprechaunism. Elsas et al (17) opined that two different recessive mutations impair high-affinity insulin receptor binding and that leprechaunism represents a compound heterozygote for these mutations: Most patients have a nonsense and missense mutation, although patients with nonsense mutations of both alleles have also been described (30,32). Target cell resistance to insulin varies according to age of onset. In leprechaunism, there is severe insulin resistance that results in small babies with almost an entire absence of subcutaneous fat and poor muscular development, poor early growth, and early death (37). Intravenous insulinlike growth factor I did not improve hyperglycemia or produce an anabolic effect (3).

Gestation tends to be short. Nearly all infants have been marasmic, and over 60% have died at less than 2 years of age (6,7,15,23,40).

Facies. The face is gaunt, with large ears and lips. The eyes appear widely spaced (43). Facial hirsutism may be marked (14,27,31,39–42) (Fig. 24–57).

Musculoskeletal changes. Muscle mass is severely wasted. The abdomen is distended. Bone age is usually retarded (1). The hands and feet appear disproportionately large (11,14,19,39,41) (Fig. 24–57).

Skin. Acanthosis nigricans has been observed in most cases (15,19,31,39,40). Hirsutism is usually marked. Periorificial skin rugosities, prominent nipples, and dysplastic nails have been noted (40,43).

Endocrine changes. The breasts and clitoris or penis have been enlarged in over 50% and 75%, respectively (6). There have been cystic alterations in the ovaries or testes (1,7,14,19,23,27,40). Bilateral granulosa cell tumors of the ovaries were reported by Brisigotti et al (5). Rogers (38a) described basophilic hyperplasia of the pituitary gland. Pancreatic islet cell hyperplasia (nesidioblastosis) with low fasting blood sugar level is common (1,14,19,21,40,41,44).

Oral manifestations. Large mouth, thick lips, and gingival hypertrophy are present at birth (12,15,39,40). Roth's (40) patient at age 5 had a dental age of 14 years. Whether other children had advanced dental age is not known.

Other findings. Hepatic cholestasis and fibrosis with excessive deposits of iron in the liver are frequent findings. There is paucity of lymphatic tissue (tonsils, thymus, mesenteric nodes, Peyer patches). The gut is often dilated. Microscopic foci of nephrocalcinosis have been noted in several cases (33). Electron microscopy on a renal biopsy specimen in one patient demonstrated renal and glomerular enlargement, as well as glomerular changes similar to that of patients with diabetic nephropathy (16).

Differential diagnosis. It is possible that the condition has been overdiagnosed, since many marasmic infants or those with emotional deprivation may develop a similar phenotype (25). There is clinical resemblance between leprechaunism and lipoatrophic diabetes. These similarities may possibly be explained by shared mechanisms involving both insulin and insulinlike growth factor cell receptors (37).

The Patterson-David syndrome has been confused with leprechaunism. The patients of both Patterson (34,35) and David (9,10) presented large redundant loose folds of skin of the hands and feet since birth, marked generalized bronzed hyperpigmentation, hirsutism largely confined to the limbs, severe mental retardation, bony deformities, and skeletal dysplasia (Fig. 24–58). The bony alterations are characterized by profound disorder of endochondral ossification with marked retardation of skeletal maturation (9,10). The ends of long bones are swollen, especially those of the knees, ankles, and wrists (Fig. 24–59). Similar changes can be observed in hands and feet. The thickening and deformity affect other bones, the calvaria, maxilla, ethmoids, and mandibular condyles. The occipital bone may exhibit a defect. The vertebral bodies are deformed as well as ribs, clavicles, and scapulae. Kyphoscoliosis, genua valga, and valgus deformities of the ankles are common features. The skeletal changes increase in severity with age (9,10). David's (9,10) patient had premature adrenarche.

Laboratory aids. Biochemical evidence for insulin resistance includes markedly elevated plasma insulin, impaired glucose homeostasis, absence of anti-insulin receptor antibodies, and altered insulin receptor binding and/or response to insulin by patients' cells (12,15,17, 24,28,29,37,39,40,45,46). The patient reported by Roth et al (40) was further seen at age 8 by Frindik et al (20) and was found to have markedly elevated urinary levels of epidermal growth factor.

References [Leprechaunism (Donohue) and pseudoleprechaunism (Patterson-David) syndromes]

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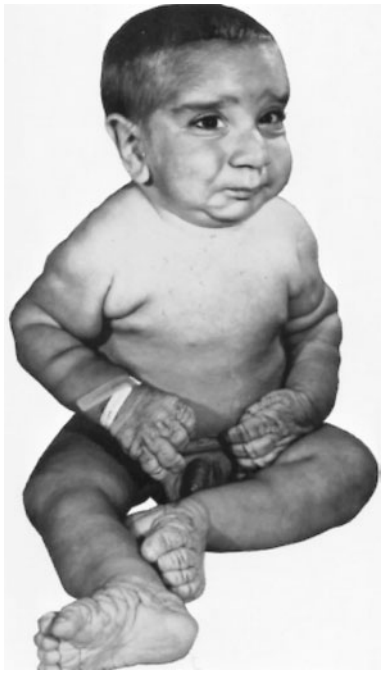

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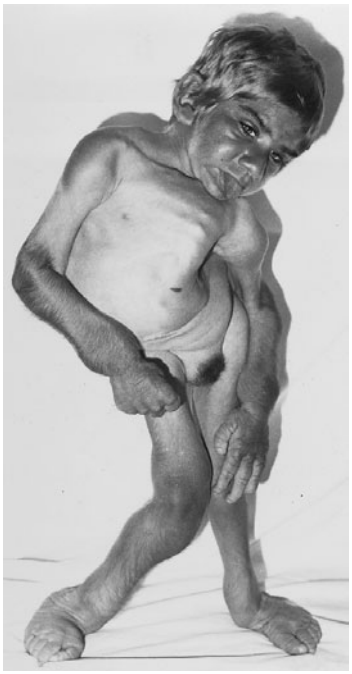
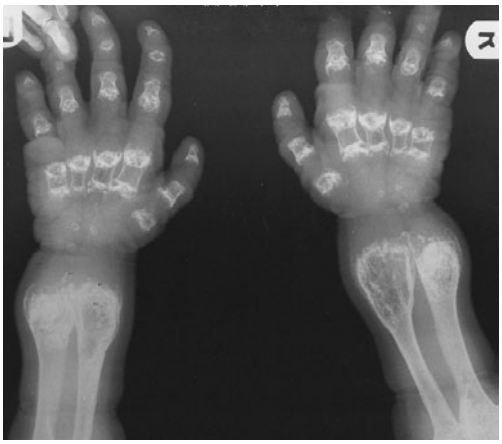


B

Fig. 24–58. *Pseudoleprechaunism (Patterson-David syndrome)*. (A) Large hands and feet in 3-year-old male, with redundancy and wrinkling of overlying skin. (B) Mentally retarded 12-year-old with coarse facies, bronze pigmentation, hirsutism, large hands and feet with redundant skin, premature sexual maturity, seizures, and generalized skeletal dysplasia, especially affecting the metaphyses and epiphyses. [A from JH Patterson, Birth Defects 5(4):117, 1969. B from TJ David et al, J Med Genet 18:294, 1982.]



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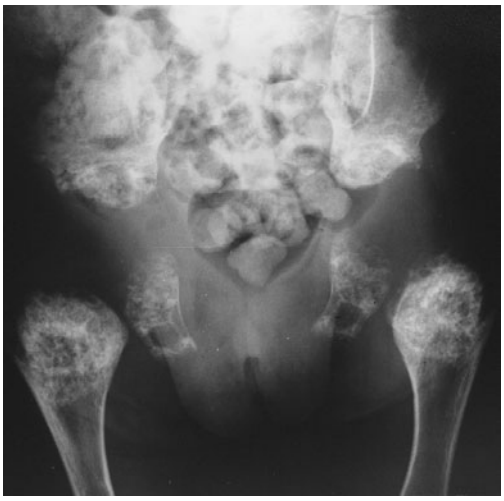

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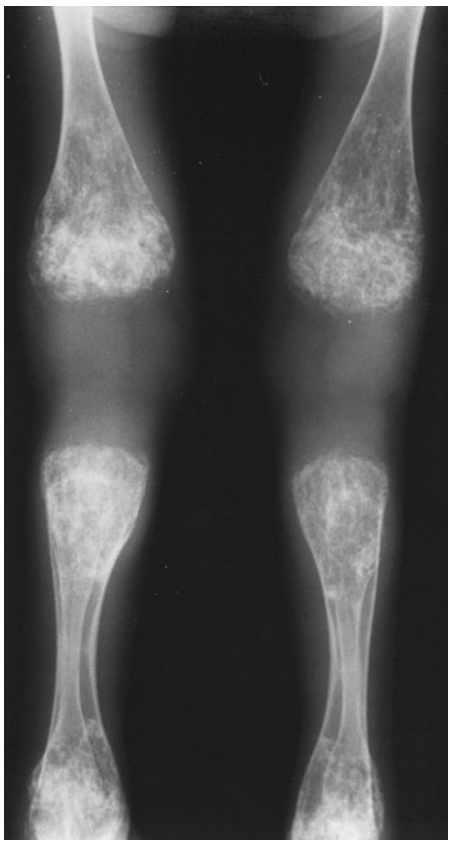

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Fig. 24–59. *Pseudoleprechaunism (Patterson-David syndrome)*. (A–C) Swollen metaphyses, late developing epiphyses, delayed bone age, especially involving the knees, ankles, and wrists. (From TJ David et al, J Med Genet 18:294, 1982.)

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Leprechaunism-like syndrome

Al-Gazali et al (1) noted a leprechaunism-like syndrome in five of eight offspring of a Yemeni couple.

All exhibited insulin resistance with paradoxical hypoglycemia, only mild growth retardation, somewhat coarse facial features, acanthosis nigricans, enlarged genitalia, and prolonged survival.

The facies was characterized by hypertelorism, depressed nasal bridge, flared alae nasi, thick lips, large pinnae, and enlarged gingivae. The abdomen was distended, the nipples prominent, and the genitalia enlarged. The acanthosis nigricans involved the neck, armpits, and groin. There was generalized hirsutism. No reduction in subcutaneous tissues was noted.

The hands and feet were enlarged. The kidneys and ovaries were larger than normal on ultrasound. Echocardiography demonstrated enlarged myocardium.

In leprechaunism, many mutations have been demonstrated in the insulin receptor gene, resulting in a decrease in the number of insulin receptors in target cells or in defects in insulin receptor function. In the leprechaunism-like syndrome described above, a novel mutation involving the insulin receptor gene (Ile119→Met) was described by Hone et al (2).

References (Leprechaunism-like syndrome)

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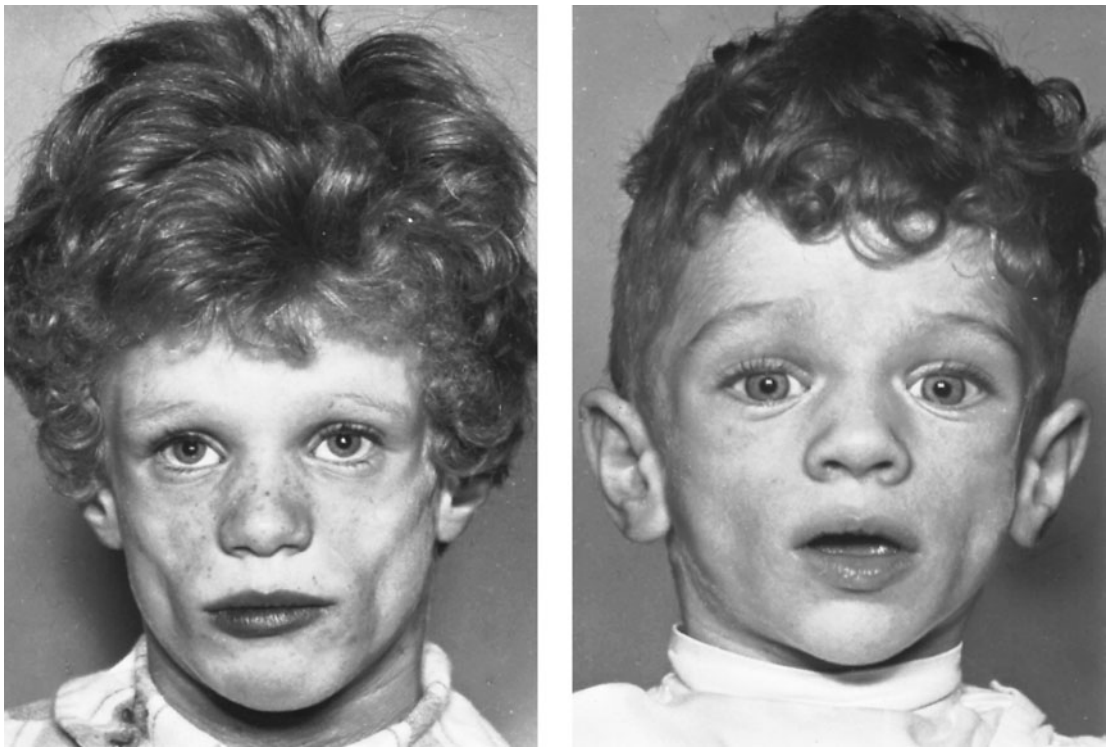
Lipoatrophic diabetes (Berardinelli syndrome, Seip syndrome, generalized lipodystrophy)

The syndrome consists of generalized disappearance of body fat, increased rate of skeletal growth, acanthosis nigricans, enlarged external genitalia, hepatomegaly, and insulin-resistant diabetes. Although Berardinelli (3) and Seip (32) are usually credited with first delineating the disorder, Miescher (26), in 1921, clearly described the condition in sibs. Approximately 120 cases have been reported (12). For a historic review, see Seip and co-workers (32–34). A good review is that of Garg (12) in 2000.

The syndrome has autosomal recessive inheritance. Parental consanguinity has been noted in approximately 25% (2,11,33). A gene has been mapped to 9q34 (13). However, there is genetic heterogeneity. The sublethal nature of the gene is suggested by the frequent history of miscarriage or death of affected children within the neonatal period.

The disorder is due to disturbed insulin binding to membrane receptors, but possibly is of secondary origin, that is, due to a disruption caused by a circulating factor (27,37). The best evidence suggests that the mechanism is via a defect in the tyrosine kinase of the beta subunit of the insulin receptor (23). A mouse model was created by Shimomura et al (36). Reversal was obtained with leptin.

A generalized loss of all subcutaneous fat causes the muscles to appear enlarged and the veins to stand out prominently. This is usually evident at birth (33). There is also absence of mesenteric and perinephric fat (33).



A B

Fig. 24–60. *Lipoatrophic diabetes*. (A,B) Absence of subcutaneous fat, especially buccal fat pad, produces gaunt appearance.

Females have a definitely masculinized body build. Skeletal growth is often accelerated during the first 10 years of life, during which time patients achieve 90% of their growth. Adult stature is anywhere from above to below the predicted height (34). Other skeletal changes include cystic changes or sclerotic foci, enlarged epiphyses, or thickened calvarium (9,43). The phenotype is further altered by the enlarged joints of the hands and feet. There is a bizarre fat distribution, almost all disappearing from the subcutaneous and intraabdominal regions, bone marrow, and parathyroid glands.

Long-term prognosis is rather poor, due to diabetes with its complications or hypertrophic cardiomyopathy (34). Most do not survive beyond the fourth decade.

Facies. The facies is quite distinctive. Loss of subcutaneous adipose tissue, especially the buccal fat pad, causes the cheeks to have a gaunt appearance (Fig. 24–60). This, combined with large ears, hypertelorism, and hirsutism, is characteristic.

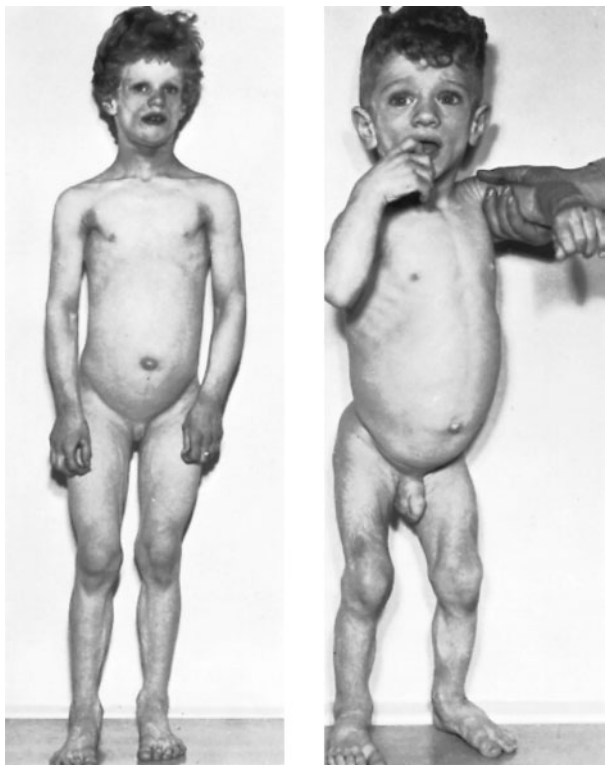
Viscera. Hepatomegaly with abdominal prominence may be pronounced in infancy; liver biopsies, taken later in life, have shown fatty infiltration with moderate early fibrosis and increased glycogen deposits. The fatty infiltration is secondary to hypertriglyceridemia and to lack of functional peripheral fat storage depots.

Cardiac murmurs and hypertrophic cardiomyopathy are not uncommon (4,32–34). Peripheral pulmonary artery stenosis has been documented (39). In most patients, the kidneys are enlarged without apparent histologic cause.

Nervous system. Mental retardation of variable degree has been noted in approximately 50% (5,32–34). Dilated brain ventricles and cisterns (43) were noted. Appetite can be voracious in early adulthood (12).

Musculoskeletal alterations. Muscular prominence, due in part to lack of subcutaneous fat, may be absolute, as some patients exhibit increased urinary creatinine levels (Fig. 24–61). Advanced bone age is a

Fig. 24–61. *Lipoatrophic diabetes*. (A,B) Marked muscular prominence, due in part to lack of subcutaneous fat. Also note evidence of axillary acanthosis nigricans in female. Hirsutism may be marked in some patients. (From M Seip, Acta Paediatr Scand 48:555, 1959.)



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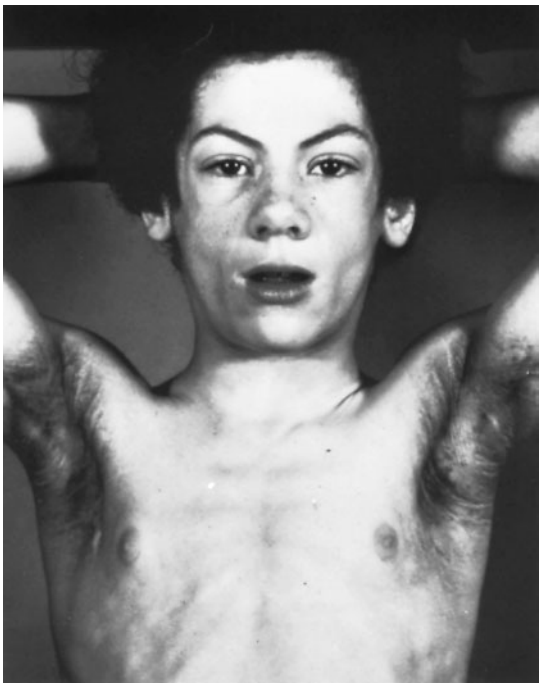

Fig. 24–62. Lipoatrophic diabetes. Acanthosis nigricans. (Courtesy of W Reed, Burbank, California.)

common feature during the first 4 years of life, and several patients have exhibited increased bone density (33,40,43). These strongly suggest an androgen excess. An increase in subcutaneous fat may occasionally be noted after puberty. Cystic radiolucencies of bone filled with red marrow have been found in a few families at adolescence (5,10,15,40,43). Umbilical hernia is a consistent finding (12).

Genital organs. Enlarged penis or clitoris and polycystic ovaries are common features (3,16,33,35). Oligomenorrhea is frequent.

Skin. Hirsutism of face, neck, arms, and legs may be present at birth and increases with age. With the onset of the lipodystrophy, the scalp hair may become excessively curly and thick, the hair growing nearly to the eyebrows.

Acanthosis nigricans is a prominent feature in almost all patients, appearing usually by age 8 years. It is especially common in the axillae, groin, neck, and on the wrists and ankles. It tends to diminish with increasing age and may disappear after puberty (Fig. 24–62). The skin is also dry and coarse with hyperkeratotic epidermal papillomatosis. Hyperhidrosis is common (34). Subcutaneous angiomatosis has been reported (5).

Oral manifestations. Enlarged tonsils and adenoids are common in the congenital type (33).

Differential diagnosis. The *Dunnigan syndrome* (familial partial lipodystrophy) exhibits many overlapping features (acanthosis nigricans, decreased subcutaneous fat with onset at puberty, enlarged clitoris, insulin-resistant diabetes, autosomal dominant inheritance). The fat accumulates under the chin giving a Cushingoid appearance. The gene has been mapped to 1q21–q22 (1,17,29). The nuclear envelope protein lamin A/C is involved (11,20,35). The mutations are in the globular C-terminal domain of lamin (37a).

The Rabson–Mendelhall syndrome includes thickened nails, pineal hyperplasia, precocious puberty, premature eruption of teeth, open bite and macrodontia of the upper central incisors with palatal cusps arising from the cingulum, and enlargement of the filiform and fungiform papillae of the tongue (2,6,25,30,44).

In the so-called partial or acquired lipodystrophy, there is symmetric disappearance of facial fat, the patient appearing gaunt and cadaverous (Voltaire-like) (19). Fat may also disappear from the arms, chest, abdomen, and hips. The characteristic adiposity of pelvis and legs is seen only in postpubertal females. We are not convinced that there is other than relative adiposity of the buttocks. Onset is usually noted between 5 and 15 years of age, but older examples have been noted (31). The wasting time ranges between 1.5 and 6 years. Renal problems (mesangiocapillary glomerulonephritis progressing to chronic sclerosing glomerulonephritis) have been noted in 25%–50% about 5–20 years after the appearance of the lipodystrophy (36). The ratio of females to males is 4:1. The disorder is sporadic. It is more common than lipoatrophic diabetes. A deficiency in the third component of complement (C3) and C3 activating factor is probably responsible for the disorder (19,24,44).

There are two X-linked dominant, lethal in the male, forms of partial lipodystrophy with onset at puberty. In the Kobberling variety, the fat loss is confined to the limbs, sparing the face and trunk. In the other, the trunk is also affected but the vulva is spared, giving the appearance of labial hypertrophy. Diabetes mellitus, tubero-eruptive xanthomata, insulin-resistant diabetes mellitus, hyperlipoproteinemia type V, and acanthosis nigricans frequently accompany the disorders (18,19,22).

Lawrence (21) reported a sporadically acquired lipoatrophic diabetes of adolescence or early adult life. There is female preponderance. Hepatosplenomegaly with cirrhosis, acanthosis nigricans, hyperlipidemia, and insulin-resistant diabetes mellitus were also found.

Many features of congenital lipodystrophy have been noted in *leprechaunism*: liver enlargement, lipodystrophy, enlarged clitoris or penis, neurologic damage, hirsutism, and insulin resistance. These are all evident at, or shortly following, birth. It is conceivable that leprechaunism represents a lethal form of lipoatrophic diabetes.

The so-called *SHORT syndrome* manifests partial lipodystrophy. Barraquer–Simons syndrome has postnatal onset lipodystrophy, as well as sensorineural deafness (38).

The diencephalic syndrome caused by a tumor in the region of the anterior hypothalamus is manifested by profound emaciation with accelerating early growth, increased motor activity, and euphoria (8). The affected infants are normal at birth but become symptomatic with age. Progressive emaciation leads to a loss of subcutaneous fat but without the muscularity of lipodystrophic patients. The hands and feet are often large. Hepatomegaly, genital enlargement, and hyperlipemia have not been reported.

Progeria and *Werner syndrome* patients also exhibit loss of body fat and an increased incidence of diabetes mellitus.

Laboratory aids. Lipoatrophic diabetes is clearly distinct from the common form of diabetes mellitus. The diabetes, which is insulin resistant and nonketotic, appears after the onset of the lipodystrophy, usually between 6 and 20 years of age. Normal glucose tolerance is observed during the first few years of life. Hyperglucagonemia has been found and may contribute to the insulin resistance.

Hyperlipemia, especially of the triglyceride fraction, is a constant feature. It usually precedes the onset of hyperglycemia. The serum of these patients is intermittently turbid or milky, with increased triglycerides, and contains very low density lipoprotein. In addition, there is slow turnover of 14C-labeled triglycerides and cholesterol and slow clearance of ingested triglycerides with failure of adipocytes to incorporate triglyceride fatty acids from the blood.

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SHORT syndrome (unusual facies, lipoatrophy, short stature, and Rieger anomaly)

Gorlin et al (5) and Sensenbrenner et al (12) reported male sibs and a female singleton, respectively, with a striking phenotype. Gorlin et al (5) suggested the acronym SHORT (Short stature, *H*yperextensibility of joints/hernia, *O*cular depression, *R*ieger anomaly, *T*eething delay). Approximately 20 examples have been reported (1–3,5,7,9,11–16).

Inheritance is probably autosomal dominant (1,2,13), but affected sibs (5,14) have been documented.

The lower face, upper limbs, and buttocks appear thin due to lipoatrophy (Fig. 24–63). The eyes are deep set, and Rieger anomaly is usually present (Fig. 24–64). The pinnae are somewhat outstanding. The nasal alae are hypoplastic with wide nasal bridge. Stature is reduced. There is poor weight gain and frequent illness during infancy. Joints are hyperextensible, and there may be inguinal hernia. Speech is delayed in spite of normal intelligence. Sensorineural hearing loss has been documented (2,3,11,15). Dental eruption is delayed. Dimples on the chin and buttocks have been reported in several cases (1,5,9,16). Diabetes mellitus has been documented in several examples (1,11,16).

Radiologic changes include large epiphyses, gracile diaphyses, and cone-shaped epiphyses (6).

Kupchik et al (8) reported a mother and daughter with Rieger anomaly, short stature, mental retardation, microcephaly, small pinnae, short nose with depressed bridge, and small hands. This combination was termed the GMS syndrome (*G*oniodysgenesis, *M*ental retardation, *S*hort stature syndrome). *DeHauwere syndrome* exhibits Rieger anomaly, hypertelorism, short stature, and mental deficiency (3).

McAlister et al (10) described a girl with short stature, lack of subcutaneous fat, wrinkled skin, macroepiphyses, lax joints, club feet, and osteoporosis. The parents were consanguineous. The child did not appear to have *OSMED*.

References [SHORT syndrome (unusual facies, lipoatrophy, short stature, and Rieger anomaly)]

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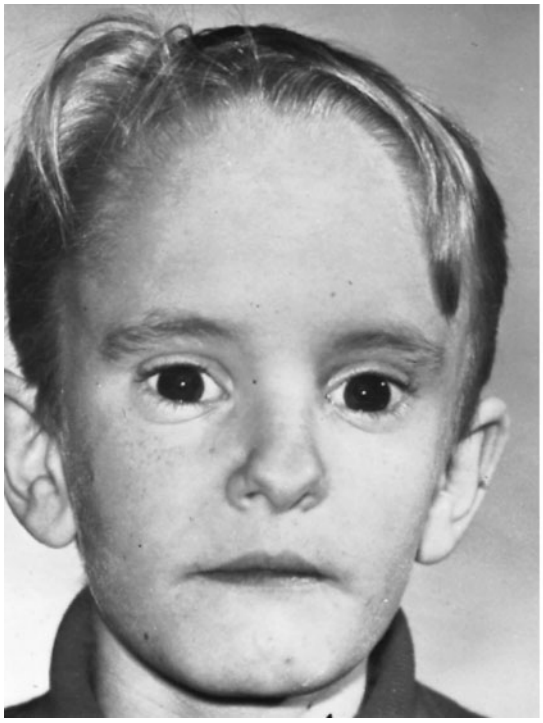

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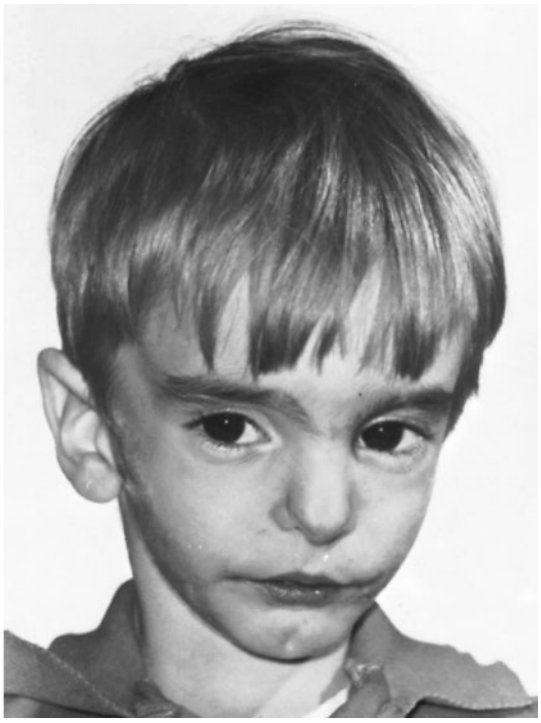

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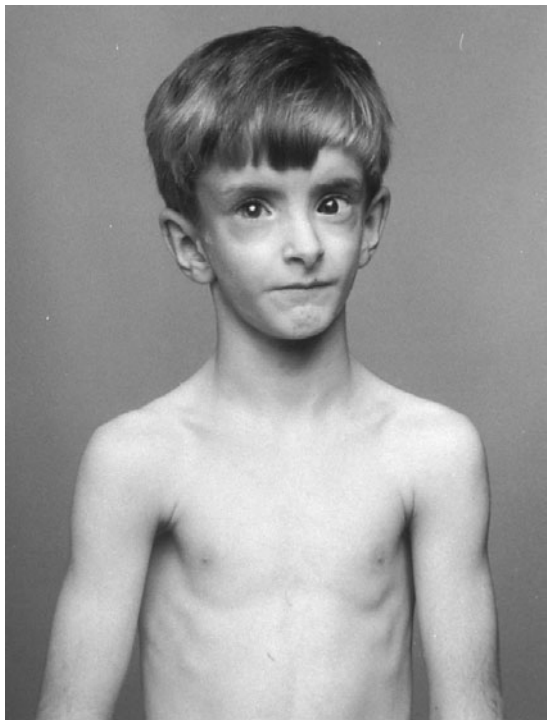

C

Fig. 24–63. *SHORT syndrome*. (A,B) Brothers exhibiting severe growth retardation, disproportionately small face, sunken eyes, Rieger anomaly, and delayed tooth eruption. (C) Note thin upper body due to lipodystrophy. (A,B from RJ Gorlin et al, Birth Defects 11(2):46, 1975.)

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Coffin-Lowry syndrome

Coffin et al (4), in 1966, and Lowry et al (22), in 1971, independently reported patients with mental and somatic retardation, characteristic facies, large soft hands with distally tapering fingers, and various skeletal

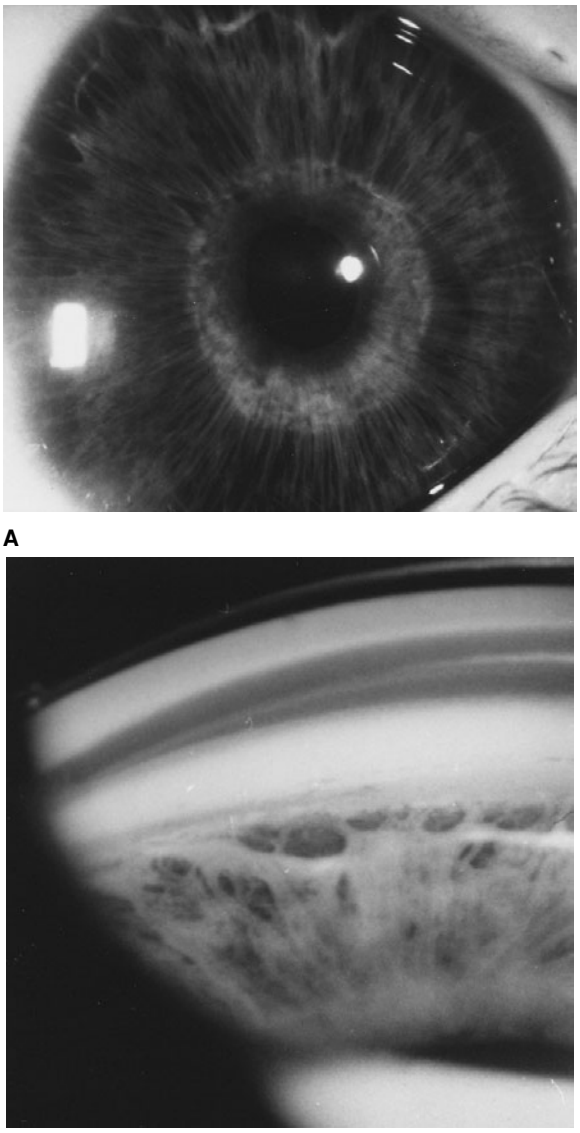


Fig. 24–64. *SHORT syndrome*. (A) Diffuse iris stromal atrophy. (B) Gonioscopic view showing iris strands adherent to Schwalbe's line. (From M Brodsky et al, Arch Ophthalmol 114:1146, 1996.)

anomalies. However, it was Temtamy et al (37), in 1975, who recognized the unity of the reports and coined the name Coffin-Lowry syndrome. An early report is that of Martinelli and Campailla (25).

The disorder has X-linked inheritance. Female heterozygotes commonly express the condition to a less severe degree, although there can be marked variable expression among female heterozygotes (31). Over 60 cases have been reported (9,42). The gene locus is on the short arm of the X chromosome at Xp22.2 (2,3,10,30), RSK2, a growth factor regulating serine-threonine protein kinase (18,24,38). There is considerable allelic heterogeneity and a high rate of new mutations (17).

Facies. Characteristic facial changes become more marked with age but are apparent by the second year of life. Hair is straight and coarse in males. The forehead is prominent and broad and the occiput is somewhat flat. There are prominent supraorbital ridges, hypertelorism, downslanting narrow palpebral fissures, heavy arched eyebrows, ptotic upper eyelids, and somewhat hypoplastic midfacial development with relative mandibular prognathism. The nose is large with a broad base and flared alae. The nostrils are anteverted and the pinnae are prominent. The philtrum appears somewhat elongated and the nasal septum is

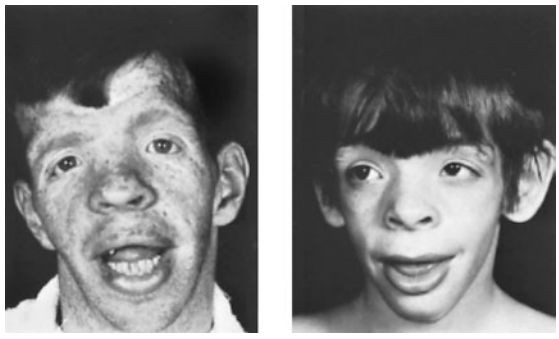
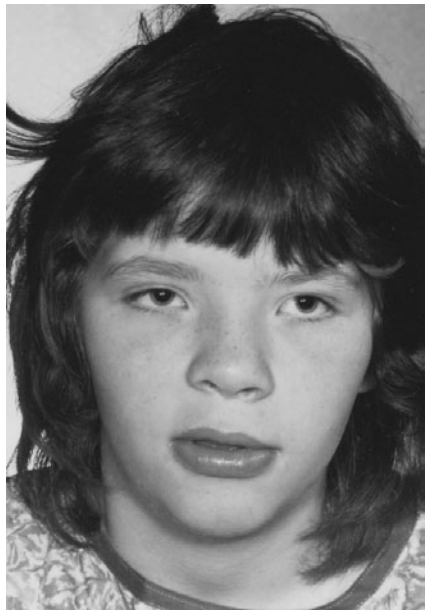


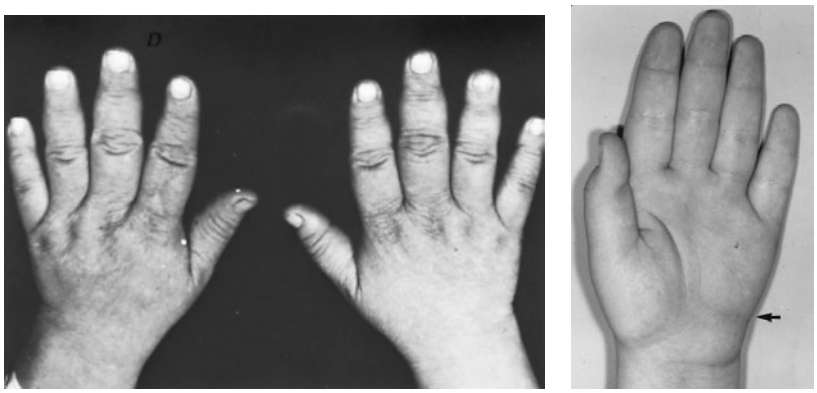
Fig. 24–65. *Coffin-Lowry syndrome*. (A,B) Twenty-three- and ten-year-old affected males. Note facial similarities: marked hypertelorism, prominent supraorbital ridges and outer margins, short upturned nostrils, open mouth with pouty lower lip, thick bulging chin, and enlarged protuberant ears. Facial features are more coarse in the older affected male. All males had straight coarse hair. (From SA Temtamy et al, J Pediatr 86:724, 1975.)

wide. The lips are thick and pouting and the mouth is usually held open (Figs. 24–65 and 24–66).

Musculoskeletal findings. Although usually normal at birth, height and weight become reduced below the third percentile in hemizygotes and in 50% of heterozygotes. There is delayed ambulation and a clumsy broad-based gait. At birth, hypotonia and/or loose ligaments with pes planus and inguinal hernia may be noted. The hands are extremely large and soft with distal tapering fingers in both sexes (Fig. 24–67A). This is the most striking feature at birth (40,41). The nails are short and broad. The finger joints are hyperextensible. Radiographically, the calvaria is thickened, especially the frontal tables, in 60%. The anterior fontanel is large and suture closure is markedly delayed (40). Pectus carinatum or excavatum found in 80% of hemizygotes and in 30% of heterozygotes is associated with thoracolumbar kyphosis/scoliosis. Commonly there is dysplasia of the vertebral bodies at the thoracolumbar junction. Calcification of the ligamenta flava has been described (16,27). The sternum is short and often bifid. Bone age is retarded in both sexes. Pseudoepiphyses

Fig. 24–66. *Coffin-Lowry syndrome*. Female heterozygote exhibiting many of same features.





A B

Fig. 24–67. *Coffin-Lowry syndrome*. (A) Hands are spade-like; digits are thick at base and taper distally. (B) Flexion crease in hypothenar area at arrow. (A from SA Temtamy et al, J Pediatr 86:724, 1975.)

at the base of each metacarpal may be seen in males during childhood. The distal phalanges are hypoplastic and tufted and have been described as drumstick shaped (29). The middle phalanges are poorly modeled. The iliac wings may be narrowed. Female heterozygotes tend to be obese. Distal muscle atrophy is not uncommon.

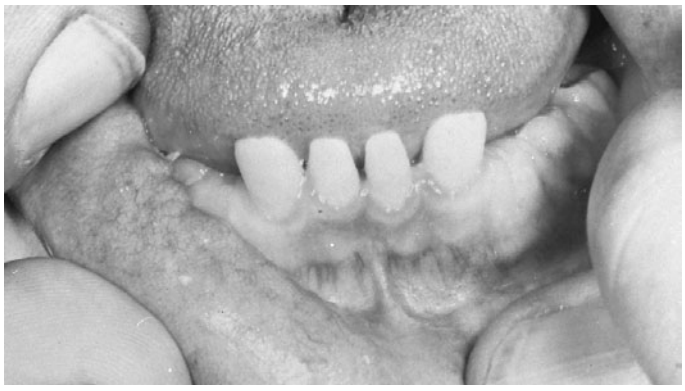
Central nervous system. Intelligence quotients in males have ranged from 5 to 50 but speech is severely retarded. Sensorineural deafness has been reported in several kindred (11,14,34). It is rarely of late onset. Female carriers have varied in intelligence from normal (20%) to 60 IQ. Another 20% of heterozygotes are severely retarded (42). Internal communicating hydrocephaly or ventricular dilatation has been noted (4,12,15,22,37) in hemizygotes and over 40% exhibit severe generalized seizures (8). Agenesis of the corpus callosum is an ocasional finding (28,35). Sensorineural deafness has been described (15,34). Psychotic behavior may also be an occasional manifestation (5,34). Crow et al (6) and Carabella et al (3a) described cataplexy in affected males; Fryns and Smeets (7) reported cataplexy in 3 of 22 boys. Others (29) have also noted this phenomenon.

Cardiovascular system. Various heart anomalies have been described (4,15,20,32,37).

Skin. The skin appears loose and easily stretched. Cutis marmorata, dependent acrocyanosis, and varicose veins are frequent. There is a flexion crease in the hypothenar area of the palms (Fig. 24–67B).

Oral manifestations. The lips are large, thick, and pouting. The tongue may have a deep midline furrow (15). Torus palatinus has been stated to be more common (37) but we have not found this to be true. The lower permanent incisors are frequently absent or have reduced crown form in 80% of affected males and in 20% of females (Fig. 24–68).

Fig. 24–68. *Coffin-Lowry syndrome*. Reduced crown form of lower anterior incisors.



Malocclusion with overjet and/or overbite appears to be a nearly constant feature. Early tooth loss due to periodontal disease has been noted.

Pathology. Ultrastructural studies of conjunctiva and skin have exhibited changes suggestive of a lysosomal storage disease but this needs confirmation (1). Lacombe et al (21) reported hyperprolinemia in a mother and child.

Differential diagnosis. During infancy, several children have presented with a diagnosis of possible hypothyroidism. With age, diagnosis becomes easier but coarseness of features may suggest a mucopolysaccharidosis or oligosaccharidosis. There is some phenotypic overlap with *ATR-X syndrome, Williams syndrome, Sotos syndrome, FG syndrome*, and *fragile X syndrome* (31). Atkin-Flaitz syndrome shares some similarities as well, including short stature, telecanthus/hypertelorism, coarse facial features, everted lower lip, and dental anomalies (19). Macrocephaly and obesity should distinguish the Atkin–Flaitz syndrome, however. Proud et al (33) described mental retardation, agenesis of the corpus callosum, acquired microcephaly, limb contractures, scoliosis, tapered digits, renal dysplasia, cryptorchidism, and hypospadias in males in three generations. The facial features in these boys resembled those of the Coffin–Lowry syndrome; however, the gene mapped to Xp11.3–21.3, thus indicating distinction from the Coffin–Lowry syndrome. The patient reported by MacDermott et al (23) surely has Coffin-Lowry syndrome.

Laboratory aids. Dermatoglyphic changes include a characteristic horizontal hypothenar crease in both sexes (4,13,32,37) (Fig. 24–67B). The "atd" angle is increased and transverse palmar creases and Sydney lines are frequent. The finger tip ridge counts are decreased. Increased cd and reduced bc triradii distances appear significant (36). Abnormal proteodermatan sulfate storage has been found (1,39). Rapid immunoblot and kinase assays have been reported (26).

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Williams syndrome (Williams-Beuren syndrome)

The syndrome of characteristic facial appearance, mental retardation, growth deficiency, cardiovascular anomalies, and infantile hypercalcemia (Figs. 24–69 to 24–72) was described in 1952 by Fanconi and coworkers (29). Important early papers are those of Williams et al (109) and Beuren and associates (6–8). A good historical account has been presented by Myers and Willis (81). Several important clinical reviews are available (15,25a,27,41,53,54,61,69,77,97,117a). Profound study of a single patient over many years (13) and a parental perspective (1) should interest the clinician (13). The frequency of the syndrome has been estimated to be 1 in 10,000 to 1 in 20,000 births (42,83).

Naming the syndrome has been problematic. The disorder has been known in the past as the idiopathic hypercalcemia-supravalvular aortic stenosis syndrome in spite of the fact that both features may be absent (54). The term "elfin face" syndrome presents the problem of naming a disorder after a mythical being. The currently accepted designation, Williams syndrome, or, less often, the Williams–Beuren syndrome, ignores the historical precedent mentioned earlier.

Delineating the phenotypic spectrum of abnormalities has been difficult because it is a contiguous gene syndrome (vide infra). The problem is further compounded by ascertainment on the basis of cardiovascular anomalies in some reports (7) and on the basis of facial features in others (54).

The syndrome arises because of a deletion that includes the elastin (ELN) gene at 7q11.23 in 90%–95% of all clinically typical cases (28,95a). The deletion usually spans more than 1–1.2 megabases and appears responsible for the vascular and connective tissue changes seen in the syndrome. The narrowing of large elastic arteries compromises blood flow. Using FISH techniques, over 95% exhibit deletion of the ELN gene (11,68,76,84,96,113). A gene-dosage PCR method for the deletions of the elastin gene has been described (24). Deletions can be maternal (40%) or paternal (60%). It has been asserted that if the deletion is maternal, there is more severe growth retardation and more severe microcephaly (91) and, in fact, the opposite has been found (118). Imprinting plays no role. Other genes whose functions may be deleted are the protein kinase, *LIM-kinase 1* (76,109) and replication factor C (*RFC2*) (95). Deletion of the *RFC2* gene may be responsible for the deficient growth and development (95). Although other genes such as "frizzled"and "syntaxin" may be deleted (87,119), they do not play any significant role in the phenotype (12). Deletion of the *LIM-kinase 1* gene may result in impaired visual/spatial perception (32,71). Dutly and Schinzel (26) showed that during gametogenesis the deletion results from unequal crossing over of homologous chromosomes 7. Phosphoserine phosphatase is decreased in lymphoblasts and fibroblasts, but this finding may not be significant (51). Although the syndrome appears to be autosomal dominant, parent-to-child transmission is truly rare because most affected adults do not reproduce (42,79,105).

Several authors have reported familial examples of the Williams syndrome (42,88,94,122), but the overwhelming number of reported cases are sporadic. The affected second cousins reported by White et al (122) do not represent a familial occurrence as elastin deletions arose de novo in each affected child.

Concordant monozygotic twins (16,80,86,91,124) are convincing. Jones and Smith (54), Martin et al (72), and Morris et al (77) found no evidence for a paternal age effect. However, Greenberg and Lewis (41) found paternal age increased.

Natural history has been particularly well documented by Morris et al (77), who tabulated data on 109 subjects. Features of infancy, childhood, and adulthood are listed together with their respective frequencies in Tables 24–4, 24–5, and 24–6. Pagon et al (89) studied physical, neurodevelopmental, and behavioral characteristics during late childhood and adolescence.

Facial features. Facial features are distinctive and remain in evidence into old age. Cephalometric study has been reported by Mass and Belostoky (73), and photoanthropometric study by Hovis and Butler (49). Approximately 35% have microcephaly (93). The combination of flat midface, depressed nasal bridge, anteverted nostrils, long philtrum, thick

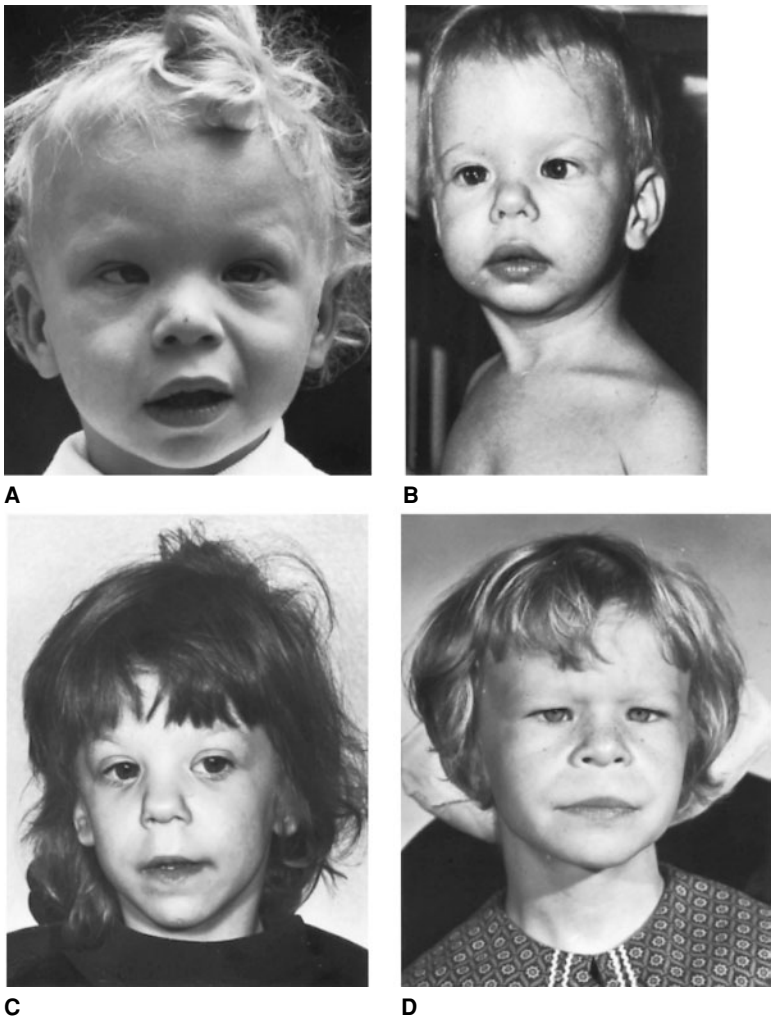


Fig. 24–69. *Williams syndrome*. (A–D) Compare facies for anteverted nostrils, long philtrum, mild midface hypoplasia, epicanthic folds, strabismus. (A from A Dupont, Dan Med Bull 17:33, 1970. B from F Roy et al, J Pediatr Ophthalmol 8:188, 1971.)

lips, wide intercommissural distance, and open mouth is characteristic (Fig. 24–69). The hair may become prematurely gray. Ocular findings may include medial eyebrow flaring (80%), short palpebral fissures (50%), hypotelorism (50%), epicanthic folds (50%), periorbital fullness, and strabismus (50%). Approximately 40% have esotropia (125). Hypermetropia has been noted in 75%. Approximately 50%–75% of blue- or hazel-eyed Williams patients have a stellate or lacy iris pattern versus 10% of the normal population (125) (Fig. 24–70). Blue eyes (77%) and green eyes (7%) are most frequently noted (7,8,29,41,46,54,104,121). Uncommonly, corneal and/or lenticular opacities (104) and ptosis of eyelids (personal observation) may be observed. Hypermetrous discs (55%) and retinal vascular tortuosity (22%) have been documented (41,48,125). In some cases, the ears are prominent. The thyroid cartilage becomes more pronounced with age (11,41).

Skeletal changes. Intrauterine growth retardation has been documented in 35% of female infants and in 22% of male babies. Until about 10 years of age, growth is at the third centile (90). Mean birth weights are lower than average (41,72). The pubertal growth spurt occurs about 1–2 years earlier than normal (10y-females, 13y-males) and menarche is

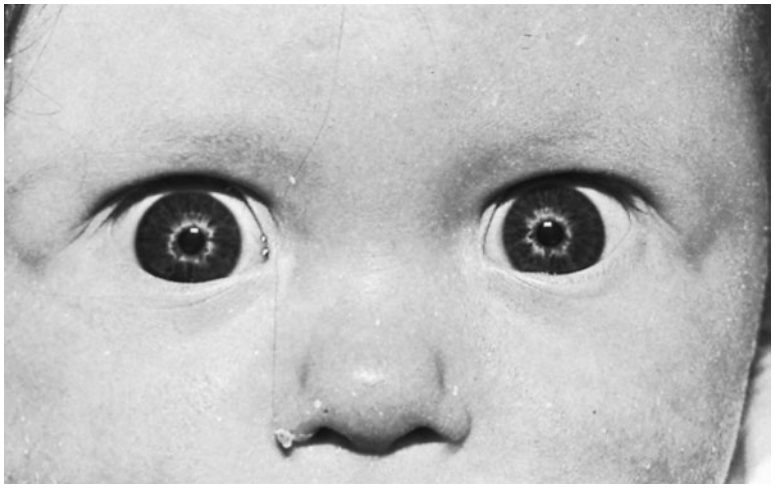
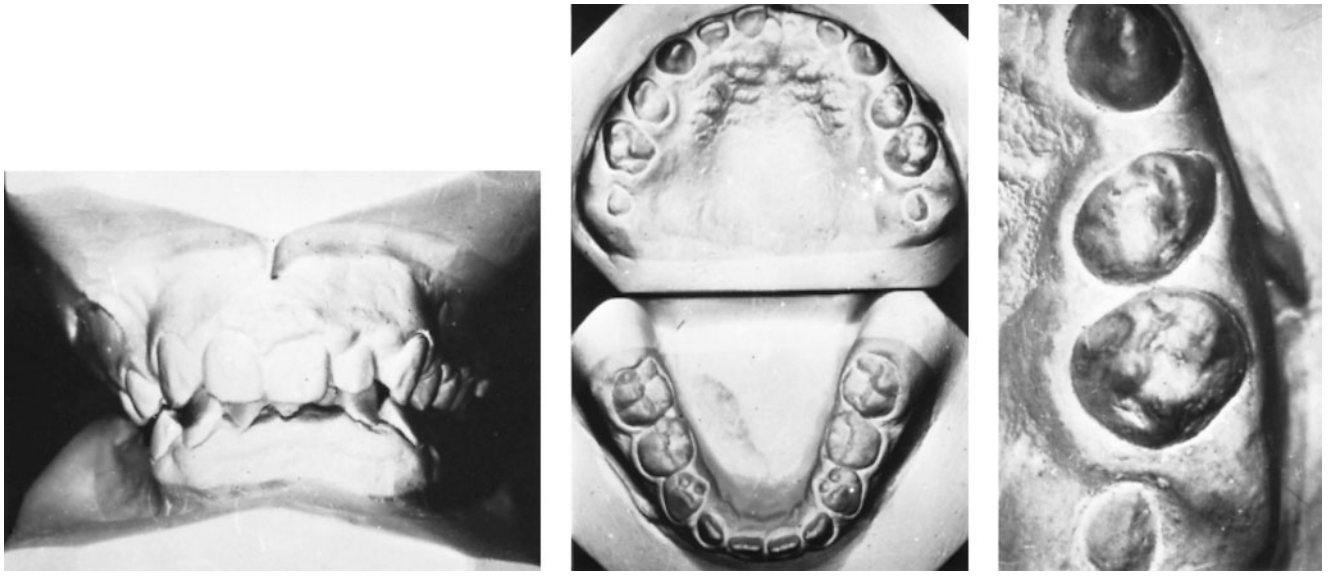


Fig. 24–70. *Williams syndrome*. Stellate iris pattern. (From FO Jensen and AC Begg, N Z Med J 68:364, 1968.)



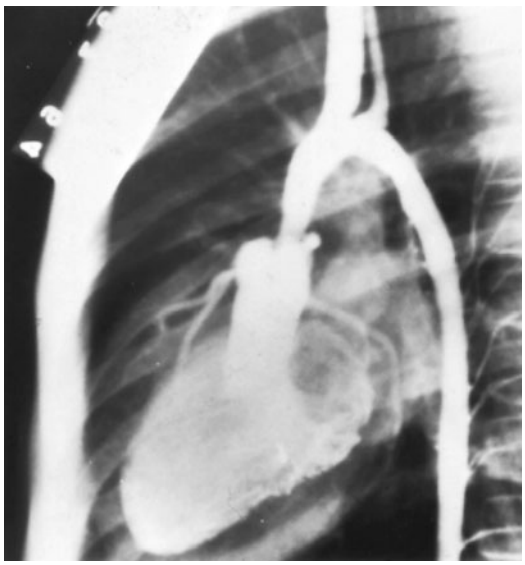
A B C

Fig. 24–71. *Williams syndrome*. (A) Upper dental arch completely overlaps lower arch. (B) Note expanded upper arch, hypoplastic upper second deciduous molar on right. (C) Detail showing bud-shaped maxillary teeth. (From AJ Beuren et al, Am J Cardiol 13:471, 1964.)

usually earlier than normal (90). Mean adult height is 165 cm in males and 153 cm in females (third centile) (94b). Mean male adult head circumference is 54.8 cm, and mean female adult head circumference is 52.8 cm (72). The elbows are often held flexed (117). Limitation of supination due to radioulnar synostosis has been reported in 8%–26% (19,92). Joint contractures, especially of the hips, heel cords, and hamstrings are very common (57,77). MCPP index is nonspecific.

The hypercalcemic phase may result in widespread osteosclerotic changes that regress in time. Craniosynostosis (secondary to microcephaly) is uncommon. Increased density of the metaphyses, epiphyses, and skull base may be present in some instances (29,58). Other findings may include pectus excavatum (40%), kyphoscoliosis (20%), minor structural and postural curvatures (55%), hallux valgus (75%), and fifth finger clinodactyly (40%) (54,72). The shoulders slope, and there is exaggerated lumbar lordosis.

Fig. 24–72. *Williams syndrome*. Note area of stenosis and hypoplasia of entire aorta distal to obstruction. (From K Jue et al, J Pediatr 67:1130, 1965.)



Central nervous system and performance. Mild microcephaly, which is most striking in bifrontal diameter, is found in 35%. Other characteristic features include mental retardation (95%), mild neurologic dysfunction (50%), and unusual personality (65%). Attention deficit disorder and restlessness are common (97). Infantile spasms are rare (112). Intelligence quotients have varied from 20 to 106 with an average IQ of 58 (37,38). There is poor visual-motor integration, the patients having problems with integration of parts into a complete picture. Developmental delay and neurologic dysfunction are highly distinctive and can be diagnostic (5,25,69,75,89,96a,114). In childhood, most patients have an echolalic, loquacious, unreserved, friendly pattern of speech that has been described as a "cocktail party manner" (54). There is a relatively better command of verbal and language skills (54,69). Vocabulary is usually excellent (39). Many play musical instruments and rarely forget a name (64). Disordered syntax, overuse of clichés, and tangential reasoning have been noted. The ability to read, to tell time, or to make change is relatively poor (2,64). In a few, impulsivity and destructive behavior predominate (54). Frank autism has also been observed (102). The loquacity is significantly less in those with more severe retardation (11).

Major motor development is relatively spared (69,72), but visual-motor integration is usually impaired to an extent that is out of proportion to

Table 24–4. Medical problems in infants with Williams syndrome

Problem	Percent ($n = 42$)
Early symptoms	
Feeding difficulty	71
Failure to thrive	81
Vomiting	40
Constipation	43
Colic	67
Chronic otitis media	38
Hypercalcemia	4/6
Birth defects	
Congenital heart defects	79
Umbilical hernia	14
Inguinal hernia	38

(Adapted from CA Morris et al, J Pediatr 113:318, 1988.)

Table 24–5. Medical problems in children with Williams syndrome

Problem	Percent ($n = 42$)
Central nervous system	
Developmental delay with specific learning disability	97
Attention deficit disorder	Common
Ocular	
Esotropia	50
Hyperopia	24
Auditory	
Chronic otitis media	43
Dental	
Enamel hypoplasia	48
Microdontia	55
Malocclusion	85
Cardiovascular	
Congenital heart defects	79
Supravalvular aortic stenosis	64
Supravalvular pulmonic stenosis	24
Ventricular septal defect	12
Patent ductus arteriosus	5
Hypertension	17
Genitourinary	
Renal anomalies	?
Enuresis	52
Gastrointestinal	
Constipation	43
Musculoskeletal	
Joint limitation	50
Kyphosis	21
Lordosis	38
Scoliosis	12
Awkward gait	60
Extra sacral crease	52

(Adapted from CA Morris et al, J Pediatr 113:318, 1988.)

Table 24–6. Medical problems of adults with Williams syndrome

Problem	Percent ($n = 17$)
Central nervous system	
Mental retardation (IQ < 70)	59
Borderline intellectual functioning (IQ 70–85)	41
Hyperreflexia in lower extremities	50
Ocular	
Hyperopia	18
Cardiovascular	
Supravalvular aortic stenosis	76
Diminished peripheral pulse	35
Pulmonic artery stenosis	35
Hypertension	47
Diffuse aortic hypoplasia	18
Other documented arterial stenoses	18
Genitourinary	
Renal anomalies	?
Urinary tract infections	29
Vesicoureter reflux	3/4
Bladder diverticuli	3/4
Nephrocalcinosis	0[a]
Gastrointestinal	
Constipation	41
Peptic ulcer	18
Cholelithiasis	12
Diverticulitis	12
Diabetes mellitus	12
Obesity	29
Integumentary	
Prematurely gray hair	60

[a] Reported as a cause of renal failure in other reports, however.
(Adapted from CA Morris et al, J Pediatr 113:318, 1988.)

the global deficit (5,69). Hyperacusis, that is, hypersensitivity to sound without physical findings, is found in 95% (1,37,60,72,83,115).

Neurologic examination is usually abnormal with infantile hypotonia progressing over time to hypertonia and hyperreflexia. Gait abnormalities are also common (17). Cases of Chiari malformation type I, producing both acute and chronic neurologic problems have been reported (98).

Cardiovascular system. Supravalvular aortic stenosis (Fig. 24–72) and pulmonary artery stenosis are the most common findings, although various other cardiovascular defects have been recorded. Approximately 75% have clinical heart disease. When studied echocardiographically, all have supravalvular aortic narrowing (43). Among patients with cardiac changes, approximately 60% have supravalvular aortic stenosis. Other changes include aortic hypoplasia (40%), coarctation or interruption of aorta, left coronary artery stenosis (21), renal artery stenosis, peripheral pulmonary stenosis (80%), various peripheral artery stenoses (carotid, innominate, subclavian, celiac, and mesenteric), atrial septal defect, ventricular septal defect, anomalous pulmonary venous return, arteriovenous fistula (lung), rarely valvular aortic stenosis or subaortic stenosis, and aplasia of the portal vein (18,29,43,44,54,65,67,70,82,100,101,120,121). Approximately 10%–15% have mitral valve prolapse or bicuspid aortic valve (43,70). This has been stated to increase to 50% of adults (77), but most series do not show this. Some Williams syndrome patients have no cardiovascular anomalies but are easily diagnosed by characteristic facial appearance and performance (54). Stroke due to stenoses of cerebral arteries appears to be increased (57,126).

Longitudinal studies indicate that supravalvular aortic stenosis tends to progress with age; pulmonary artery stenosis improves (50). Coronary artery stenosis can lead to myocardial infarction and sudden death and probably contributes to the increased risk of death at cardiac catheterization (10,21,106,111). Up to half of individuals develop systemic hypertension, which occasionally is due to renal artery stenosis (23,43,67,72,94,106,124).

Genitourinary and endocrine abnormalities. Limited information about reproductive function is available. Delayed acquisition of urinary continence is common and approximately 10% have associated multiple bladder diverticulae (3,77,107). Nephrocalcinosis can be a complication of hypercalcemia but may not be visualized by standard radiographic technique (23,29,72,99). Ultrasonography or computerized tomography are likely to be more helpful. Renal calculi and urethral stenosis have also been recorded (72,77). Renal insufficiency, cystic dysplasia, and criteria for investigation have been discussed by Biesecker et al (9). Pober et al (99) described marked asymmetry in kidney size, small kidneys, and solitary kidney. Mild renal artery stenosis was found

in four of nine patients with persistent hypertension, and was unrelated to renal artery status in two of the nine patients. Renal artery narrowing was found in 44%, and renal anomalies, ranging from bladder diverticula to unilateral renal agenesis, in 18% by Pankau et al (94). A duplicated kidney was noted in 7%.

Onset of puberty and menarche are early (19a,108). Approximately 25% have hypothyroidism or compensated hypothyroidism (B Pober, personal communication, 2000).

Oral manifestations. Thick lips, wide intercommissural distance, and long philtrum are characteristic. The voice is often hoarse or brassy (7,8,37,54,59). The maxillary arch has been described as being too broad for the mandibular arch. Hypodontia, microdontia, small slender roots, and dens invaginatus have been reported (7,8,33,123). Hypoplastic bud-shaped maxillary deciduous second molars and mandibular permanent first molars (Fig. 24–71) have been noted by some authors (7,8). In a series of 45 patients studied metrically, microdontia, hypodontia, anterior crossbite, increased interdental spacing, and persistent tongue thrust were noted in at least 35% (45). Mild micrognathia, widened mandibular angle, osteosclerotic changes in the lamina dura (particularly in the premolar-molar region), delayed mineralization of teeth, folding and thickening of the buccal mucous membranes, and prominent and accessory labial frenula have also been noted (7,8,58).

Other findings. Hypoplastic, deeply set nails are found in 65% (54). Other findings include inguinal hernia (38%), umbilical hernia (14%), and rectal prolapse (12%) (54,72). Contractures (50%) and prematurely gray hair (60%) have been recorded (77). Chronic constipation has been documented in adults (78).

Hypercalcemia. Hypercalcemia has not been documented in most cases (54) but has been a feature in approximately 15% of infants (56; C Morris, personal communication, 1998). When present, it usually disappears during the second year of life but can recur later in life. Prolonged symptomatic hypercalcemia has been rarely observed (103). Retrospective interviewing may reveal a history of failure to thrive, hypotonia, anorexia, constipation, or renal impairment (59).

From the earliest descriptions, a disorder of vitamin D has been repeatedly implicated in some way (4,36,110). Forfar and associates (31) advanced the postulate that Williams syndrome infants are abnormally sensitive to vitamin D in utero or in early infancy. Similar craniofacial, dental, and cardiovascular anomalies were noted in newborn rabbits born to mothers who had received prodigious amounts of vitamin D (34,35). Although there has been an enormous number of papers written about vitamin D dysmetabolism in this syndrome, there is no compelling evidence that it is disturbed (62).

In contrast, there seems to be general agreement that the response of serum calcium to a calcium-loading test is abnormal, even in individuals with no history, clinical or radiographic findings, or laboratory evidence of hypercalcemia (22). Although both control of endogenous parathyroid hormone and response to exogenous parathormone are not abnormal, endogenous response of calcitonin to a calcium load is strikingly deficient (22).

Differential diagnosis and laboratory aids. Supravalvular aortic stenosis and peripheral pulmonary artery stenosis without the Williams phenotype have autosomal dominant inheritance (30,34,52,55,63,66, 74,106). These patients have 30Kb deletions or point mutations in exons 3, 16, 21, 25, and 26 of the elastin gene (85). Peripheral pulmonary stenosis may also be found in *thalidomide embryopathy*, *rubella embryopathy*, *Down syndrome*, and *Alagille syndrome*. Other causes of hypercalcemia, such as familial hypocalciuric hypercalcemia (47), hyperparathyroidism, and vitamin D intoxication can usually be distinguished by history and routine laboratory tests. Martin et al (72) distinguished benign infantile hypercalcemia (Lightwood syndrome) from severe Fanconi-type hypercalcemia (what we now classify as Williams syndrome) on the basis of absence of associated anomalies, normal development, and lack of hypercalcemia symptoms. Ultrasonography is a valuable tool for noninvasive detection of subtle cardiovascular and renal abnormalities. Cross-sectional echocardiography or MRI scan is helpful for diagnosing supravalvular aortic stenosis (116).

Low MSAFP levels have been noted in mothers of affected children (20). Mutations in the elastin gene in exons 30 and 32 cause autosomal dominant *cutis laxa*.

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Chapter 25
Syndromes with Unusual Facies: Other Syndromes

Coffin-Siris syndrome (absent fifth finger- and toenails, unusual facies, and mental deficiency)

In 1970, Coffin and Siris (8) reported three children with coarse facial features, low birthweight, retarded somatic and mental growth, and hypoplastic to absent fifth finger- and toenails. Over 40 cases (1–3,7,10, 12,14–20,22–25,27,33–35,37) have been documented, although included are many cases which are doubtful or more consistent with a milder form described by Senior (30), Mace and Gotlin (21), Verloes et al (36), Ounap et al (26) and Bonioli et al (4). Rabe et al (28) also described sisters who have a similar phenotype but had hyperphosphatasia. Although most have been isolated examples, affected sibs (1,7,14,17,23) have been described; however, Levy and Baraitser (19) are doubtful about some of these cases, and suggest a 10% recurrence risk be given. About 85% are females, possibly implying lethality in males. Mild expression in a parent has also been noted (8,17,33,37). Perhaps some examples really have *fetal hydantoin syndrome, dup(9p) syndrome*, or some other condition. Burlina et al (6) described partial biotinidase deficiency in a child they had diagnosed as having Coffin-Siris syndrome: Bonneau et al (5) were unable to confirm this finding in a patient of theirs with Coffin-Siris syndrome. Therefore this is unlikely to be a helpful diagnostic aid. McPherson et al (24) described a child with an apparently balanced translocation with breakpoints 1q21.3 and 7q34, thus providing clues to possible gene location. McGhee et al (23a) also found a candidate region at 7q32→q34.

Half have low birthweight (19). Feeding problems and recurrent respiratory infections are common during infancy. Redundant gastric mucosa at the antrum has been reported (3). Craniofacial findings include microcephaly (65%), coarse facial features (100%), transient facial hypertrichosis, sparse scalp hair (80%), bushy eyebrows, flat nasal root, bulbous upturned nose, thick lips, and wide mouth. Those with Senior syndrome (brachymorphism-onychodysplasia-dysphalangism) (4,21,26,30,36) have a less coarse facial appearance, particularly because the lips are not as thick or full.

Mental deficiency (100%), hypotonia (100%), postnatal growth deficiency (85%), and short stature are consistent. Also found are hypoplastic to absent fifth finger- and toenails and terminal phalanges with less severe involvement of other digits (100%), lumbosacral hirsutism (85%), lax joints, dislocation of radial heads, coxa valga, retarded bone age, and small to absent patellae (Fig. 25–1). Radiographs of the hands and feet consistently demonstrate absent or hypoplastic distal and middle phalanges, particularly of the fifth digits. Various low frequency anomalies have included eyelid ptosis, strabismus, cleft palate, choanal atresia, herniae, cutis marmorata, single transverse palmar crease (10,12,19,33,34), and various congenital heart anomalies (30%). There appears to be a characteristic hand profile (1). Central nervous system anomalies include Dandy–Walker malformation (8,33), partial agenesis of corpus callosum, and agenesis of anterior commissure (9,33). Swillen et al (32) reported data on mental development, language, behavior, and social skills in children with Coffin-Siris syndrome. In general, most had moderate mental retardation, severely delayed speech with first words appearing at 3–5 years; increased frequency of aggressive behavior, pervasive developmental disorder, or unusual fears also were noted. Coffin and Siris (8a) added aplasia of the uterus. Good reviews are those of Levy and Baraitser (19) and Rabe et al (28).

References [Coffin-Siris syndrome (absent fifth finger- and toenails, unusual facies, and mental deficiency)]

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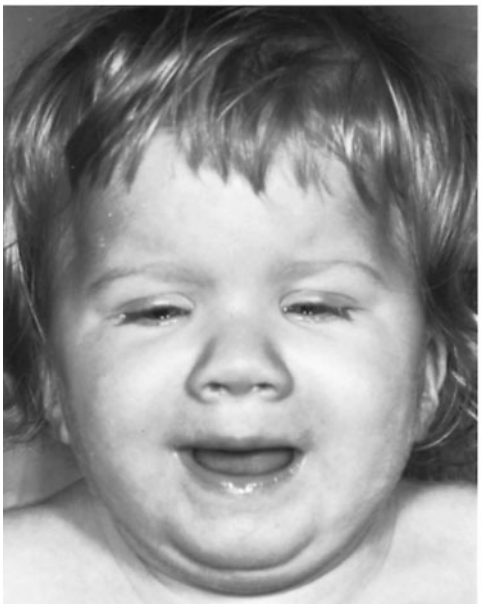
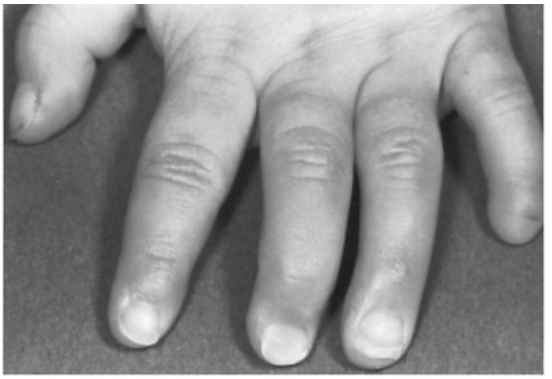
Fig. 25–1. *Coffin-Siris syndrome*. (A) Broad nose with anteverted nostrils. (B,C) Hypoplasia of terminal fifth phalanges. (D) Hypoplastic patella. (Courtesy of E Siris, Eldridge, California.)



A



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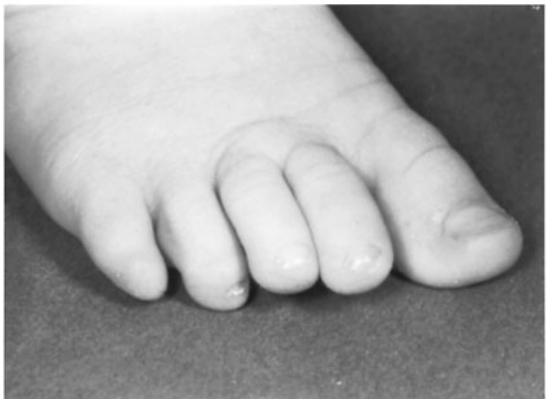

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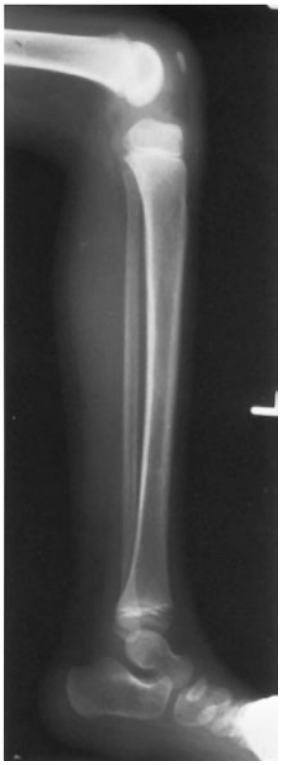

D

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Absent corpus callosum, coloboma, and craniofacial anomalies

Three sibs whose parents were first cousins. were reported by Temtamy et al (1). Facial phenotype included macrodolichocephaly, apparently low-set, simple ears, hypertelorism, beaked nose, micrognathia, and dental anomalies (malposition, hypoplasia). Additional manifestations included ocular colobomas (iris, choroid, and retina), agenesis of the corpus callosum, mild mental retardation, brachydactyly, genua valgga, and talipes equinovarus. Connective tissue defects were also noted: aortic dilatation, aortic regurgitation, and joint hyperextensibility. Inheritance is autosomal recessive.

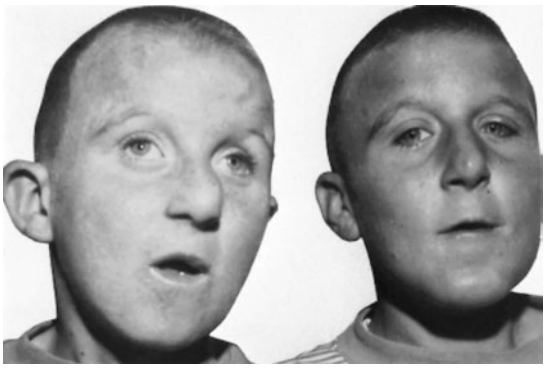
Reference (Absent corpus callosum, coloboma, and craniofacial anomalies)

1. Temtamy SA et al: New autosomal recessive multiple congenital abnormalities/mental retardation syndrome with craniofacial dysmorphism, absent corpus callosum, iris colobomas and connective tissue dysplasia. Clin Dysmorphol 5: 231–240, 1996.

Ruvalcaba syndrome

In 1971, Ruvalcaba et al (6) described male sibs and first cousins with severe mental and somatic retardation, microcephaly, hypoplastic skin, hypoplastic genitalia, delayed adolescence, cryptorchidism, and unusual facies characterized by downslanted palpebral fissures, small narrow beaked nose with hypoplastic alae, microstomia, narrow maxilla, and crowded teeth (Fig. 25–2). Other cases have been reported (2,7). We

Fig. 25–2. *Ruvalcaba syndrome*. Downslanting palpebral fissures, small narrow nose. (From R Ruvalcaba et al, J Pediatr 79:450, 1971.)



suspect marked heterogeneity. In spite of normal karyotype, the patient of Bialer et al (1) facially resembles del(2q) syndrome. The cases of Hunter et al (4) have since been termed the Hunter–McAlpine syndrome, which is associated with deletion 17q (8). The family described by Sugio and Kajii (7) was later suggested to have *tricho-rhino-phalangeal syndrome III* instead (5).

Musculoskeletal anomalies include short stature, narrow trunk, pectus carinatum, kyphoscoliosis and/or scoliosis with osteochondritis of spine, limitation of elbow extension, prominent elbows, short limbs, short hands and feet, short metapodial bones and phalanges, broad hips, and inguinal hernia.

At least 50% of the patients had pubertal delay and renal anomalies (1).

References (Ruvalcaba syndrome)

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Schinzel-Giedion syndrome

In 1978, Schinzel and Giedion (22) described a syndrome of midface retraction, hirsutism, multiple skeletal anomalies, mental retardation, and seizures. Over 20 patients have been reported (1–23). The disorder has occurred in sibs (1,4,22). Autosomal recessive inheritance is probable, although an autosomal dominant mutation with somatic mosaicism accounting for the recurrences is also possible.

Over 95% of patients have exhibited severe somatic and mental retardation, spasticity, and seizures (2). Subependymal pseudocytes have been noted (14), and neurodegenerative changes have been documented (23). Death has usually occurred before 2 years, often of pneumonia. Recurrent apneic spells are common.

In infancy, the face is coarse with frontal bossing, hypertrichosis, and midface retraction. The skull sutures are widely patent and there is ocular hypertelorism or telecanthus. The nose is short, saddled, and upturned. Choanal stenosis has been noted in 30%. The ears may be low set and the teeth delayed in eruption. Facial hemangioma may be present (3). The neck is short and the skin is redundant (Figs. 25–3 and 25–4). In older children the face is "coarse," hirsutism decreased, and midface retraction less striking.

Dermatologic anomalies include hypoplastic dermal ridges, hypoplastic nipples, transverse palmar creases, and hyperconvex nails (50%) (Fig. 25–5).

Genitourinary anomalies, noted in 90%, include congenital hydronephrosis, hypospadias, short penis, and deep interlabial sulcus. Congenital megacalyces were present in one child (10), and duplicated vagina with bifid uterus in another (12).

Heart defects, often ASD, have been reported in 50%.

Sacrococcygeal embryonic tumors (teratoma, neuroectodermal tumor) may be a component manifestation (4,15,19,20).

Skeletal anomalies, seen in 90% or more, include orbital hypertelorism, short steep skull base, wide occipital synchondrosis, undermineralization of the skull, multiple Wormian bones, broad ribs, mild mesomelic brachymelia, bowed tibiae, long clavicles, hypoplasia of distal phalanges, short first metacarpals, thick diaphyses of long bones, hypoplasia of pubic bones, and talipes (24).

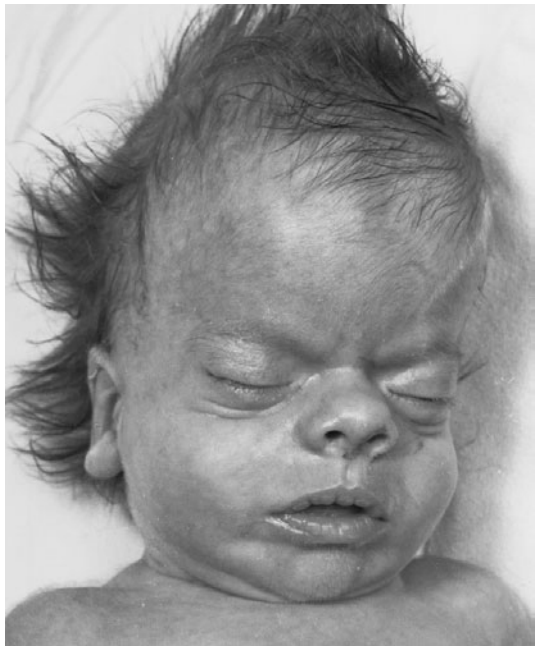

Fig. 25–3. *Schinzel-Giedion syndrome*. Note high bulging forehead, depressed nasal bridge with short root, protrusion of eyes, short neck, and hypertrichosis. (From A Schinzel and A Giedion, Am J Med Genet 1:361, 1978.)

CT scans of the brain have revealed ventricular dilatation (1,11,15), hypoplastic corpus callosum (17,19), periventricular leukomalacia (8), or brain atrophy and arachnoid cysts (21). Infrequently reported anomalies include microcornea (18), optic atrophy (6), or hypothyroidism and diabetes insipidus (21).

Congenital hydronephrosis is extremely rare and has been seen in few syndromes: *Johanson–Blizzard syndrome, trisomies 13 and 18, triploidy, Turner syndrome*, and *urofacial syndrome*. The facies is reminiscent of infants with a storage disease.

References (Schinzel-Giedion syndrome)

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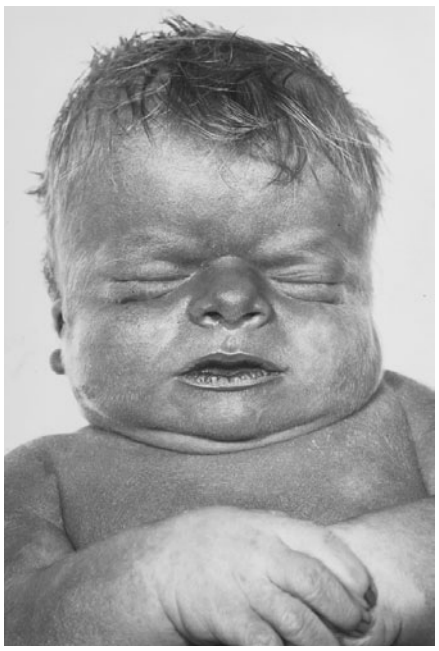
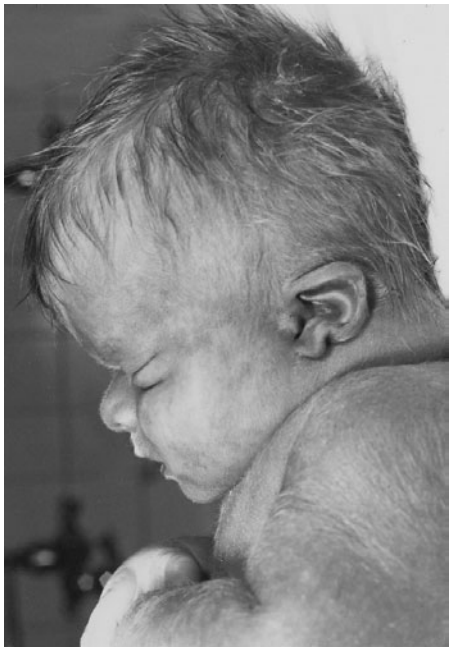


A



B

Fig. 25–4. *Schinzel-Giedion syndrome*. (A,B) Sib of child shown in Fig. 25–3. Note bulging forehead, short nose with low bridge, short neck with redundant skin fold, small broad pinna, and hypertrichosis. (From A Schinzel and A Giedion, Am J Med Genet 1:361, 1978.)

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21. Santos H et al: Schinzel-Giedion syndrome. A patient with hypothyroidism and diabetes insipidus. Genet Couns 5:187–188, 1994.
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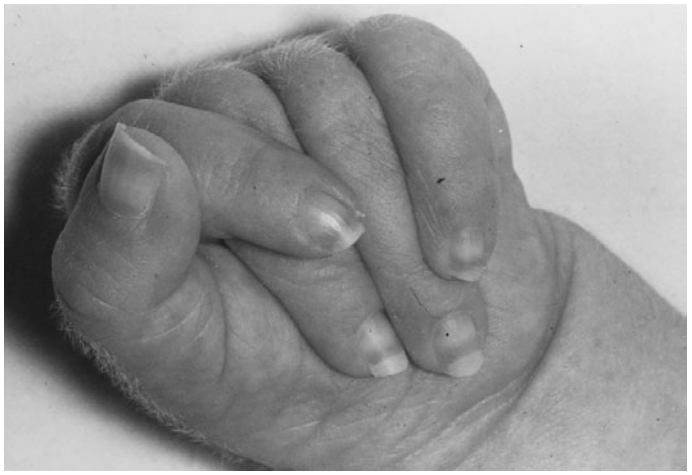
Fig. 25–5. *Schinzel-Giedion syndrome*. Narrow hyperconvex nails. (From A Schinzel and A Giedion, Am J Med Genet 1:361, 1978.)



23. Shah AM et al: Schinzel-Giedion syndrome: Evidence for a neurodegenerative process. Am J Med Genet 82:344–347, 1999.
24. Verloes A et al: Schinzel-Giedion syndrome. Eur J Pediatr 152:421–423, 1993.

Growth retardation, alopecia, pseudoanodontia, and optic atrophy (GAPO syndrome)

Andersen and Pindborg (1), in 1947, were the first to publish a case of what Tipton and Gorlin (18) chose to term the GAPO (*G*rowth retardation, *A*lopecia, *P*seudoanodontia, *O*ptic atrophy) syndrome. A Brazilian patient who was described in 1977 (4) as an example of Rothmund–Thomson syndrome, was republished in 1982 under a corrected title (19). To date, over 20 patients have been described (1–4,6,10–15,19,20).

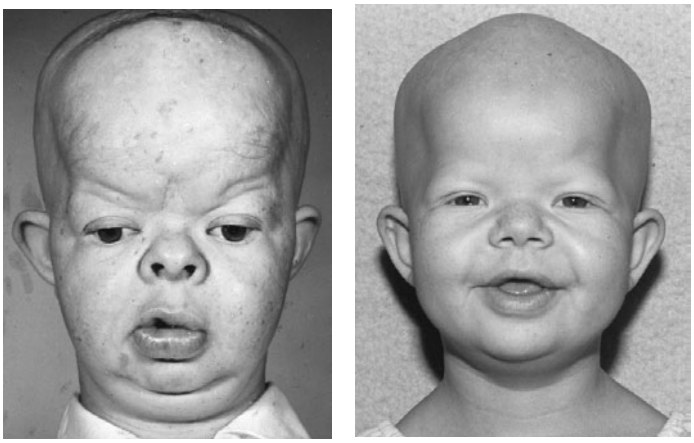
Inheritance is clearly autosomal recessive, there being affected sibs and parental consanguinity (8a).

Birthweight is normal, but birth length is somewhat reduced. Growth retardation becomes quite evident at the sixth month checkup. Body build is proportional, although some have described their patients as appearing rhizomelic (2,15). Bone age is severely retarded (2). A muscular habitus is common. Umbilical hernia is apparently a constant feature.

Scalp hair is present at birth, but, after the first years of life, the hair is completely lost and never regrows (Fig. 25–6). The jaw bones are crowded with both dentitions, neither of which erupts (Fig. 25–7). Frontal bossing, high forehead, dilated scalp veins due to absent or occluded transverse and sigmoid sinuses (3,6,8,11), mild midfacial hypoplasia, and delayed closure of the anterior fontanel are common. Craniosynostosis was found in one case (1). The facial differences include periorbital fullness or puffy eyelids, anteverted wide nostrils, long philtrum, and thick, full lips. Optic atrophy is variable in onset (1,3–5,7,8) and found in about 30% (3,8a). It may be attributable to increased intraocular pressure (3). Keratoconus and glaucoma (11,12) have also been reported. Eyelashes are white (15). Ears are large.

Other changes include mild pectus excavatum, scythelike lower ribs, hypoplastic middle and distal phalanges, hypogonadism, nephrocalcinosis (1,7), and polycystic kidneys (1,10).

Skin biopsies done in several patients (13,20) show deposition of an anomalous hyaline substance in the dermis which appears over time. Autopsy studies showed interstitial fibrosis of most visceral organs. Electron microscope studies of gingiva have also shown excessive



A B

Fig. 25–6. *Growth retardation, alopecia, pseudoanodontia, and optic atrophy (GAPO syndrome)*. (A) Note 26-year-old female with alopecia. Patient had optic atrophy. (B) Compare facies with that in A. (A from TH Andersen and JJ Pindborg, Odont T 55:484, 1947.)

collagen fiber deposition (10). Differential diagnosis of disorders with severe alopecia is elegantly discussed by Feinstein et al (3).

References [Growth retardation, alopecia, pseudoanodontia, and optic atrophy (GAPO syndrome)]

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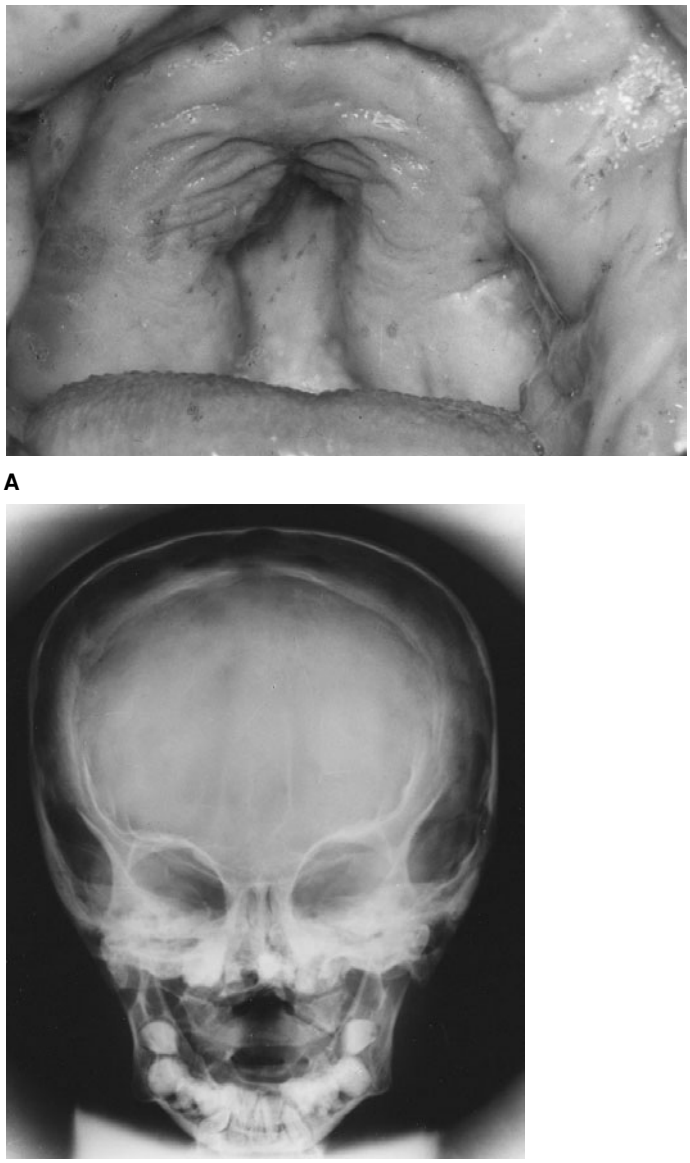

A B

Fig. 25–7. *Growth retardation, alopecia, pseudoanodontia, and optic atrophy (GAPO syndrome)*. (A) Edentulous jaws. (B) Note numerous unerupted teeth. (From TH Andersen and JJ Pindborg, Odont T 55:484, 1947.)

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Brachymetapody, anodontia, hypotrichosis, and albinoid trait (Tuomaala-Haapanen syndrome)

Tuomaala and Haapanen (1) reported three sibs affected with short stature and shortening of all digits other than thumbs and halluces due to brachymetapody. Hypoplastic maxilla, anodontia, generalized hypotrichosis, hypoplastic breasts and genitalia, convergent strabismus, distichiasis, hypoplastic tarsus, cataracts, myopia, irregular nystagmus, and albinoid skin were found (Fig. 25–8). The syndrome presumably has autosomal recessive inheritance.

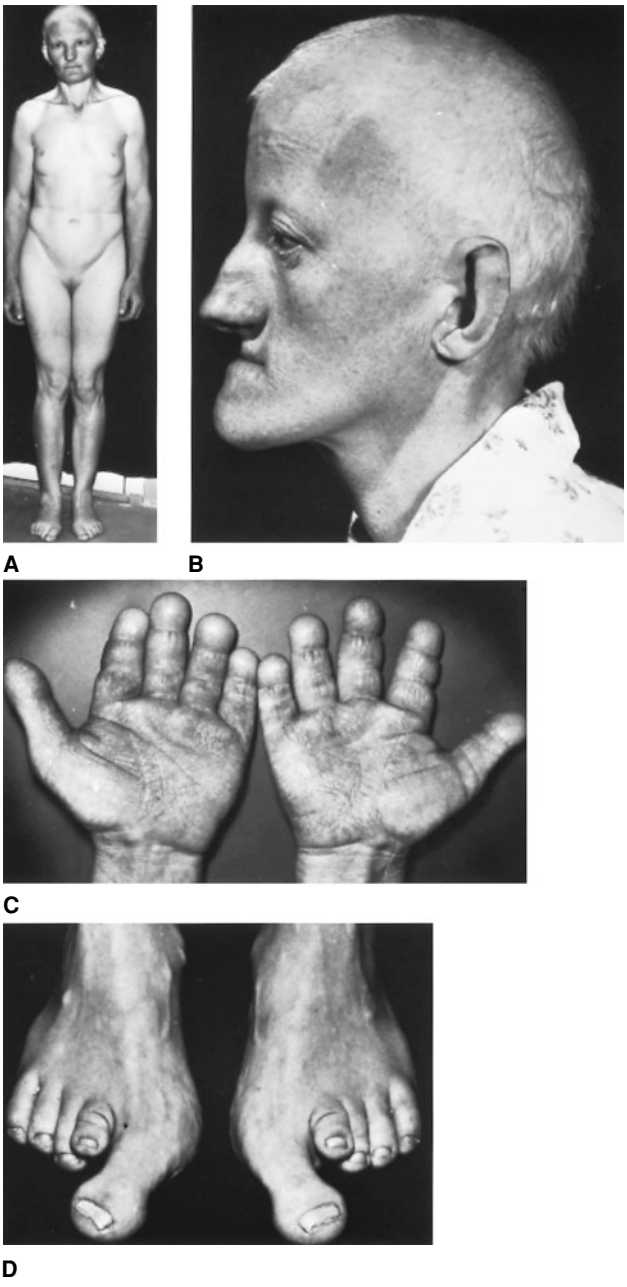

Fig. 25–8. *Brachymetapody, anodontia, hypotrichosis, and albinoid trait (Tuomaala-Haapanen syndrome).* (A) Albinoid skin, hypoplastic breasts, generalized hypotrichosis. (B) Sunken midface with loss of vertical height due to anodontia. (C,D) Shortening of all digits except thumbs and halluces. (From P Tuomaala and E Haapanen, Acta Ophthalmol 46:365, 1968.)

Reference [Brachymetapody, anodontia, hypotrichosis, and albinoid trait (Tuomaala-Haapanen syndrome)]

1. Tuomaala P, Haapanen E: Three siblings with similar anomalies in the eyes, bones, and skin. Acta Ophthalmol 46:365–371, 1968.

Broad terminal phalanges and facial abnormalities (Keipert syndrome, nasodigitoacoustic syndrome)

Male sibs with severe sensorineural hearing loss, unusual facies, and broad terminal phalanges were described by Keipert et al in 1973 (2). Balci and Dagli (1) also reported male sibs. Autosomal or X-linked recessive inheritance is likely.

The facies was marked by a large nose with a high bridge, large rounded columella, and prominent nasal alae. The upper lip protruded, with a cupid's bow configuration overlapping the rather straight lower lip laterally (Fig. 25–9A,B). The distal phalanges of the thumbs, the first, second, and third fingers, and all the toes were remarkably broad. The fifth fingers were short and clinodactylous. The toes were rotated medially (Fig. 25–9C,D). Radiographically, one sib had bifid terminal phalanges in both index fingers. In the halluces of both patients, the proximal phalanges were short and the terminal phalanges were short with large, rounded epiphyses. Mild sensorineural hearing loss and hoarse voice were present in the patients of Balci and Dagli (1); voice quality was not noted in the cases of Keipert (2).

References [Broad terminal phalanges and facial abnormalities (Keipert syndrome, nasodigitoacoustic syndrome)]

1. Balci S, Dagli S: Keipert syndrome in two brothers from Turkey. Clin Genet 50:223–228, 1996.

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Cardio-facio-cutaneous syndrome (CFC syndrome)

In 1986, Reynolds et al (29) described eight patients having a characteristic facial appearance, ectodermal abnormalities, growth failure, mental retardation, and variable cardiac defects. About 55 bona fide patients have been reported (1,2,4,7,10a,12,17,20,23,27,28,30–32,34,36,37), as have many doubtful cases (3,8,9,13,16,18,19,21,33,34). Some of these doubtful cases likely have Noonan syndrome, and contribute to the argument that Noonan and CFC syndromes are allelic (vide infra). Neri et al (24,26) presented a convincing argument for separation of these conditions, and suggested the following diagnostic criteria for CFC syndrome: (a) Noonan-like face, (b) mental retardation, usually severe, (c) hyperkeratotic skin lesions, (d) sparse, curly hair and absent eyebrows, (e) heart defects, and (f) sporadic occurrence.

Inheritance is unknown, with legitimate cases being sporadic occurrences. Fathers have been older (6). Legius et al (15) found allelism with Noonan syndrome at 12q24. Further, Rauen et al (27a) mapped the gene at 12q21.2. However, most patients had no deletion of 12q (38), and we suspect that the phenotypes of these patients more closely resemble *Noonan syndrome*. About 60 examples have been described. The reported familial cases (8,10,14,16,27) almost certainly have a different condition.

Craniofacial findings. The cranial vault is high and somewhat boxy. The face is characterized by high forehead with bitemporal constriction, hypoplasia of supraorbital ridges, sparse or absent eyebrows, ptosis, downslanting palpebral fissures, low nasal bridge, upturned nose, and posteriorly angulated pinnae with prominent helices. Scalp hair is sparse, friable, and unusually curly; the eyebrows are hypoplastic or absent (Fig. 25–10). The irides are rarely the blue or blue-green seen in Noonan syndrome.

Submucous cleft palate is common (5,7). The face is reminiscent of that seen in Noonan syndrome, but hypertelorism does not occur in CFC.

Growth and development. Postnatal growth retardation is present in 75%, but prenatal growth is usually normal or slightly elevated. Relative macrocephaly is present in 70%. Hydrocephalus is noted in 30%. Feeding problems are encountered in 35%. In contrast to Noonan syndrome, neurologic manifestations include moderate to severe mental retardation (95%), hypotonia (30%), markedly delayed or absent speech, autistic-like behavior, seizures, and abnormal EEGs (5,11,25,28,29).

Eyes. Ptosis (50%), nystagmus (30%),and strabismus (40%) are striking (30,37).

Skin. Skin changes vary from dry patchy hyperkeratosis to a severe generalized ichthyosislike condition, with the distribution occurring preferentially over the extensor surfaces of the limbs. Keratosis pilaris is seen in 10%. Hypopigmentation, hyperpigmentation, and hemangiomata have also been described (17).

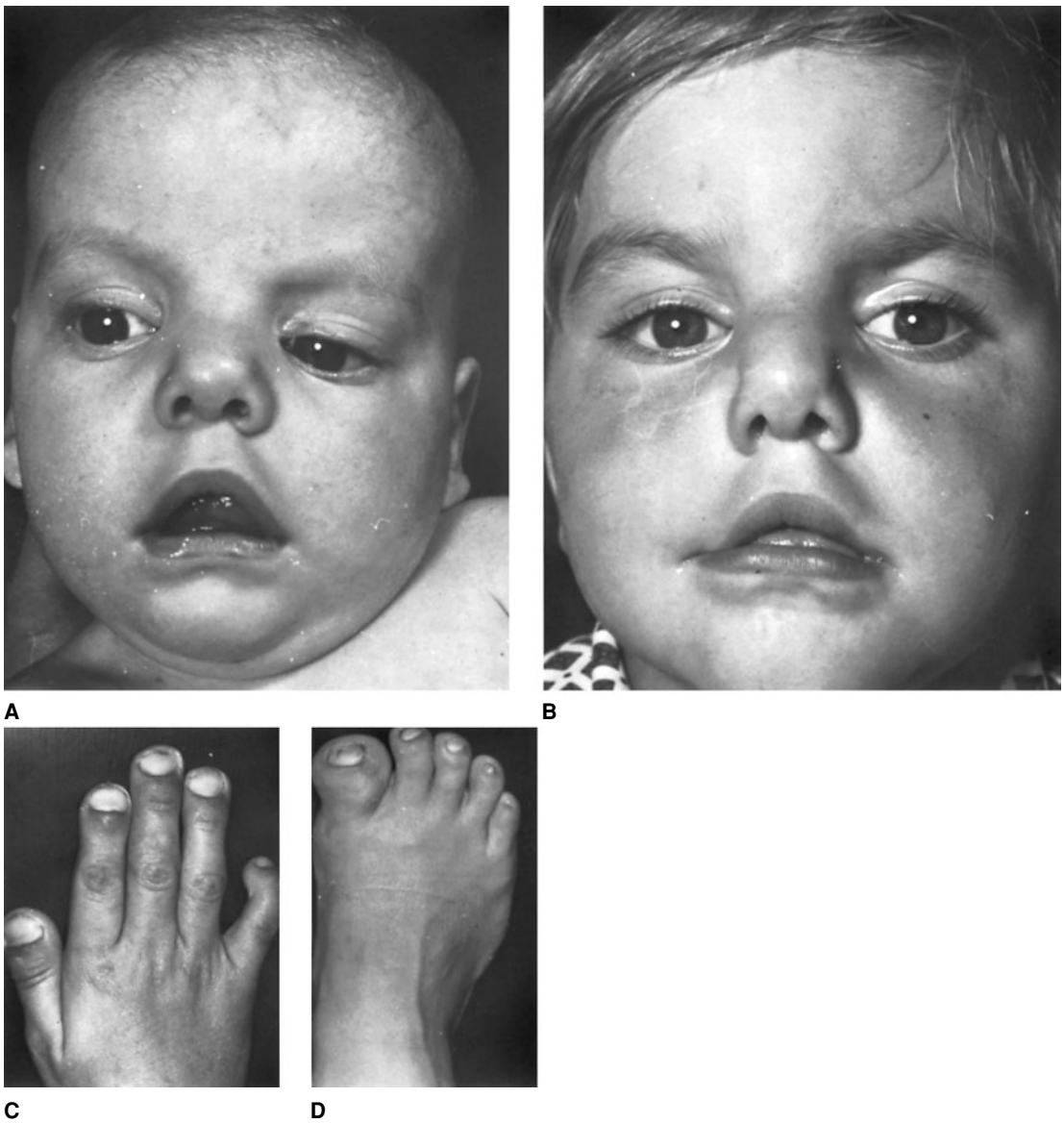

Fig. 25–9. *Broad terminal phalanges and facial abnormalities (Keipert syndrome)*. (A,B) Nine-month- and three-year-old sibs exhibiting large nose with high bridge, large rounded columella, and prominent alae. Upper lip protrudes with cupid's bow configuration. (C) Terminal phalanges are short and broad. Fifth fingers are short and clinodactylous. (D) Toes short and broad, especially hallux. (From JA Keipert et al, Aust Paediatr J 9:10, 1973.)

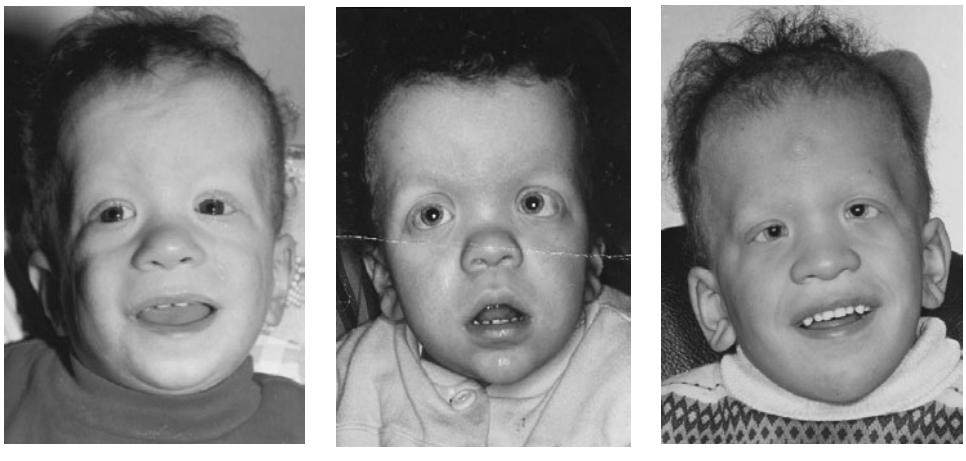

Fig. 25–10. *Cardio-facio-cutaneous syndrome*. (A,B) High forehead, bitemporal constriction, sparse, friable, curly hair, hypoplasia of supraorbital ridges, low nasal bridge, dysmorphic pinnae, short neck. Patients had dry hyperkeratotic skin over extensor surface of limbs, pulmonary stenosis, and atrial septal defect. (C) Compare facies of patient seen by RJ Gorlin. (A from JF Reynolds et al, Am J Med Genet 25:413, 1986. B from G Raymond and L Holmes, Dev Med Child Neurol 35: 727, 1993.)

Musculoskeletal findings. The chest is deformed in 70%.

Heart. The most common cardiac anomalies are pulmonic stenosis (40%), ASD (30%), cardiomyopathy (25%), and VSD (10%), although other cardiac defects have also been described (31,36).

Other. Acute lymphoblastic leukemia has been reported (33a). *Noonan syndrome, neurofibromatosis/Noonan phenotype, Costello syndrome,* and *cranio-facio-cardio-skeletal syndrome* must be excluded.

References [Cardio-facio-cutaneous syndrome (CFC syndrome)]

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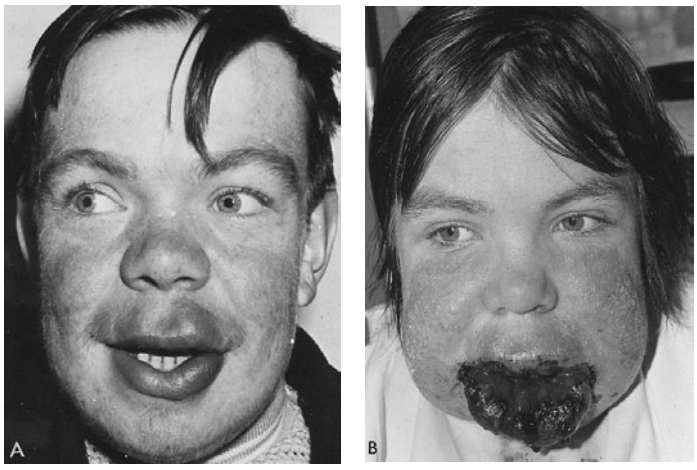
Coarse face, mental retardation, sensorineural hearing loss, and skeletal abnormalities (Fountain syndrome)

Fountain (1), in 1974, briefly described four sibs. Two exhibited generalized facial edema with massive swelling of the upper and lower lips. All were mentally retarded with profound congenital sensorineural hearing loss. One sib died in early infancy but had profound hearing loss, mental retardation, and spina bifida. Three sibs had granulomatous swelling of the lips (Fig. 25–11). Three of four showed gross thickening of the calvaria (Fig. 25–12). In 1986, Fryns et al (3) confirmed the syndrome by reporting sibs with hearing loss, mental retardation, seizures, and round and coarse face with mild swelling of subcutaneous tissues, particularly those of the cheeks and lips. The hands and feet were short and plump with

Fig. 25–11. *Coarse face, mental retardation, sensorineural hearing loss, and skeletal abnormalities (Fountain syndrome).* (A,B) Affected sibs exhibiting coarse facies and skin granulomata. (From RB Fountain, Proc R Soc Med 67:878, 1974.)



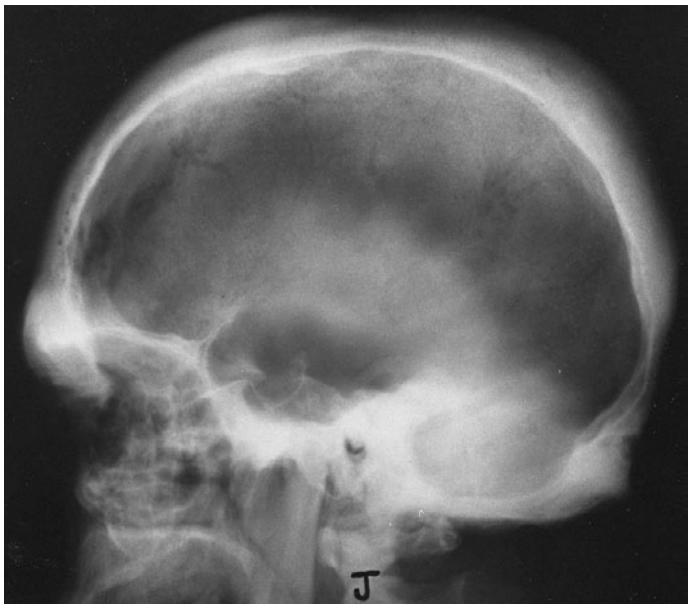


Fig. 25–12. *Coarse face, mental retardation, sensorineural hearing loss, and skeletal abnormalities (Fountain syndrome)*. Radiograph showing marked thickening of calvaria. (From RB Fountain, Proc R Soc Med 67:878, 1974.)

broad and short terminal phalanges (2). Short stature may occur. Manifestations present in only one or two patients each include high palate, ear pits, blindness, omphalocele, and scoliosis. The phenotype is fairly indistinct in infancy and early childhood but becomes more apparent with age. Behavior is described as extremely friendly (4).

Radiographically, there was marked thickening of the calvaria and thickened cortices of the bones of the hands and feet. Tomography of the temporal bones showed absence of cochlear windings.

Inheritance is presumably autosomal recessive.

There is some physical similarity to *mannosidosis* and *aspartylglycosaminuria*, but biochemical studies have been normal.

References [Coarse face, mental retardation, sensorineural hearing loss, and skeletal abnormalities (Fountain syndrome)]

1. Fountain RB: Familial bone abnormalities, deaf mutism, mental retardation, and skin granulomas. Proc R Soc Med 67:878–879, 1974.

2. Fryns JP: Fountain's syndrome: Mental retardation, sensorineural deafness, skeletal anomalies and coarse facies with full lips. J Med Genet 26:722–724, 1989.

3. Fryns JP et al: Mental retardation, deafness, skeletal abnormalities and coarse face with full lips: Confirmation of the Fountain syndrome. Am J Med Genet 26:551–556, 1987.

4. Van Buggenhout GJCM et al: Fountain syndrome: Further delineation of the clinical syndrome and follow-up data. Genet Couns 7:177–186, 1996.

Cranio-facio-cardio-skeletal dysplasia

Cantú et al (1) reported four unrelated females with short stature (below the third centile), delayed psychomotor development (60–70 IQ), macrodolichocephaly (above 90th centile) with prominent forehead, scanty thin and hypopigmented hair, coarse facies, hypertelorism with flat nasal bridge, exophthalmos, short nose with anteverted nares, long philtrum, low-set ears, short neck, short wide thorax, prominent abdomen, cubitus valgus, cutis laxa with joint hyperelasticity, and wrinkled palms and soles (Fig. 25–13).

The ribs were slender but wider in the middle. The long bones were also slender and the vertebral bodies somewhat small.

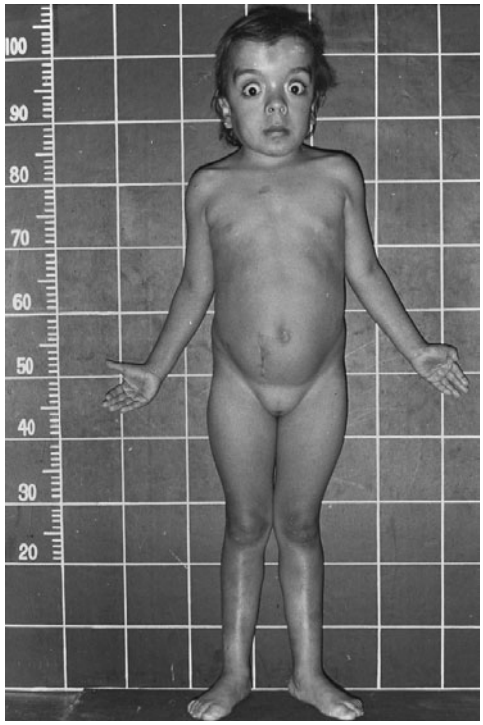


Fig. 25–13. *Cranio-facio-cardio-skeletal dysplasia*. Child with short stature and delayed psychomotor development. Note macrodolichocephaly with prominent forehead, scanty hair, hypertelorism, flat nasal bridge, exophthalmus, short nose with anteverted nostrils, long philtrum, and short neck. The abdomen was prominent and there was cubitus valgus. (From JM Cantú et al, Clin Genet 22:172, 1982.)

Reference (Cranio-facio-cardio-skeletal dysplasia)

1. Cantú JM et al: Individualization of a syndrome with mental deficiency, macrocranium, peculiar facies, and cardiac and skeletal anomalies. Clin Genet 22: 172–179, 1982.

Familial osteodysplasia (Anderson syndrome)

Under this unfortunately nonspecific title, Anderson et al (1) reported four sibs with an apparently unique disorder. The parents were consanguineous. Inheritance is autosomal recessive.

The facies was characterized by prominent brows, flat nasal bridge, marked midface hypoplasia with relative mandibular prognathism, pointed chin, and large ear lobes (Fig. 25–14A–D). The feet were described as paddle shaped.

Radiographically, thinning of calvaria, pointed mastoids and spinous processes of the cervical vertebrae, kyphoscoliosis, abnormal ribs, cortical thickening of femoral shafts, and thinning of the superior pubic rami were noted. The mandible had a widened angle, increased body length, reduced ramus height, and severely decreased bigonial width (2) (Fig. 25–14E–G).

We have termed the naming of the disorder "unfortunate" because there are many different "osteodysplasias" and, in particular, Melnick-Needles syndrome has been called "familial osteodysplastia." The confusion has been compounded by Schendel and Delaire (3), who employed the same term to report an autosomal dominant condition in which craniosynostosis is a variable feature but which, in our opinion, has little in common with the Anderson syndrome.

References [Familial osteodysplasia (Anderson syndrome)]

1. Anderson LG et al: Familial osteodysplasia. JAMA 220:1687–1693, 1972.

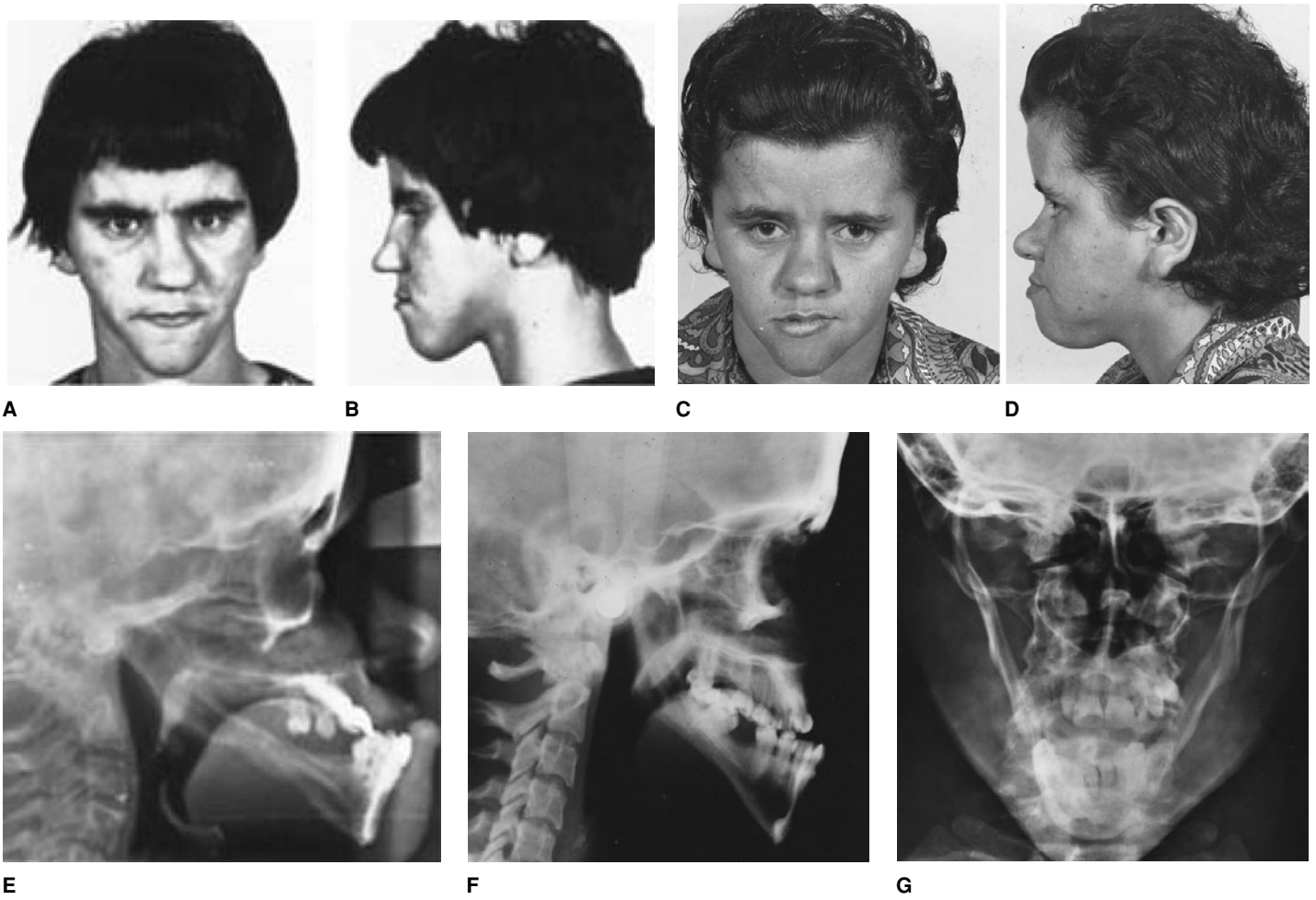


Fig. 25–14. *Familial osteodysplasia (Anderson syndrome)*. (A,B) Triangular face with pointed chin and hypoplastic midface. (C,D) Sib of woman in A and B. (E) Mandible with widened angle, increased body length, reduced ramus height. (F,G) Note pointed symphysial area and marked thinning of body and ramus of mandible. (From LG Anderson et al, JAMA 220:1687, 1972.)

2. Buchignani JS et al: Roentgenographic findings in familial osteodysplasia. Am J Roentgenol 116:602–608, 1972.
3. Schendel S, Delaire J: Familial osteodysplasia. Head Neck Surg 4:335–343, 1982.

Flexion and extension deformities of the hands and unusual facies (Emery-Nelson syndrome)

Mild mental and somatic retardation, increased US/LS ratio, deformities of the first three metacarpophalangeal joints of both thumbs, clawed toes, and an unusual facies (long philtrum, flat midface) were described in a mother and daughter by Emery and Nelson (1) (Fig. 25–15). RJ Gorlin has seen the same anomalies in a mother and her two sons.

Reference [Flexion and extension deformities of the hands and unusual facies (Emery-Nelson syndrome)]

1. Emery AEH, Nelson MM: A familial syndrome of short stature, deformities of the hands and feet and an unusual facies. J Med Genet 7:379–382, 1970.

Hemimaxillofacial dysplasia (segmental odontomaxillary dysplasia)

In 1987, Miles et al (2) reported a disorder in two patients consisting of unilateral enlargement of maxillary alveolar bone and gingiva associated with hypoplastic teeth, and facial asymmetry.

One patient had hypertrichosis and missing maxillary premolars on the affected side (Figs. 25–16 to 25–18). Since then, several other patients have been described (1,2,4,5). Whereas this sporadically occurring disorder is presumed to be present at birth, age of diagnosis is often not until midchildhood. Asymmetry was nonprogressive, and noncranial abnormalities were noted. Enamel defects of primary molars and/or absent permanent teeth on the affected side were a constant finding. The right side is involved more often (1), and facial hypertrichosis is present in approximately 25%.

In a review of the radiographic and biopsy material of eight cases, Danforth et al (1) suggested that this condition be termed "segmental odontomaxillary dysplasia." This was based on the absence of facial hypertrichosis in the patients. However, examination of their material clearly shows that it is the same condition as hemimaxillofacial dysplasia because facial hypertrichosis is not an obligatory abnormality. While the term is descriptive, it does not convey the facial asymmetry that allows early recognition by the pediatrician.

An excellent review is that of Prusack et al (6).

References [Hemimaxillofacial dysplasia (segmental odontomaxillary dysplasia)]

1. Danforth RA et al: Segmental odontomaxillary dysplasia: Report of eight cases and comparison with hemimaxillofacial dysplasia. Oral Surg Oral Med Oral Pathol 70:81–85, 1990.
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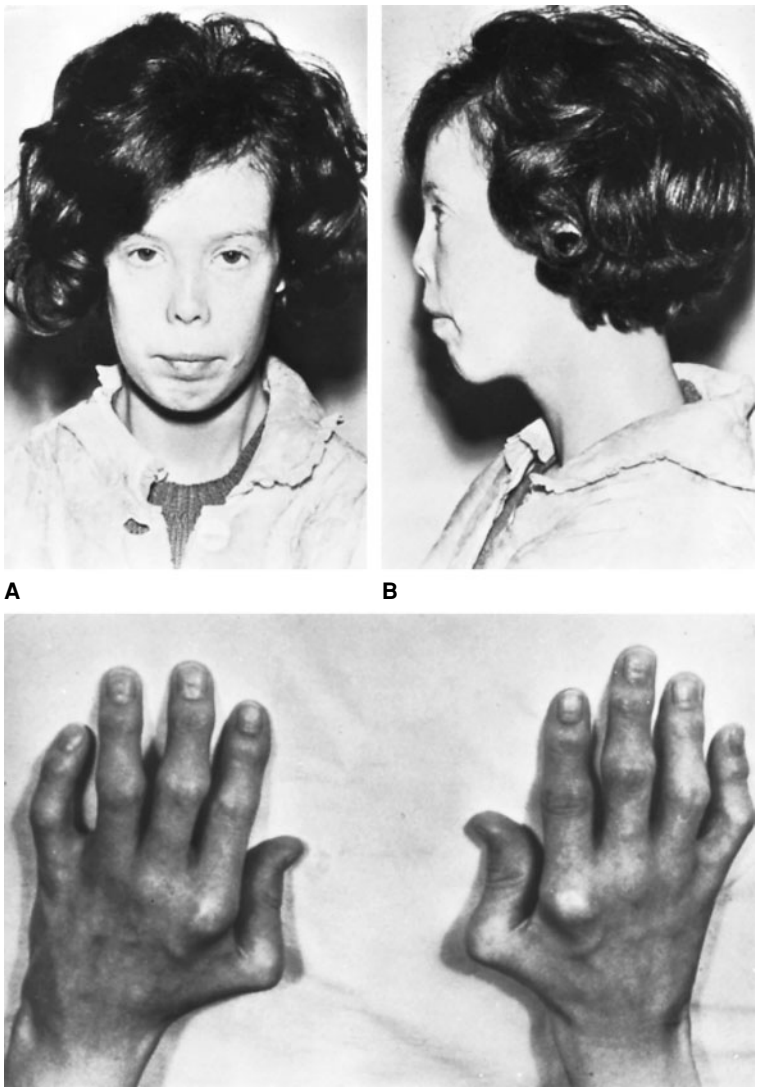


Fig. 25–15. *Flexion and extension deformities of the hands and unusual facies (Emery-Nelson syndrome)*. (A,B) Flat midface with long philtrum. (C) Flexion deformity of first three metacarpophalangeal joints, extension deformity of interphalangeal joints of thumbs. (From AEH Emery and MM Nelson, J Med Genet 7:379, 1970.)

Fig. 25–16. *Hemimaxillofacial dysplasia*. Facial asymmetry and unilateral hypertrichosis. (From DA Miles et al, Oral Surg Oral Med Oral Pathol 64:445, 1987.)

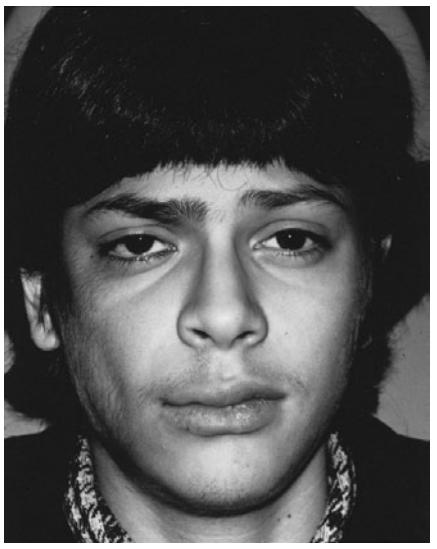
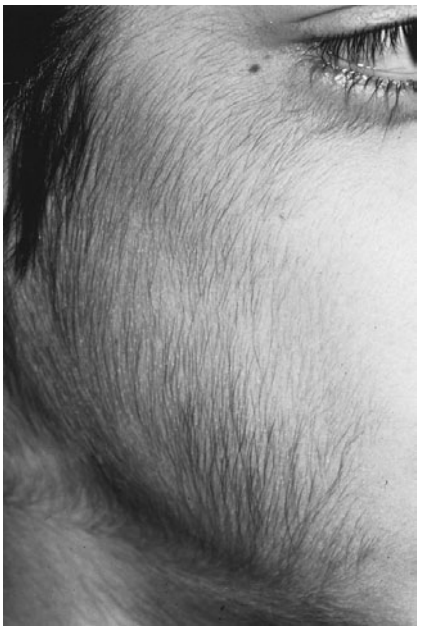


Fig. 25–17. *Hemimaxillofacial dysplasia*. Close-up showing hypertrichosis. (From DA Miles et al, Oral Surg Oral Med Oral Pathol 64:445, 1987.)



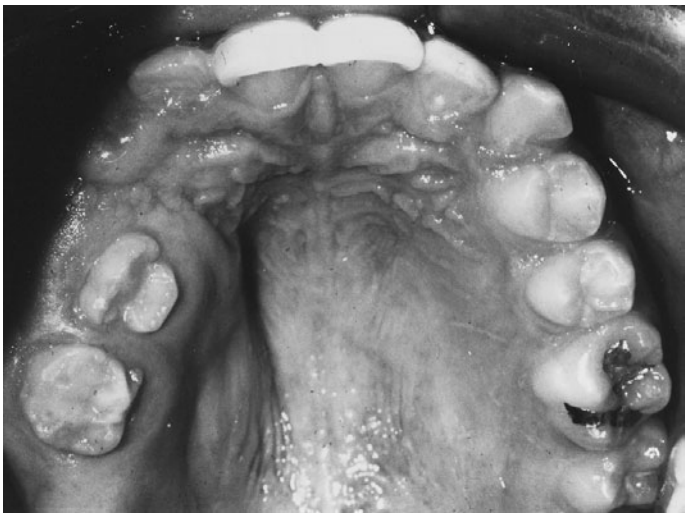


Fig. 25–18. *Hemimaxillofacial dysplasia*. Unilateral maxillary enlargement in association with hypoplastic and missing teeth. (From DA Miles et al, Oral Surg Oral Med Oral Pathol 64:445, 1987.)

3. Miles DA et al: Hemimaxillofacial dysplasia: A newly recognized disorder of facial asymmetry, hypertrichosis of the facial skin, unilateral enlargement of the maxilla, and hypoplastic teeth in two patients. Oral Surg Oral Med Oral Pathol 64:445–448, 1987.

4. Packota GV et al: Radiographic features of segmental odontomaxillary dysplasia. A study of 12 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 82:577–584, 1997.

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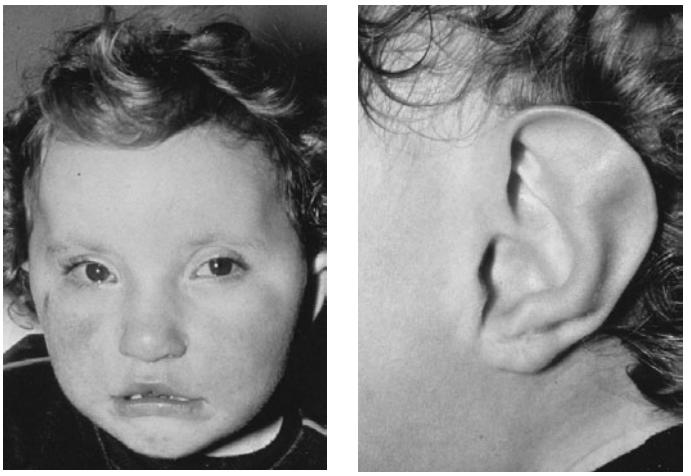
Oto-onycho-peroneal syndrome

Pfeiffer (3) described two male sibs with minor craniofacial malformations, multiple contractures, dysplastic pinnae, hypoplasia of nails, and hypoplasia of fibulae. The craniofacies was characterized by dolichocephaly, flaring of temporal regions, flat facial contour, upward slanting palpebral fissures, large low-set posteriorly angulated pinnae with unfolded helix, prominent anthelix and superior crus, and hypoplastic lobule (Fig. 25–19).

The thumb, index, and middle fingers were stiff with flattened knuckle creases and absent to rudimentary nails. The hallux and second toes were similarly affected (Fig. 25–20). The thighs were short with abnormally shaped lower limbs. Pes calcaneovalgus was evident. The fibulae were hypoplastic to absent. Radiographic examination revealed hypoplasia of malar bones and lateral clavicles. The metaphyses of the long bones were somewhat widened. The terminal phalanges of the thumbs and halluces were abbreviated. Carpal and tarsal synostosis was evident. DeVriendt et al (1) reported two affected sibs.

The condition appears similar to that reported by Leiba et al (2), although the skeletal changes are somewhat different. Leiba et al (2) described a male with mild mental retardation, short stature, ptosis of eyelids, downslanting palpebral fissures and agenesis or hypoplasia of nails and terminal phalanges. The parents were consanguineous. Eyelashes were on the medial half of the lids and there were bilateral colobomas of the retina. The pinnae were dysmorphic with prominent anthelix. The halluces were broad with absence of toenails. The thumbs were not broad but had dysplastic nails like those of the index fingers. The phallus was enlarged and there was hypospadias.

The sisters reported by DeVriendt et al (1) had abnormalities of the clavicle and scapula and small corneae with unusual pigmentation of the fundus.



A B

Fig. 25–19. *Oto-onycho-peroneal syndrome*. (A) Mildly abnormal facies characterized by flaring of temporal regions, flat facial contour, upward-slanting palpebral fissures. (B) Pinna with unfolded helix, prominent anthelix and superior crus, hypoplastic lobules. (Courtesy of R Pfeiffer, Erlangen, Germany.)

Inheritance is autosomal recessive.

References (Oto-onycho-peroneal syndrome)

1. DeVriendt K et al: Oto-onycho-peroneal syndrome: Confirmation of a syndrome. J Med Genet 35:508–509, 1998.

2. Leiba S et al: Oculootonasal malformations associated with osteoonychodysplasia. Birth Defects 11(2):67–73, 1975.

3. Pfeiffer RA: The oto-onycho-peroneal syndrome. Eur J Pediatr 138:317–320, 1982.

Short stature, characteristic facies, mental retardation, skeletal anomalies, and macrodontia (KBG syndrome)

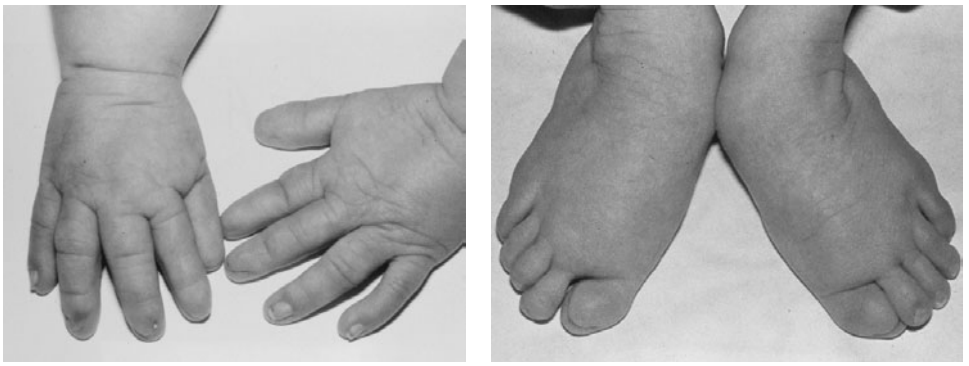
In 1975, Herrmann et al (3) described an autosomal dominantly inherited syndrome of mild mental retardation, short stature, characteristic facies, macrodontia, and various skeletal anomalies. Similarly affected individuals were described by several authors (1,2,4–6,8,9), and Soekarman et al (7) provided follow-up data on the boys reported by Parloir et al (4).

Height is below the third centile. Intelligence quotients have ranged between 40 and 65. Several patients have a speech defect.

The craniofacial appearance is characterized by brachycephaly, wide biparietal diameter, round face, wide bushy eyebrows with synophrys, long palpebral fissures, anteverted nostrils in some instances, outstanding pinnae, widely arched maxilla with short alveolar ridge (Figs. 25–21 and 25–22), thin upper lip, and outstanding pinnae. Several patients have manifested oligodontiala. The central and lateral incisors are enlarged. Their incisal edges have supernumerary mamelons, some as many as five (Fig. 25–23). The philtrum tends to be long. The vermilion of the lips is thin and lip shape is that of a hunter's bow. Seizures have been present in some, more so in childhood than in adulthood (7). One child had conductive hearing loss and pulmonary artery stenosis (5); another had a VSD (1).

Skeletal changes include those previously described as well as Wormian bones, cervical ribs, various vertebral anomalies (anterior notching, hypoplasia of upper and lower plates, open neural arches, block vertebrae), pectus excavatum, short tubular hand bones, short femoral neck, and delayed bone age (Fig. 25–24). Cerebellar vermis hypoplasia may be a relatively common component manifestation (9).

Dermatoglyphic findings consist of single palmar crease and distal axial triradius.



A B

Fig. 25–20. *Oto-onycho-peroneal syndrome*. (A,B) Hands and feet showing absent to rudimentary nails of middle and index fingers and thumb; similar changes in toes. Knuckle creases flattened. (Courtesy of R Pfeiffer, Erlangen, Germany.)

Differential diagnosis includes *Kabuki syndrome*, which also comprises long palpebral fissures, and minor nasal and ear anomalies. However, those with Kabuki syndrome do not have prominent incisors and do have fetal pads on the fingers.

References [Short stature, characteristic facies, mental retardation, skeletal anomalies, and macrodontia (KBG syndrome)]

1. DeVriendt K et al: Further delineation of the KBG syndrome. Genet Couns 9:191–194, 1998.

1a. Dowling PA et al: The KBG syndrome, characteristic dental findings. Int J Paediatr Dent 11:131–134, 2001.

2. Fryns JP, Haspeslagh M: Mental retardation, short stature, minor skeletal abnormalities, craniofacial dysmorphism and macrodontia in two sisters and their mother. Another variant example of the KBG syndrome. Clin Genet 26:69–72, 1984.

3. Herrmann J et al: The KBG syndrome—a syndrome of short stature, characteristic facies, mental retardation, macrodontia and skeletal anomalies. Birth Defects 11(5):7–18, 1975.

4. Parloir C et al: Short stature, craniofacial dysmorphism and dento-skeletal abnormalities in a large kindred. Clin Genet 12:263–266, 1977.

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7. Soekarman D et al: The KBG syndrome: Follow-up data on three affected brothers. Clin Genet 46:283–286, 1994.

8. Tollaro I et al: Anomalie dento-maxillo-facciali nella "Sindrome KBG." Minerva Stomatol 33:437–446, 1984.

9. Zollino M et al: Six additional cases of the KBG syndrome: Clinical reports and outline of the diagnostic criteria. Am J Med Genet 52:302–307, 1994.

Fig. 25–21. *Short stature, characteristic facies, mental retardation, skeletal anomalies, and macrodontia (KBG syndrome)*. Sibs with short stature, cryptorchidism. The facies is triangular with redundant eyebrows, telecanthus, high nasal bridge, outstanding pinnae. [From J Herrmann et al, Birth Defects 11(5):7, 1975.]

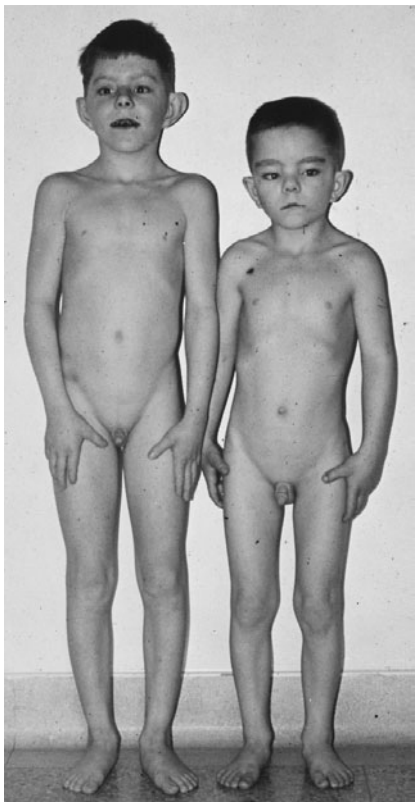
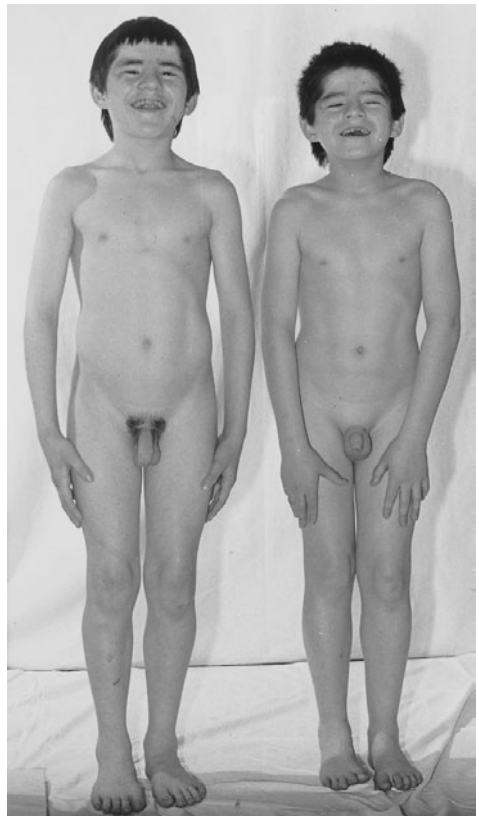


Fig. 25–22. *Short stature, characteristic facies, mental retardation, skeletal anomalies, and macrodontia (KBG syndrome)*. Compare Fig. 25–21 with short mentally retarded sibs with similar facies, low implantation of frontal and temporal hair, small palpebral fissures, telecanthus. (From C Parloir et al, Clin Genet 12:263, 1977.)



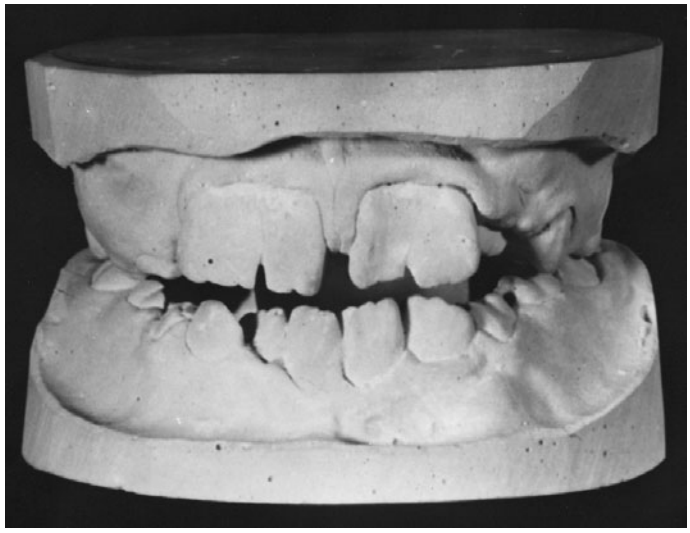
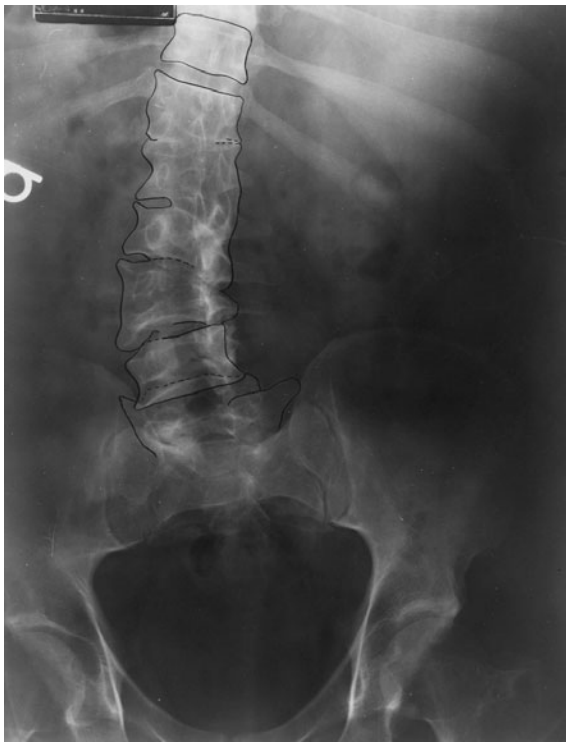


Fig. 25–23. *Short stature, characteristic facies, mental retardation, skeletal anomalies, and macrodontia (KBG syndrome).* Cast of teeth showing macrodontia. [From J Herrmann et al, Birth Defects 11(5):7, 1975.]

Unusual facies, abnormal scalp hair, and diarrhea

Stankler et al (1) reported two sibs with low birthweight, unusual facies characterized by prominent eyes with flat supraorbital ridges, broad flat nose, large mouth, cleft uvula (in one), and large low-set simple pinnae. The buttocks were excoriated before the onset of diarrhea. The skin had a rubbery feel. The scalp hair was woolly and easily removed. The hair shafts exhibited budding. Persistent diarrhea began in the third week and failure to thrive became evident. Galactosuria without galactosemia, hepatic cirrhosis, renal cortical microcysts, and islet cell hyperplasia were noted on autopsy.

Fig. 25–24. *Short stature, characteristic facies, mental retardation, skeletal anomalies, and macrodontia (KBG syndrome).* Block vertebrae of lower spine. [From J Herrmann et al, Birth Defects 11(5):7, 1975.]



Reference (Unusual facies, abnormal scalp hair, and diarrhea)

1. Stankler L et al: Unexplained diarrhea and failure to thrive in 2 siblings with unusual facies and abnormal scalp hair shafts: A new syndrome. Arch Dis Child 57:212–216, 1982.

Unusual facies, tetra-amelia, hypotrichosis, and developmental retardation

Ohdo et al (1) reported siblings (one liveborn, one an aborted fetus) affected with tetra-amelia, hypotrichosis, upslanting palpebral fissures, absent lacrimal openings with hypoplastic ducts and sacs opening toward the exterior, prominent bulbous nose, large downturned mouth, preauricular pits, and developmental retardation (Fig. 25–25). Hyperthermia and constipation occurred in later life. The child in the original report died at age 8 years, 7 months. He was profoundly retarded (2).

Inheritance is probably autosomal recessive.

References (Unusual facies, tetra-amelia, hypotrichosis, and developmental retardation)

1. Ohdo S et al: Association of tetra-amelia, ectodermal dysplasia, hypoplastic lacrimal ducts and sacs opening toward the exterior, peculiar face and developmental mental retardation. J Med Genet 24:609–612, 1987.

2. Ohdo S et al: Natural history and postmortem anatomy of a patient with tetra-amelia, ectodermal dysplasia, peculiar face, and developmental retardation. J Med Genet 31:980–981, 1994.

Patulous lips, ptosis, patent ductus arteriosus, and phalangeal anomalies (Char syndrome)

Char (1) reported autosomal dominant inheritance of a syndrome characterized by broad forehead and slightly wide-set eyes with ptosis of the lids and internal strabismus. The eyebrows flare and the midface is somewhat flat. The nose was short with somewhat anteverted nostrils and flat nasal bridge. The pinnae appeared normal, but were low set and posteriorly rotated. The mouth was large with extremely patulous lips and very short philtrum (Figs. 25–26 and 25–27). Only two phalanges were in each fifth finger of the proband. Intelligence was low normal. Patent ductus arteriosus was found in several members of the kindred.

The syndrome has been mapped to 6p12–p21 (4). The gene, *TFAP2B*, is a transcription factor expressed in neural crest cells (4a).

Temple (7) confirmed the syndrome. In one of her patients, a 40–50 dB hearing loss was found in both ears. Height was reduced. Others have added examples (5–7). Another patient with only patent ductus and short nose has been described (2). With age, the lips become less patulous. Interstitial polydactyly of the toes and polythelia have been reported, possibly adventitious findings (9).

Patent ductus may be seen as an isolated finding, as an isolated autosomal dominantly inherited anomaly (8) in *Robinow syndrome,* in *Gorlin–Chaudhry–Moss syndrome*, and as a dominant syndrome with bicuspid aortic valve and fifth metacarpal hypoplasia and brachydactyly (3).

We are skeptical of the family reported by Sweeney et al (6a).

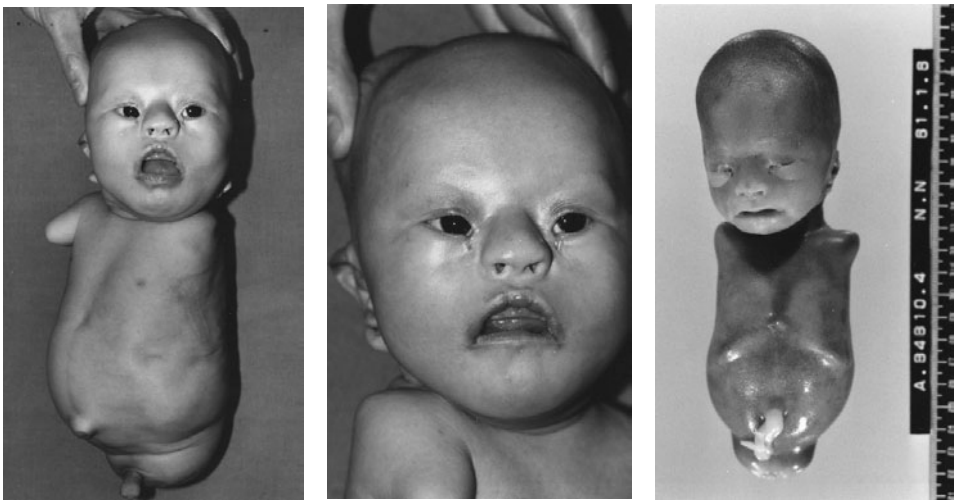
References [Patulous lips, ptosis, patent ductus arteriosus, and phalangeal anomalies (Char syndrome)]

1. Char F: Peculiar facies with short philtrum, duck-bill lips, ptosis, and low-set ears—a new syndrome? Birth Defects 14(6B):303–305, 1978.

2. Davidson HR: A large family with patent ductus arteriosus and unusual face. J Med Genet 30:503–505, 1992.

3. Gelb BD et al: Familial patent ductus arteriosus and bicuspid aortic valve with hand anomalies: A novel heart-hand syndrome. Am J Med Genet 87:175–179, 1999.

4. Satoda M et al: Char syndrome, an inherited disorder with patent ductus, maps to chromosome 6p12–p21. Circulation 99:3036–3042, 1999.



A B C

Fig. 25–25. *Unusual facies, tetra-amelia, hypotrichosis, and developmental retardation*. (A,B) Male child with tetra-amelia, hypotrichosis, upslanting palpebral fissures, and hypoplastic lacrimal ducts and sacs opening toward the exterior. (C) Sib of infant seen in A, B. (From S Ohdo et al, J Med Genet 24:609, 1987.)

4a. Satoda M et al: Mutations in *TFAP2B* cause Char syndrome, a familial form of patent ductus arteriosus. Nat Genet 25:42–46, 2000.

5. Slavotinek A et al: Familial patent ductus arteriosus: A further case of Char syndrome. Am J Med Genet 71:229–232, 1997.

6. Sletten LJ, Pierpont MEM: Familial occurrence of patent ductus arteriosus. Am J Med Genet 57:27–30, 1995.

6a. Sweeney E et al: Char syndrome: A new family and review of the literature emphasizing the presence of symphalangism and the variable phenotype. Clin Dysmorphol 9:177–182, 2000.

7. Temple IK: Char syndrome (unusual mouth, patent ductus arteriosus, phalangeal anomalies). Clin Dysmorphol 1:17–21, 1992.

8. Woods CG: Sheffield LJ: Further family with autosomal dominant patent ductus arteriosus. J Med Genet 31:659, 1994.

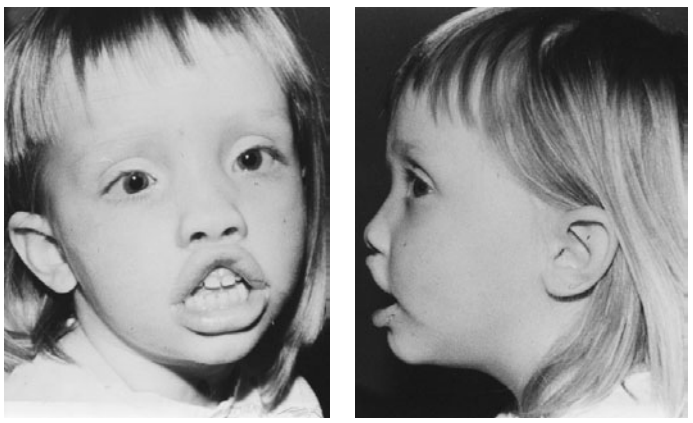
9. Zannolli R et al: Char syndrome: An additional family with polythelia, a new finding. Am J Med Genet 95:201–203, 2000.

Unusual facies, mental retardation, short stature, hemolytic anemia, and delayed puberty

Hurst et al (2), in 1987, described male and female sibs exhibiting short stature, hypertonia, and moderate retardation with significant delay in speech and language development. In 1973, Beutler et al (1) described a similar phenotype in a male patient.

The facies was characterized by midface hypoplasia, ptosis, epicanthic folds, small mandible, cup-shaped pinnae, short neck, posterior hairline, and delayed puberty (Fig. 25–28). The male had a small penis.

Fig. 25–26. *Patulous lips, ptosis, patent ductus arteriosus, and phalangeal anomalies (Char syndrome)*. (A,B) Child has broad forehead, extremely short philtrum with patulous lips, internal strabismus, and short nose. Mother has similar appearance. (Courtesy of CI Scott, Wilmington, Delaware.)



A B

References (Unusual facies, mental retardation, short stature, hemolytic anemia, and delayed puberty)

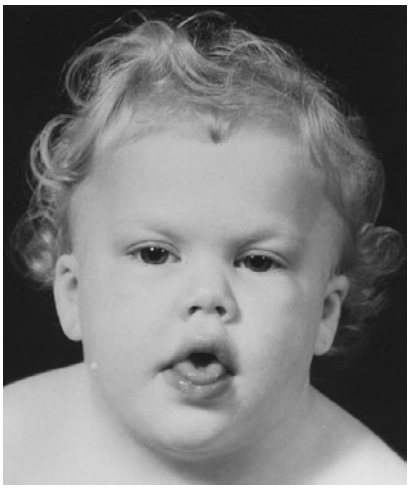
1. Beutler E et al: Red cell aldolase deficiency and haemolytic anaemia: A new syndrome. Trans Assoc Am Physicians 86:154–166, 1973.

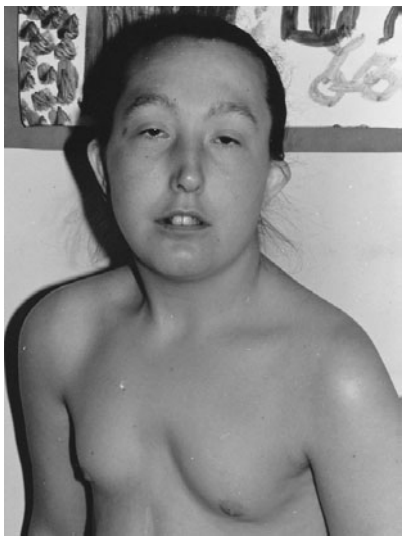
2. Hurst JA et al: A syndrome of mental retardation, short stature, hemolytic anemia, delayed puberty, and abnormal facial appearance: Similarities to a report of aldolase A deficiency. Am J Med Genet 28:965–970, 1987.

Unusual facies, osteosarcoma, and malformation syndrome

In 1979, Schuman and Burton (1) described two unrelated females with frontal bossing, highly arched palate, low-set ears, small auditory canals, prominent beaked nose, malocclusion, and micrognathia. One had exotropia and bilateral cataracts; the other had severe myopia. One had sensorineural hearing loss, and the other had conductive hearing loss. Both had repeated urinary infections, one having deformed ureterovesical junctions and the other having duplicated right kidney and ureter. Each had osteosarcoma of an extremity.

Fig. 25–27. *Patulous lips, ptosis, patent ductus arteriosus, and phalangeal anomalies (Char syndrome)*. Similar phenotype in another child. [From F Char, Birth Defects 14(6B):303, 1978.]





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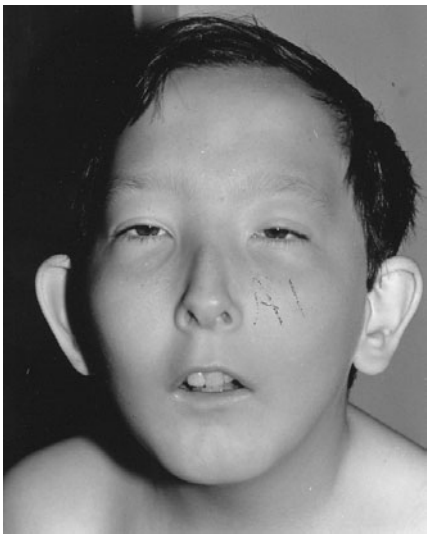


B

Fig. 25–28. *Unusual facies, mental retardation, short stature, hemolytic anemia, and delayed puberty*. (A) Twenty-six-year-old sib exhibiting ptosis, prominent pinnae, short neck, and absent breast development. (B) Same facial appearance and anomalies as in his sister. (From JA Hurst et al, Am J Med Genet 28:965, 1987.)

Reference (Unusual facies, osteosarcoma, and malformation syndrome)

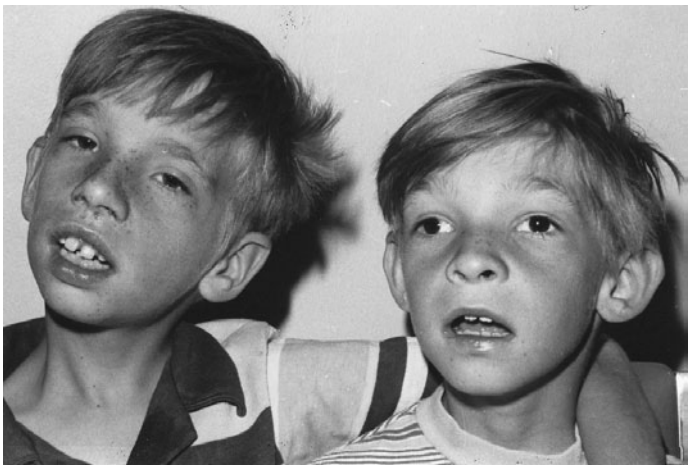
1. Schuman SH, Burton WE: A new osteosarcoma/malformation syndrome. Clin Genet 15:462–463, 1979.

Unusual facies, short stature, and mental deficiency (Smith-Fineman-Myers syndrome)

Smith et al (3) and others (1,2,4,5) reported a syndrome of unusual facial appearance, short stature, and mental retardation. Inheritance is probably X-linked recessive, since all affected were males, and learning disabilities affected the sister of one boy (1).

Microdolichocephaly was combined with decreased frontonasal angle, flat philtrum, prominent maxillary central incisors, and micrognathia (Fig. 25–29). Hypertelorism and downslanting palpebral fissures are occasional manifestations. Short stature, usually of prenatal onset, seizures, hypertonia, hyperreflexia, and severe mental retardation with marked delay in speech acquisition occur. Other findings have included seizures, asplenia, optic nerve hypoplasia, chest deformity, mild foot deformities, hyperconvex nails, and bridged palmar creases.

Fig. 25–29. *Unusual facies, short stature, and mental deficiency*. Microdolichocephaly, flat philtrum, prominent central maxillary incisor. (From RD Smith et al, Am J Med Genet 7:5, 1980.)



Differential diagnosis includes *Coffin–Lowry syndrome, FG syndrome*, and *alpha-thalassemia mental retardation syndrome*.

References [Unusual facies, short stature, and mental deficiency (Smith-Fineman-Myers syndrome)]

1. Adès LC et al: Smith-Fineman-Myers syndrome in two brothers. Am J Med Genet 40:467–470, 1991.
2. Guion-Almeida ML et al: Smith-Fineman-Myers syndrome in apparently monozygous twins. Am J Med Genet 79:205–208, 1998.
3. Smith RD et al: Short stature, psychomotor retardation, and unusual facial appearance in two brothers. Am J Med Genet 7:5–9, 1980.
4. Stephenson LD, Johnson JP: Smith-Fineman-Myers syndrome: Report of a third case. Am J Med Genet 22:301–304, 1985.
5. Wei J et al: Smith-Fineman-Myers syndrome: Report on a large family. Am J Med Genet 47:307–311, 1993.

Urofacial syndrome (Ochoa syndrome)

Elejalde (2), in 1979, described a syndrome of hydronephrosis, hydroureter, megalocystis, and unusual facies in seven children from three families. Ochoa and Gorlin (4), in 1987, found 36 examples in 22 families from around Medellin, Colombia. A few other isolated cases have been described (5,6) in children of Arabic origin. RJG has recently seen an example of Scandinavian origin. Ochoa (3), in 1992, increased the number to 50 patients from 32 families.

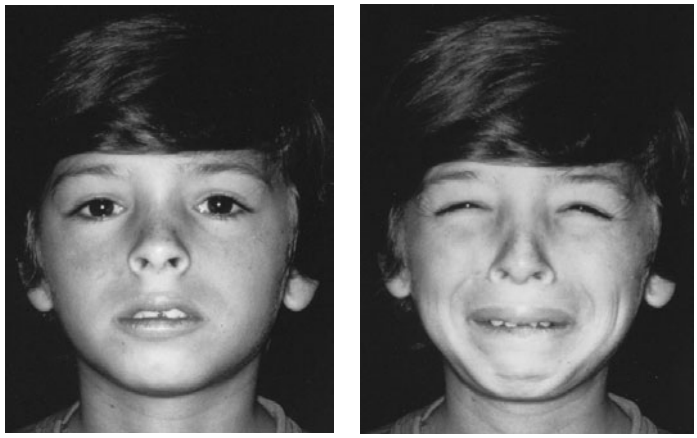
Inheritance clearly is autosomal recessive (3). The gene has been mapped to 10q23–q24 (7–9). There appears to be genetic homogeneity (1,8).

Facial expression is that of crying while the patient is smiling (Fig. 25–30). Obstructive abnormalities of the urinary tract due to occult neuropathic bladder results in mucosal hypertrophy, trabeculation, and diverticula of the bladder, hydroureter and hydronephrosis (Fig. 25–31). Enuresis, urinary tract infection, hypertension, and uremia are seen at various stages of the disorder. Many die in adolescence in their early twenties due to renal failure if not diagnosed or treated. All affected males have cryptorchidism. About 65% experience moderate to severe constipation.

Aqueductal stenosis resulting in hydrocephalus has been found (6).

References [Urofacial syndrome (Ochoa syndrome)]

1. Chauve X et al: Genetic homogeneity of the urofacial (Ochoa) syndrome confirmed in a new French family. Am J Med Genet 95:10–12, 2000.

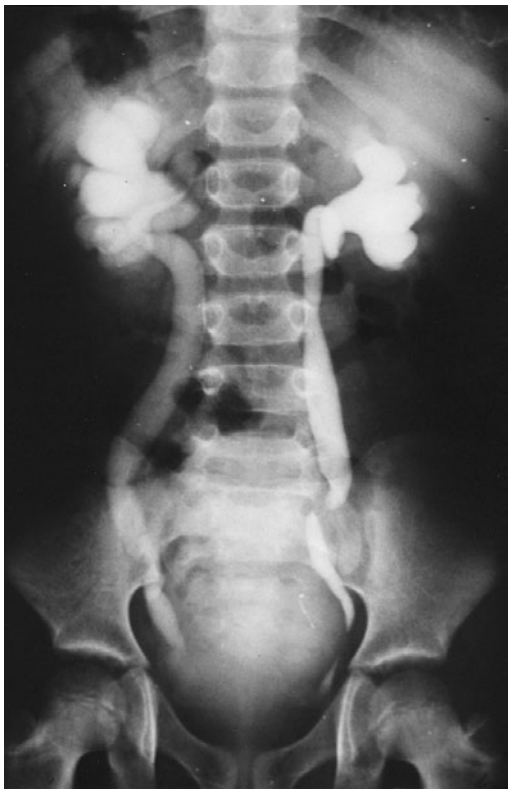


A B

Fig. 25–30. *Urofacial syndrome*. (A,B) Normal facies, except when smiling. (From B Ochoa and RJ Gorlin, Am J Med Genet 27:661, 1987.)

2. Elejalde BR: Genetic and diagnostic considerations in three families with abnormalities of facial expression and congenital urinary obstruction. The Ochoa syndrome. Am J Med Genet 3:97–108, 1979.
3. Ochoa B: The urofacial (Ochoa) syndrome revisited. J Urol 148:580–583, 1992.
4. Ochoa B, Gorlin RJ: Urofacial syndrome. Am J Med Genet 27:661–668, 1987.
5. Teebi AS, Besisso MS: Urofacial syndrome. Am J Med Genet 34:608, 1989.
6. Teebi AS, Hassoon MM: Urofacial syndrome associated with hydrocephalus due to aqueductal stenosis. Am J Med Genet 40:199–200, 1991.
7. Wang C-Y et al: Homozygosity and linkage-disequilibrium mapping of the urofacial (Ochoa) syndrome gene to a 1-cM interval on chromosome 10q23–q24. Am J Hum Genet 60:1461–1467, 1997.

Fig. 25–31. *Urofacial syndrome*. Radiograph showing hydroureter and hydronephrosis. (From B Ochoa and RJ Gorlin, Am J Med Genet 27:661, 1987.)



8. Wang C-Y et al: Genetic homogeneity, high-resolution mapping, and mutation analysis of the urofacial (Ochoa) syndrome and exclusion of the glutamate oxaloacetate transaminase gene (GOT1) in the critical region as the disease gene. Am J Med Genet 84:454–459, 1999.
9. Wang C-Y et al: Construction of a physical and transcript map for a genomic region containing the urofacial (Ochoa) syndrome gene on 10q23–q24 and localizing the disease gene within two overlapping BAC clones (< 360 kb). Genomics 60:12–19, 1999.

FACES syndrome

Friedman and Goodman (1), in 1984, described a new syndrome with unique *F*acies, *A*norexia, *C*achexia, and *E*ye and *S*kin lesions, employing the acronym *FACES syndrome* as an acronym. Affected were two sisters and their mother. They stemmed from a consanguineous union of Yemenite Jewish ancestry. The mode of inheritance has not been established.

The facies was characterized by mild eyelid ptosis, xanthelasma, and a nose with anteverted nostrils with bifid tip (Fig. 25–32A,B). The two daughters also exhibited nasal speech (apparently associated with a short palate) and retinitis pigmentosa. Most striking was severe muscle wasting and cachexia, the individuals appearing almost cadaverous (Fig. 25–32C). They exhibited numerous lentigines and café-au-lait spots (Fig. 25–32D). The daughters had pectus excavatum and asymmetry of the chest. All exhibited genu varum and pes planus. One daughter had papillary carcinoma of the thyroid while diffuse enlargement of the thyroid was noted in the other. Mild soft-tissue syndactyly was found in digits 2–4 of the hands and in digits 3–4 of the feet (Fig. 25–32E,F).

Reference (FACES syndrome)

1. Friedman E, Goodman RM: The "FACES" syndrome: A new syndrome with unique facies, anorexia, cachexia, and eye and skin lesions. J Craniofac Genet Dev Biol 4:227–231, 1984.

Unusual facies, cataract, short stature, joint contractures, and spondyloepimetaphyseal dysplasia

Borochowitz (1) described female sibs of Moroccan Jewish ancestry with unusual facies, cataract, short stature, inguinal hernia, joint contractures, and spondyloepimetaphyseal dysplasia. The parents were consanguineous. Inheritance is probably autosomal recessive.

Both had reduced height, weight, and head circumference. Intelligence was normal. Ambulation was difficult due to severe knee and hip joint contractures. The facies was old appearing with a large nose and mouth and a pointed chin. Radiographic changes included spondyloepimetaphyseal dysplasia and marked precocious calcification of costochondral cartilages.

A somewhat similar disorder was reported by Kozlowski et al (2). The female child had cataract, outstanding ears, scant subcutis, lordosis, and genu valgum. The patient also had hypoplasia of the labia majora and mental retardation.

References (Unusual facies, cataract, short stature, joint contractures, and spondyloepimetaphyseal dysplasia)

1. Borochowitz Z: Unusual facies, cataract, short stature, joint contractures, and spondyloepimetaphyseal dysplasia in sibs. A new premature aging-like autosomal syndrome? Proc Greenwood Genet Ctr 9:104–105, 1990.
2. Kozlowski K et al: Metaphyseal and epiphyseal dysplasia with unusual facies and cataract. Am J Dis Child 125:553–556, 1973.

Widow's peak, ptosis, and skeletal abnormalities (Kapur syndrome)

Kapur et al (1) described a large family with unusual facies and skeletal abnormalities. The patients had widow's peak, ptosis of eyelids, apparently low-set angulated pinnae, difficulty in supination of

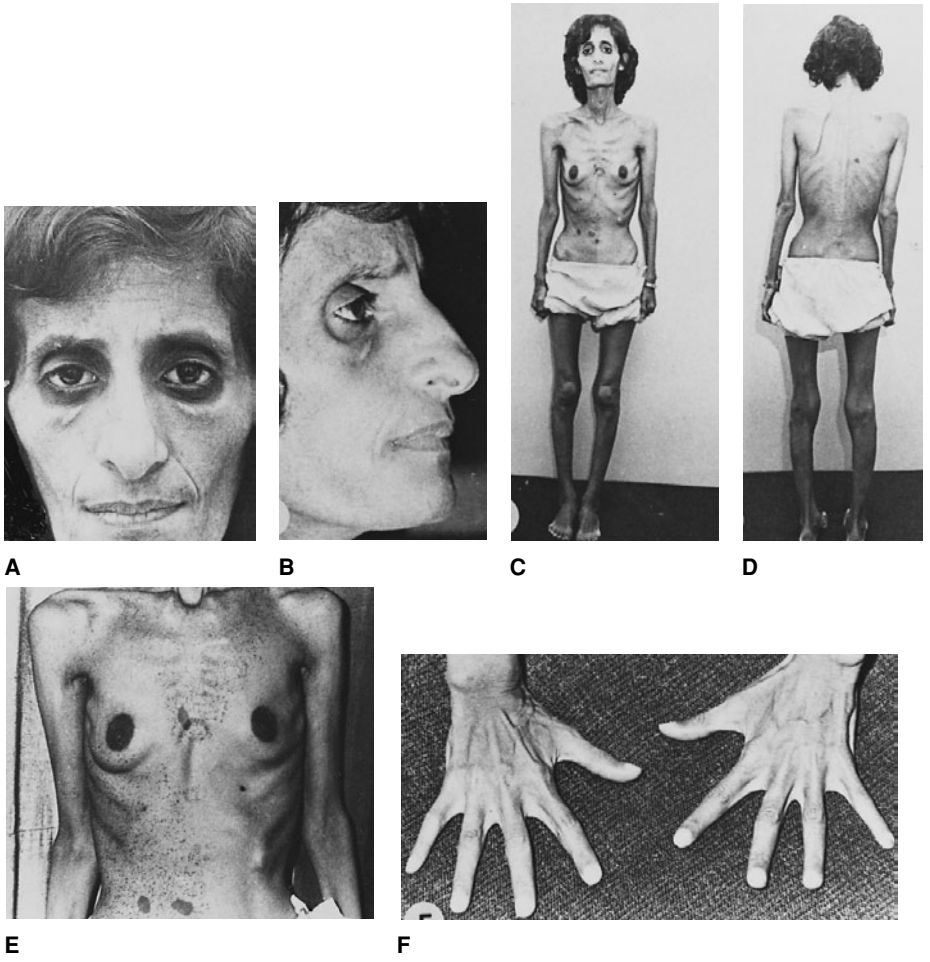


Fig. 25–32. *FACES syndrome*. (A,B) Mild ptosis, xanthelasma. (C,D) Extreme cachexia, genu varum. (E) Multiple lentigines and café-au-lait spots. (F) Mild soft tissue syndactyly. (From E Friedman and RM Goodman, J Craniofac Genet Dev Biol 4:227, 1984.)

forearms, recurrent dislocation of the patella, and pain in various joints (Fig. 25–33).

Affected males were relatively short (162–171 cm). The patella dislocated early in life was followed later by pain in the knees. Inability to supinate the forearm or touch the shoulder was noted in affected adult males. With age, the elbow, shoulder, wrist, hip, and interphalangeal joints showed progressive pain and radiologic changes of arthritis. There was flattening of the femoral condyles. At the elbow, the capitulum of the humerus was tilted with its medial edge placed proximally at the elbow. At the wrist, there was a V-shaped angulation of radius and ulna. A lateral view of the foot showed subluxation of the navicular and cuboid on the talus and calcaneus.

Inheritance appears to be X-linked dominant. Affected females had a less marked facies but exhibited ptosis and widow's peak.

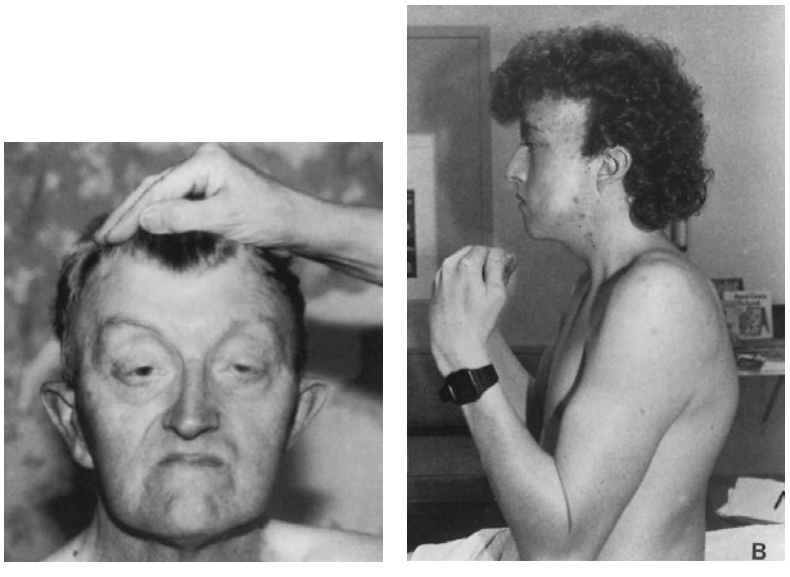


Fig. 25–33. *Widow's peak, ptosis, and skeletal abnormalities (Kapur syndrome)*. (A) Note widow's peak and ptosis. (B) Inability to touch shoulders with fingers. (From S Kapur et al, Am J Med Genet 33:357, 1989.)

Reference [Widow's peak, ptosis, and skeletal abnormalities (Kapur syndrome)]

1. Kapur S et al: Apparently previously undescribed X-linked dominant syndrome with facial and skeletal anomalies. Am J Med Genet 33:357–363, 1989.

Andersen syndrome (unusual facies, potassium-sensitive periodic paralysis, ventricular arrhythmia)

Andersen et al (1), in 1971, described a syndrome characterized by somewhat unusual facies, low-set pinnae, hypertelorism, broad nasal root, mandibular hypoplasia, cleft palate, scaphocephaly, clinodactyly, short stature, extra systoles, and attacks of muscular weakness (Fig. 25–34). Tawil et al (4) proposed a clinical triad including the facies, cardiac arrhythmia, and potassium-sensitive periodic paralysis. Sansone et al (3) described 11 patients from five kindred. Canún et al (2) added another family.

Inheritance is autosomal dominant. The genetic defect is not linked to any other form of sensitive periodic paralysis nor is it related to that of the long QT syndrome.

References [Andersen syndrome (unusual facies, potassium-sensitive periodic paralysis, ventricular arrhythmia)]

1. Andersen ED et al: Intermittent muscular weakness, extrasystoles, and multiple developmental anomalies: A new syndrome? Acta Paediatr Scand 60:559–564, 1971.

2. Canún S et al: Andersen syndrome. Autosomal dominant in three generations. Am J Med Genet 85:147–156, 1999.

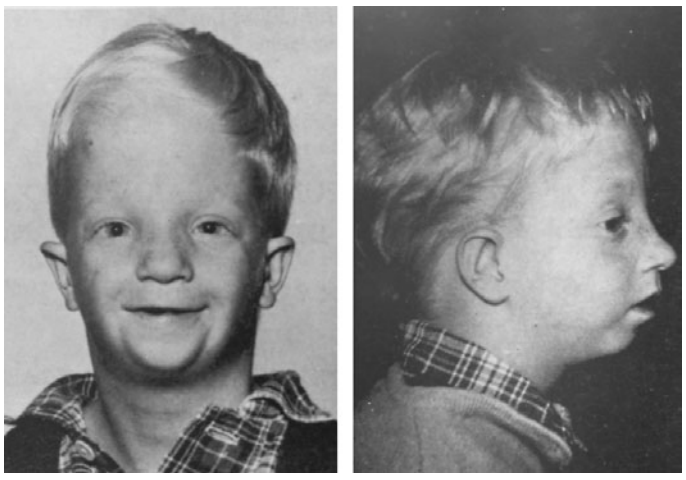
3. Sansone V et al: Andersen syndrome: A distinct periodic paralysis. Ann Neurol 42:305–312, 1997.

4. Tawil R et al: Andersen syndrome: Potassium sensitive periodic paralysis, ventricular ectopi and dysmorphic features. Ann Neurol 35:326–330, 1994.

Cerebral anomalies, cardiac defects, and facial anomalies

Thakker and Donnai (1) described sibs with multiple major anomalies and facial anomalies characterized by long downslanting palpebral fissures, hypertelorism, short nose with a bulbous tip, microstomia with downturned corners, and posteriorly rotated ears (Fig. 25–35). Major malformations included brain anomalies (dilated ventricles in one, agenesis of the corpus callosum in the other), cardiac defects, short esophagus in one, anal atresia in the other, and vertebral anomalies. Muscle biopsy was consistent with atrophy.

Fig. 25–34. *Andersen syndrome*. (A,B) Scaphocephaly, low-set pinnae, hypertelorism, broad nasal root, and micrognathia. (From ED Andersen, Acta Paediatr Scand 60:559, 1971.)



A B

Reference (Cerebral anomalies, cardiac defects, and facial anomalies)

1. Thakker Y, Donnai D: A new recessive syndrome of unusual facies and multiple structural abnormalities. J Med Genet 28:633–635, 1991.

Cerebro-facio-articular (Van Maldergem) syndrome

Van Maldergem et al (1), in 1992, reported a female child followed for 10 years. From two prior marriages, the mother had four boys and a girl, three of whom were mentally retarded but not dysmorphic. Zampino et al (2) described another example and used the term *cerebro-facio-articular syndrome*.

Generalized hypotonia was found at birth. In addition to microcephaly, the forehead was large with a low hairline, broad and prominent nasal bridge and large bulbous nose, telecanthus with epicanthic folds, downslanting short palpebral fissures, macrostomia with trapezoidal upper lip and full lower lip, and dysmorphic pinnae.

Camptodactyly of fingers 2 and 5 and axial clinodactyly of all fingers were noted. Genua recurvatum and laxity of fifth metacarpals were seen.

Intelligence quotient of 50 was determined.

Differential diagnosis included *blepharo-naso-facial syndrome*.

References [Cerebro-facio-articular (Van Maldergem) syndrome]

1. Van Maldergem L et al: Mental retardation with blepharo-naso-facial malformations: A new syndrome? Clin Genet 41:22–24, 1992.

2. Zampino G et al: Cerebro-facio-articular syndrome of Van Maldergem: Confirmation of a new MR/MCA syndrome. Clin Genet 45:140–144, 1994.

Coarse facies, acne conglobata, thick skin, gingival enlargement, osteoporosis, and mitral valve prolapse (Borrone dermato-cardio-skeletal syndrome)

Borrone et al (1), in 1993, noted two brothers with coarse facies, thick skin, acne conglobata, gingival enlargement, osteolysis, camptodactyly, and mitral valve prolapse.

The disorder was progressive and involved the skin, heart, bones, and joints. Before the end of the first year, thoracolumbar gibbus was noted. The vertebrae had reduced sagittal diameter and exhibited anterior beaking. Scheuermann osteochondritic changes were seen in late adolescence. In early childhood, there was delayed tooth eruption due to gingival enlargement. Intelligence was normal. The facies became progressively coarse with severe acne beginning in puberty. Inguinal hernias were noted. One brother died at age 24 from heart failure. Mitral valve prolapse was found.

Radiographs of the hands at 3 years resembled those of dysostosis multiplex but changes decreased with age. There was mild generalized osteoporosis.

Biochemical studies excluded lysosomal storage diseases.

Inheritance is either autosomal or X-linked recessive.

Reference [Coarse facies, acne conglobata, thick skin, gingival enlargement, osteoporosis, and mitral valve prolapse (Borrone dermato-cardio-skeletal syndrome)]

1. Borrone C et al: New multisystemic disorder involving heart valves, skin, bone, and joints in two brothers. Am J Med Genet 46:228–234, 1993.

Coarse facies, mental retardation, microcephaly, epilepsy, and skeletal anomalies

Battaglia et al (1) noted male and female sibs with mental retardation, microcephaly, seizures, skeletal anomalies, hirsutism, and coarse facies. Both had short stature and hypotonia.

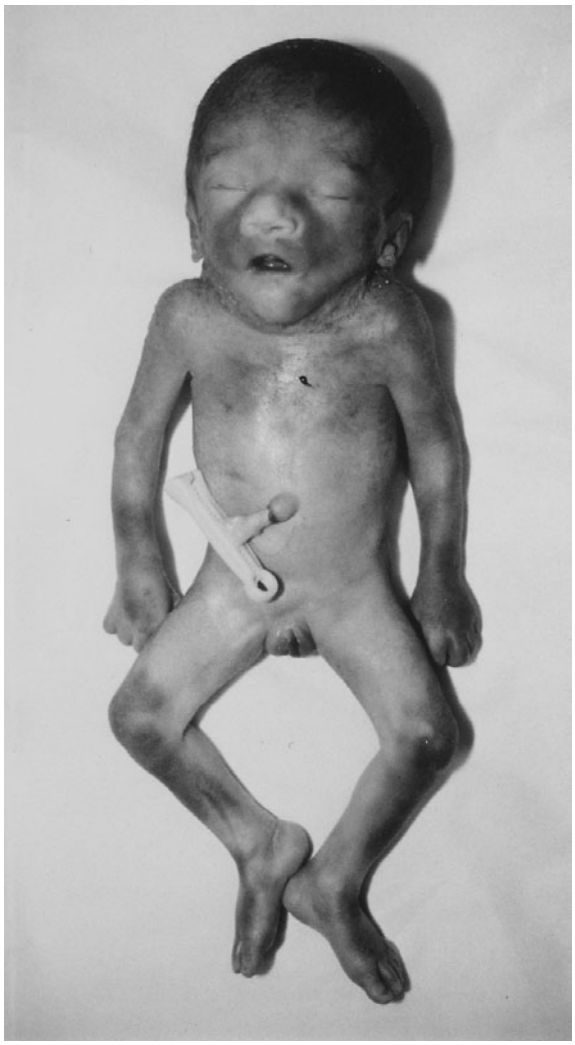


Fig. 25–35. *Cerebral anomalies, cardiac defects and facial anomalies*. Hypertelorism, short nose with bulbous tip, microstomia with downturned corners, and very short webbed neck. (From Y Thakker and D Donnai, J Med Genet 28:633, 1991.)

The facies was characterized by prominent brows, broad nose, short philtrum, large open mouth, and thick lower lip.

Musculoskeletal anomalies included dorsolumbar scoliosis, stooped posture, and retarded bone age.

Reference (Coarse facies, mental retardation, microcephaly, epilepsy, and skeletal anomalies)

1. Battaglia A et al: New autosomal recessive syndrome of mental retardation, coarse facies, microcephaly, epilepsy, and skeletal anomalies. Clin Dysmorphol 5:41–47, 1996.

Unusual facies, atrophic skin, and hirsutism (Barber-Say syndrome)

Barber et al (1), in 1982, reported a syndrome consisting of growth retardation, characteristic facies, atrophic skin, and hypertrichosis. Although Cesarino et al (2) stated that their patient had ablepharon-macrostomia, we believe that the child had Barber–Say syndrome. Additional examples are those of David et al (4), Martínez Santana et al (5), and Mazzanti et al (6). A mildly affected boy was reported by Sod et al (7). Janssen and de Lange (4a) appear to have reported the syndrome in 1945.

Although there was parental consanguinity in one case (5), all examples have been isolated, save that of Dinulos and Pagon (4).

Face. The face is characterized by shallow orbits, telecanthus, sparse eyebrows and lashes, partial agenesis of eyelids, strabismus, ectropion of lower eyelids, hypoplastic nasal alae, large bulbous nasal tip, narrow vermilion of upper lip, and macrostomia (Fig. 25–36). Due to exposure, opacification of the cornea has been noted in one case (2). The pinnae, low and posteriorly rotated, have a prominent anthelix and absent tragus and lobule. The ear canals are tortuous but there is no hearing loss (1–3,5).

Skin. Hypertrichosis, especially over the forehead, back, and neck, has been a constant feature (2,3). General laxity of skin and atrophy produce an older appearance. A deficiency of fingerprints has been noted (5).

Growth and body build. Growth retardation has been observed in all patients. The shoulders slope and the nipples have been hypoplastic in all examples.

Intelligence. Moderate mental retardation has been found in two cases (1,2) and normal intelligence in two others (3,5).

Miscellaneous findings. Cryptorchidism was noted in one case (3).

Oral findings. All examples have some degree of macrostomia. A natal tooth has been reported in one case (2).

Differential diagnosis. Although there is slight overlap of signs with *ablepharon-macrostomia*, the syndromes are clearly different.

References [Unusual facies, atrophic skin, and hirsutism (Barber-Say syndrome)]

1. Barber N et al: Case report 83: Macrostomia, ectropion, atrophic skin, hypertrichosis and growth retardation. Syndrome Ident 8(1):6–9, 1982.

2. Cesarino EJ et al: Lid agenesis-psychomotor retardation-forehead hypertrichosis—a new syndrome. Am J Med Genet 31:299–304, 1988.

3. David A et al: Macrostomia, ectropion, atrophic skin, hypertrichosis: Another observation. Am J Med Genet 39:112–115, 1991.

4. Dinulos MB, Pagon RA: Autosomal dominant inheritance of Barber-Say syndrome. Am J Med Genet 86:54–56, 1999.

4a. Janssen TAE, de Lange C: Familial congenital hypertrichosis totalis (trichostasis). Ann Paediatr 33:69–78, 1945.

5. Martínez Santana S et al: Hypertrichosis, atrophic skin, ectropion, and macrostomia (Barber-Say syndrome): Report of a new case. Am J Med Genet 47:20–23, 1993.

6. Mazzanti L et al: Barber-Say syndrome: Report of a new case. Am J Med Genet 78:188–191, 1998.

7. Sod R et al: Macrostomia, hypertelorism, atrophic skin, severe hypertrichosis without ectropion: Milder form of Barber-Say syndrome. Am J Med Genet 73:366–367, 1997.

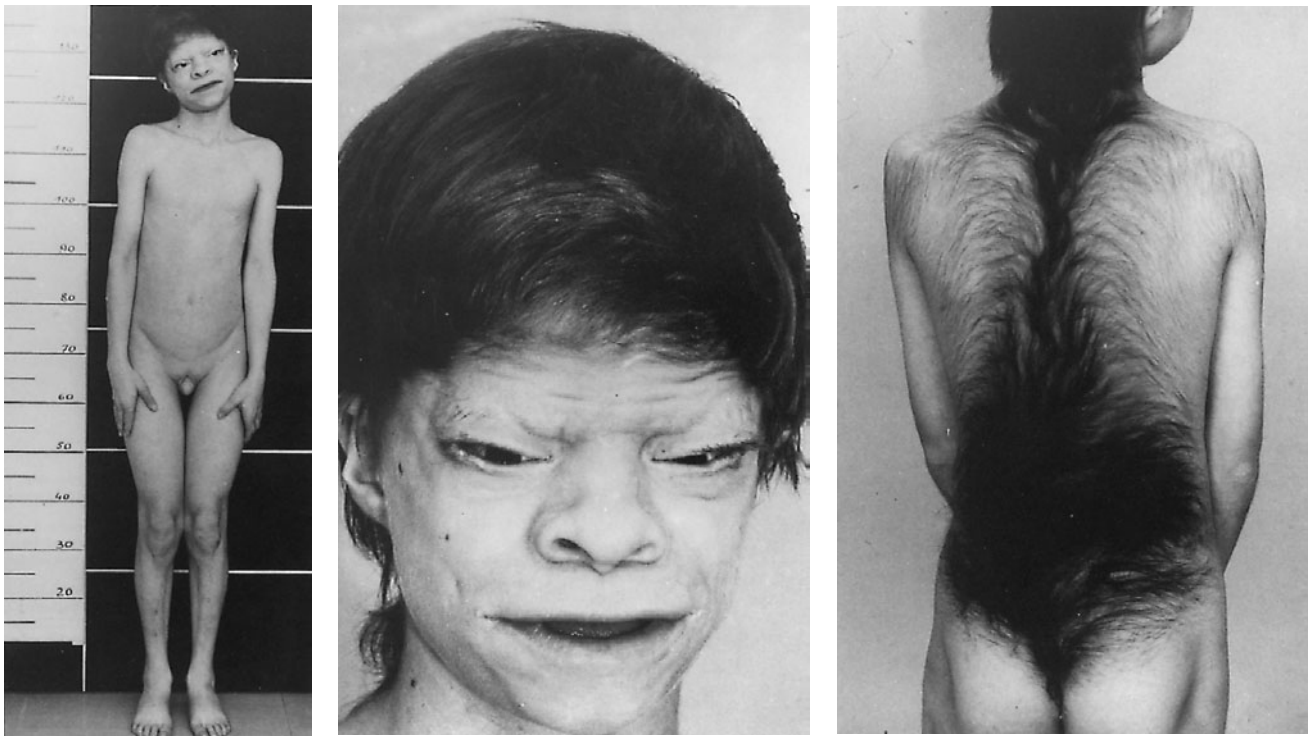
Cranio-cerebello-cardiac (3C) syndrome (Ritscher-Schinzel syndrome)

In 1987, Ritscher et al (13) reported two sisters with cerebellar vermis hypoplasia (Dandy-Walker malformation) with postnatal growth retardation, unusual facies, and atrioventricular septal defects of the heart. About 20 examples have been described to date (1–18).

Affected sibs (8,11) and parental consanguinity (11) suggest autosomal recessive inheritance, but most examples have been sporadic. The gene apparently maps to the 22q11 area (1,8).

Weight and length tend to be below the 10th centile with the OFC above the 75th centile. Postnatal growth has been retarded in most patients. One patient is described with growth hormone deficiency (17).

Craniofacial findings. The skull is macrocephalic in 20% and dolichocephalic with a very prominent forehead and occiput in at least 50%. About 50% have hydrocephaly or enlarged ventricles. Scalp hair and eyebrows tend to be thin and sparse. Ocular hypertelorism (80%),



A B C

Fig. 25–36. *Barber-Say syndrome*. (A) Eleven-year-old with atrophy of thoracic skin, hypoplastic nipples, bilateral cryptorchidism. (B) Hypertrichosis, ectropion, bulbous nose, macrostomia, thin lips, unusual pinna. (C) Hypertrichosis of back. (From A David et al, Am J Med Genet 39:112, 1991.)

downslanting palpebral fissures (75%), and flat nasal bridge (50%) are evident (Fig. 25–37A,B). Bilateral colobomata have been noted in 30% (2,8,11,16). The philtrum tends to be long and somewhat hypoplastic. The pinnae are large and posteriorly rotated. Radiographically, the anterior fontanel is always large and somewhat ragged. Parietal foramina has been seen (13). Cleft palate has been noted in 35% (3,5,10,13,16).

Central nervous system. Hypotonia, gross motor delay, and speech retardation are constant features. Vermis hypoplasia, enlarged fourth ventricle, and enlarged cysterna magna (Dandy–Walker malformation), and hydrocephalus are noted in 75% (Fig. 25–37C).

Musculoskeletal system. The hands are short with somewhat redundant skin and short terminal phalanges. There is usually clinodactyly of the fifth fingers. The nails are small. The muscles are poorly developed.

Radiographic changes. The anterior fontanel is large and late-closing with ragged edges. Some patients have hydrocephalus. The brain appears large. About 50% have aplasia of the vermis (Dandy–Walker malformation). Some patients have only 11 pairs of ribs (13,16).

Cardiovascular system. Two different types of cardiac anomalies occur: (a) endocardial cushion defects ranging from anomalies of the mitral or tricuspid valves to complete AV canal and (b) conotruncal anomalies. These have included ASD (11,13), VSD (3,11,13,16), tetralogy of Fallot (2,10), and AV valvular defects (5,13). An excellent review is that of Lurie and Ferencz (7).

Anogenital malformations. Some authors have documented gaping vulva and hypospadias (5). Anal atresia and misplaced anus have been described (11).

Diagnosis. There are many syndromes with vermis hypoplasia (15). One must exclude such conditions as *Coffin-Siris syndrome* with short fifth finger and congenital heart disease. However, the facies in that condition tends to be coarse with prominent eyebrows, thick lips, and hirsutism. Dandy–Walker malformation may be seen in association with Joubert–Boltshauser syndrome, *Meckel syndrome, Aase–Smith syndrome*, and a host of other conditions.

Laboratory findings. Immunodeficiency has been described (6).

References [Cranio-cerebello-cardiac (3C) syndrome (Ritscher-Schinzel syndrome)]

1. Butler MG, Mowrey P: Should the 3C (craniocerebellocardiac) syndrome be included in the spectrum of velocardiofacial syndrome and DiGeorge sequence? J Med Genet 33:719–720, 1996.
2. Digilio MC et al: Atrioventricular canal and 3C (cranio-cerebello-cardiac) syndrome. Am J Med Genet 58:97–98, 1995.
3. Gurrieri F, Neri G: An additional patient with the 3C syndrome. Clin Genet 41:263–265, 1992.
4. Hoo JJ et al: 3C (cranio-cerebello-cardiac) syndrome: A recently delineated and easily recognizable congenital malformation syndrome. Am J Med Genet 52:66–69, 1994.
5. Kosaki K et al: Ritscher-Schinzel (3C) syndrome: Documentation of the phenotype. Am J Med Genet 68:421–427, 1997.
6. Lauener R et al: Immunodeficiency associated with Dandy-Walker-like malformation, congenital heart defect and craniofacial abnormalities. Am J Med Genet 33:280–281, 1989.
7. Lurie IW, Ferencz C: "Shifted" threshold may explain diversity of cardiovascular malformations in multiple abnormalities syndromes: 3C (Ritscher-Schinzel) syndrome as an example. Am J Med Genet 66:72–74, 1996.
8. Lynch DR et al: Cerebellar atrophy in a patient with the velocardiofacial syndrome. J Med Genet 32:561–563, 1995.
9. Marles SL et al: Evidence for Ritscher-Schinzel syndrome in Canadian native Indians. Am J Med Genet 56:343–350, 1995.
10. Mims LRC, Say B: 3C syndrome: Another case. Clin Genet 36:465, 1989.
11. Ørstavik KH et al: Sibs with Ritscher-Schinzel (3C) syndrome and anal malformations. Am J Med Genet 75:300–303, 1998.
12. Quintana A et al: Dandy-Walker malformation cardiac defect and deafness: A variation of the cranio-cerebello-cardiac dysplasia (Ritscher-Schinzel syndrome). Genet Couns 5:114A, 1994.

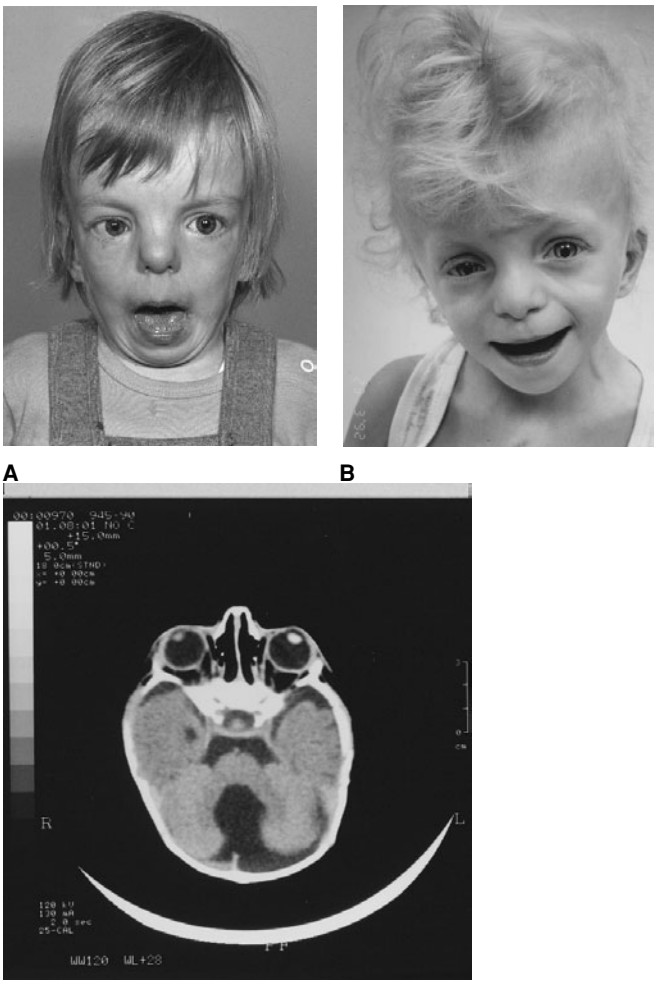


Fig. 25–37. *Cranio-cerebello-cardiac (3C) syndrome (Ritscher-Schinzel syndrome).* (A) Prominent forehead, low-set pinnae, hypertelorism, downslanting palpebral fissures, and depressed nasal bridge. (B) Triangular facies, hypertelorism, bilateral colobomas of iris, rounded nasal tip, and thin lips. (C) Cerebellar vermis hypoplasia. (A courtesy of A Schinzel, Zürich, Switzerland. B,C courtesy of B Kohler and H Wörle, Stuttgart, Germany.)

13. Ritscher D et al: Dandy-Walker (like) malformation, atrioventricular septal defect and a similar pattern of anomalies in 2 sisters. A new syndrome? Am J Med Genet 26:481–491, 1987.

14. Saraiva JM et al: First report of glaucoma as a feature of the 3C syndrome. Clin Dysmorphol 4:156–160, 1995.

15. Verloes A, Lambotte C: Further delineation of a syndrome of cerebellar vermis hypo/aplasia, oligophrenia, congenital ataxia, coloboma, hepatic fibrosis. Am J Med Genet 32:227–232, 1989.

16. Verloes A et al: 3C syndrome: Third occurrence of cranio-cerebello-cardiac dysplasia (Ritscher-Schinzel syndrome). Clin Genet 35:205–208, 1989.

17. Wheeler PG et al: The 3C syndrome: Evolution of the phenotype and growth hormone deficiency. Am J Med Genet 87:61–64, 1999.

18. Wörle H et al: Another case of Ritscher-Schinzel syndrome: Cranio-cerebello-cardiac dysplasia (3C-syndrome) with associated bilateral colobomata. Eur J Pediatr 153:140, 1994.

Hunter-MacDonald syndrome

Hunter and MacDonald (2), in 1989, described a man with unusual facies, multiple epiphyseal dysplasia, hearing loss, and congenital heart anomaly. Ardinger et al (1) reported a three-generation family with the same disorder.

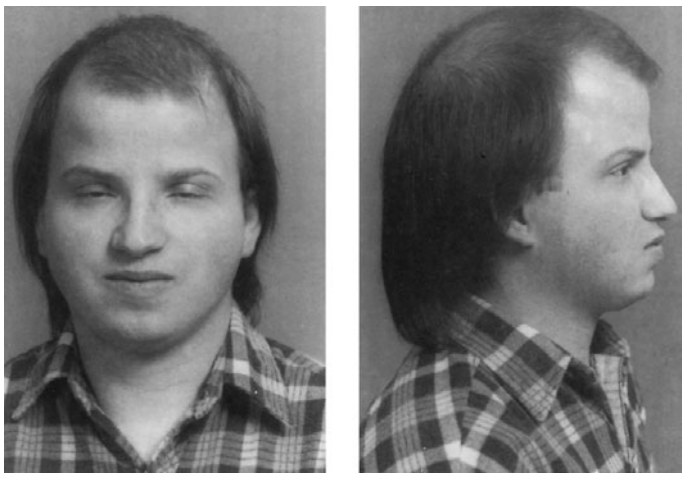


Fig. 25–38. *Hunter-MacDonald syndrome*. (A,B) Premature hair loss, bitemporal grooving, flared alae, midface hypoplasia, short philtrum. [From AGW Hunter and I MacDonald, Dysmorphol Clin Genet 3(1):8, 1989.]

Stature is proportionately short. Adult height ranges between 4′11″ and 5′2″. There is a tall forehead, bitemporal narrowing, ptosis, premature hair loss, thin upper lip, short philtrum, and long neck (Fig. 25–38).

Skeletal anomalies include pectus carinatum, hyperextensible joints with subluxation of thumbs and elbows, metatarsus adductus, and skewed fingers. Radiographic changes comprise pseudoepiphyses of middle phalanges, delayed bone age, small, flat, distal radial epiphyses, and constriction of distal shafts of humeri.

Heart anomalies consisted of mitral valve prolapse, bicuspid aortic valve, mild mitral and aortic regurgitation, and pulmonic valve stenosis.

The hearing loss is low-frequency sensorineural in one family (1) and conductive in another (2).

References (Hunter-MacDonald syndrome)

1. Ardinger HH et al: Delineation of the Hunter-MacDonald syndrome. XX David W. Smith Workshop on Malformations and Morphogenesis, Schlangenbad, Germany 3–9 August, 1999.

2. Hunter AGW, MacDonald I: Mild multiple epiphyseal dysplasia with subtle dysmorphic features and joint limitation. Dysmorphol Clin Genet 3(1):8–12, 1989.

Hypertelorism, malar hypoplasia, low-set ears, and joint anomalies

Seaver and Cassidy (1) described a mother and son with multiple minor facial anomalies, curly hair, and mild delay; cubitus valgus, and hyperextensible joints were present in the mother, and umbilical hernia, diastasis recti, shawl scrotum, and cryptorchidism in the son. Facial features resemble those in *Noonan syndrome* and include hypertelorism, ptosis, downslanting palpebral fissures, epicanthal folds, broad nasal bridge, malar hypoplasia, smooth philtrum, thin upper lip, apparently low-set, posteriorly angulated ears, and low posterior hairline. Similarities to *Aarskog syndrome* and *Teebi hypertelorism syndrome* are also present.

Reference (Hypertelorism, malar hypoplasia, low-set ears, and joint anomalies)

1. Seaver LH, Cassidy SB: New syndrome: Mother and son with hypertelorism, downslanting palpebral fissures, malar hypoplasia, and apparently low-set ears associated with joint and scrotal anomalies. Am J Med Genet 41:405–409, 1991.

Lumbar malsegmentation, short stature, and facial anomalies

Liepala and Kaitila (1) reported two male sibs with the combination of short stature of prenatal onset, webbed neck, micrognathia, apparently low-set ears, highly arched palate, pectus excavatum, and on spine radiographs, platyspondyly and vertebral malsegmentation were noted. Cognition was not impaired. Inheritance is most likely autosomal recessive.

Reference (Lumbar malsegmentation, short stature, and facial anomalies)

1. Leipala JA, Kaitila I: Apparently new syndrome of short stature, lumbar malsegmentation, and minor facial anomalies in two brothers. Am J Med Genet 52:103–107, 1994.

Macrocephaly, facial abnormalities, disproportionate tall stature, and mental retardation

Bakker and Hennekam, 1997, reported two brothers with macrocephaly, high and narrow forehead, frontal upsweep of hairline, hypotelorism, tall stature, short limbs, mild hypermobility, and developmental delay. The father was similarly affected.

Reference (Macrocephaly, facial abnormalities, disproportionate tall stature, and mental retardation)

1. Bakker HD, Hennekam RCM: Macrocephaly, facial abnormalities, disproportionate tall stature, and mental retardation—a sib observation. Am J Med Genet 70:312–314, 1997.

Macrocephaly, rhizomelia, and conductive hearing loss

Bagatelle and Cassidy (1) described a boy with macrocephaly, apparent rhizomelia, conductive deafness, sparse hair, hypertelorism, downslanting palpebral fissures, depressed nasal bridge, and short nose with anteverted nares. The anterior fontanel was large and late to close. The child's smile was described as a wrinkling of the forehead, eyes, and nose but without upward curve of the lips. Skeletal survey was essentially normal. Toriello (personal communication, 1998) has also seen a child with similar manifestations.

Reference (Macrocephaly, rhizomelia, and conductive hearing loss)

1. Bagatelle R, Cassidy SB: New syndrome of macrocephaly, hypertelorism, short limbs, hearing loss, and developmental delay. Am J Med Genet 55:367–371, 1995.

"Long thumb" brachydactyly, maxillary hypoplasia, mental retardation, and unusual facies

Halal et al (2) described a metaphyseal dysplasia with associated short stature, nasal beaking, absent nasal alae, maxillary hypoplasia, and brachydactyly in a four-generation family. The brachydactyly was of the "long thumb" variety. Hollister and Hollister (3) also described autosomal dominant inheritance of "long thumb" brachydactyly, skeletal anomalies, and cardiac conduction defects. Stratton et al (4) reported a mentally retarded male with marfanoid habitus, "long thumb" brachydactyly, mesomelia, aortic dilatation, mitral valve prolapse, and very unusual face. Fryer (1) described a retarded female with a similar face and mitral valve prolapse (Fig. 25–39).

While there are clinical overlaps among these various families, we await their separation. One of us (RJG) has seen a similarly affected mother and son. *Velocardiofacial syndrome* must be excluded.

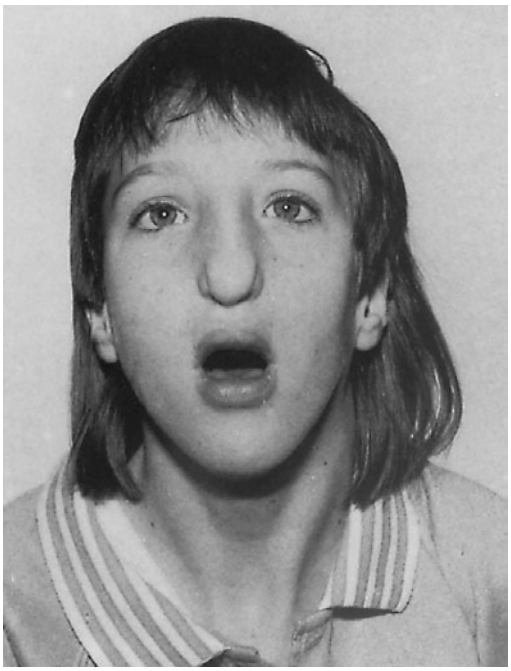


Fig. 25–39. *"Long thumb" brachydactyly, maxillary hypoplasia, mental retardation, and unusual facies*. Wide nasal bridge without alar flare. (From A Fryer, Am J Med Genet 51:277, 1994.

References ("Long thumb" brachydactyly, maxillary hypoplasia, mental retardation, and unusual facies)

1. Fryer A: Mental retardation, mitral valve prolapse and characteristic face: Another report? Am J Med Genet 51:277, 1994.
2. Halal F et al: Metaphyseal dysplasia with maxillary hypoplasia and brachydactyly. Am J Med Genet 13:71–79, 1982.
3. Hollister DW, Hollister WG: The "long-thumb" brachydactyly syndrome. Am J Med Genet 8:5–16, 1981.
4. Stratton RF et al: Brachydactyly, mesomelia, mental retardation, aortic dilatation, mitral valve prolapse, and characteristic face. Am J Med Genet 46: 138–141, 1993.

Lateral meningocele (Lehman) syndrome

Lateral meningocele syndrome was first described by Lehman et al (3) in 1977. It consists of multiple bilateral meningoceles in the thoracolumbar area, unusual facies, and skeletal changes (1–4).

Inheritance is uncertain. A possibly affected parent and child were reported by Lehman et al (3). All other cases have been sporadic (1,2,4).

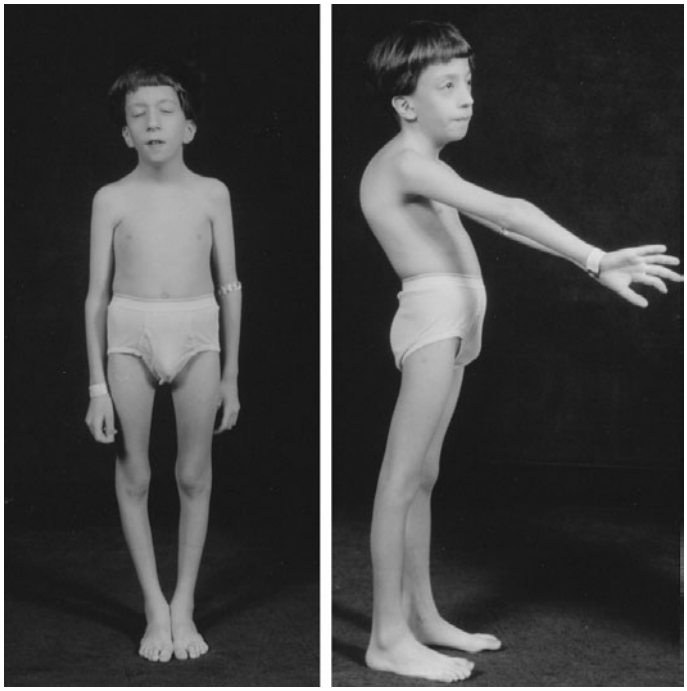
The facies is characterized by hypertelorism, malar hypoplasia, downslanting palpebral fissures, ptosis, proptosis, low-set posteriorly rotated pinnae, and small lower jaw. The neck may be somewhat short or webbed (Fig. 25–40A,B).

Hypotonia and developmental delay have been variable features.

Lateral meningoceles are protrusions of the dura and arachnoid through inter- and intravertebral foramina, probably secondary to dural ectasia. They present as widening of the neural canal, thinning of the bony cortex of the vertebral body and pedicles, dilation of the neural foramina, and protrusion of the dura outside of the neural canal (5). Lateral meningoceles found in the syndrome have been in the thoracolumbar area. They are easily seen in MRI or CT scans (Fig. 25–40C).

Skeletal changes include prominent metopic suture, thickened calvaria, wormian bones, and possibly enlarged sella and flattened mandibular angle. Pectus excavatum or carinatum and scoliosis have been reported.

Miscellaneous findings include cryptorchidism, keloids, and short umbilical cord.



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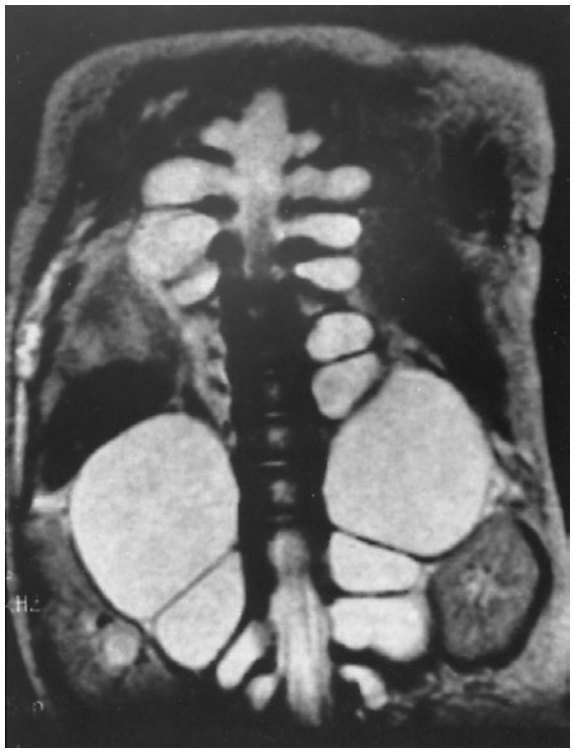


C

Fig. 25–40. *Lateral meningocele (Lehman) syndrome*. (A,B) Note slender build, marked thoracic kyphosis, exaggerated lumbar lordosis, long fingers. (C) Coronal T2 weighted image of thoracolumbar spine showing multiple bilateral meningoceles, widened spinal canal, enlarged neural foramina, lateral displacement. (From KW Gripp et al, Am J Med Genet 70:229, 1997.)

Dural ectasia, some as severe as meningoceles, may be seen in over 60% of patients with *Marfan syndrome*. Again, over 60% of thoracic lateral meningoceles have been associated with *neurofibromatosis, type 1* (5).

References [Lateral meningocele (Lehman) syndrome]

1. Gripp KW et al: Lateral meningocele syndrome: Three new patients and review of the literature. Am J Med Genet 70:229–239, 1997.
2. Katz SG et al: Thoracic and lumbar dural ectasia in a two-year-old boy. Pediatr Radiol 6:238–240, 1978.
3. Lehman RA et al: Familial osteosclerosis with abnormalities of the nervous system and meninges. J Pediatr 90:49–54, 1977.
4. Philip N et al: Multiple lateral meningoceles, distinctive facies, and skeletal anomalies: A new case of Lehman syndrome. Clin Dysmorphol 4:347–351, 1995.
5. Pyeritz RE et al: Dural ectasia is a common feature of the Marfan syndrome. Am J Hum Genet 43:726–732, 1988.

Mandibular condyle hypoplasia and prominent constricted pinnae (question mark ear, congenital auricular cleft)

Uuspää (7), in 1978, described a mother and two sons with prominent constricted ears and hypoplastic mandibles. Jampol et al (4), in 1998, reported a five-generation family with prominent ears constricted between lower and middle thirds with disjunction of the lobule, malformed mandibular condyles, microstomia, and temporomandibular joint abnormalities (Fig. 25–41). Range of motion was reduced. Hearing was not affected. Storm et al (5), in 1998, described a four-generation family with prominent malformed ears and mandibular condylar hypoplasia, micrognathia, and microstomia. Similar examples are those of Brodovsky and Westreich (2), Uysal et al (8), and Takato et al (6). The pinna anomaly is the same as "question mark" ear or congenital auricular cleft (3) of which there are about 15 published examples (1). Priolo et al (4a) suggested that hypotonia is a component.

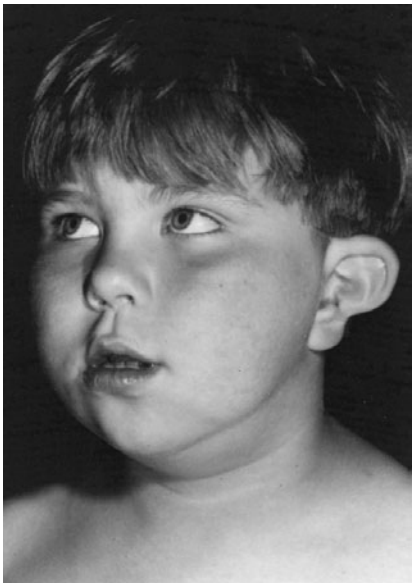
Inheritance is autosomal dominant.

References [Mandibular condyle hypoplasia and prominent constricted pinnae (question mark ear, congenital auricular cleft)]

1. Al-Qattan MM: Cosman (question mark) ear: Congenital auricular cleft between the fifth and sixth hillocks. Plast Reconstr Surg 102:439–440, 1998.
2. Brodovsky S, Westreich M: Question mark ear: A method for repair. Plast Reconstr Surg 100:1254–1257, 1997.
3. Cosman B: The question mark ear: An unappreciated major anomaly of the auricle. Plast Reconstr Surg 73:572–576, 1984.
4. Jampol M et al: Prominent, constricted ears with malformed condyle of the mandible. Am J Med Genet 75:449–452, 1998.
4a. Priolo M et al: Question mark ears, temporomandibular joint malformation and hypotonia: Auriculo-condylar syndrome or a distinct entity? Clin Dysmorphol 9:277–280, 2000.
5. Storm AL et al: Mandibular condyle hypoplasia and prominent constricted ears: A distinct autosomal dominant disorder with widely variable expression. 19th David W. Smith Workshop on Malformations and Morphogenesis. Whistler, BC, Canada, 1998.
6. Takato T et al: The question mark ear: A familial case. Ann Plast Surg 22:69–73, 1989.
7. Uuspää V: Combined bilateral external ear deformity and hypoplastic mandible. Scand J Plast Reconstr Surg 12:165–169, 1978.
8. Uysal OA et al: Congenital auricular clefts. Eur J Plast Surg 13:178–181, 1990.

Mental and somatic retardation, generalized muscular hypertrophy, joint limitations, unusual facies, and mixed hearing loss (Myhre syndrome, GOMBO syndrome)

Myhre et al (3), in 1981, described a syndrome of growth and mental deficiency, unusual facies, generalized muscular dystrophy, joint limitation, skeletal deformities, and mixed hearing loss in two unrelated males. Other examples were reported by Soljak et al (4), Garcia-Cruz et al (2), and, possibly, Verloes et al (1,5).



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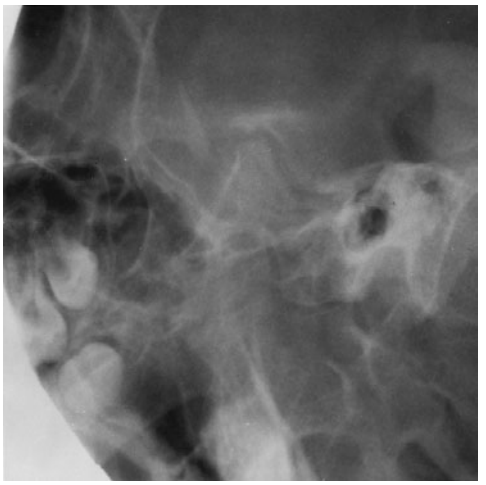

B

Fig. 25–41. *Mandibular condyle hypoplasia and prominent constricted pinnae (question mark ear, congenital auricular cleft).* (A) Prominent malformed pinna ("question mark" ear). (B) Condylar head shows flattening of superior surface. Glenoid fossa is significantly anterior to and separated from external auditory canal. (From M Jampol et al, Am J Med Genet 75:449, 1998.)

Six of seven patients are males, raising the question of X-linked recessive inheritance, with rare manifesting heterozygotes. Verloes et al (6), however, demonstrated that it is due to a cryptic translocation involving the short arm of chromosome 3 and the long arm of chromosome 22.

There was both prenatal and postnatal growth deficiency. The muscles were enlarged and there was decreased joint mobility (Fig. 25–42A,B). The midface was hypoplastic with relative mandibular prognathism. Blepharophimosis and short philtrum were evident. One patient had cleft lip–palate (3). Hypospadias and cryptorchidism were noted.

Mixed hearing loss ranging from moderate to severe has been reported (1,2).

Radiographically, the calvaria was thickened (Fig. 25–42C). The iliac wings were hypoplastic (champagne-glass configuration), the ribs broad. The long and short tubular bones were somewhat abbreviated (Fig. 25–42D). and the vertebrae were large and somewhat flattened with large short pedicles (Fig. 25–42E).

References [Mental and somatic retardation, generalized muscular hypertrophy, joint limitations, unusual facies, and mixed hearing loss (Myhre syndrome, GOMBO syndrome)]

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Microcephaly, distal lymphedema, and choreoretinal dysplasia with distinctive facies

Microcephaly in combination with choreoretinopathy was first reported by Alzial et al (1), in 1980. Microcephaly, in combination with distal lymphedema, was reported by Leung (10), in 1985, and Crowe and Dickerman (3), in 1986, and others (8,16). The triad of findings was reported by Angle et al (2), in 1994. The combination was also reported by Limwongse et al (11), in 1999, who reexamined individuals from the kindred described by Crowe and Dickerman (3). Other kindred have been reported (4,5,7,9,12,14–19).

The microcephaly is quite significant (−6 SD) (Fig. 25–43A). Intelligence ranges from normal to mildly retarded, in spite of the severe microcephaly. The facies is characterized by downslanting palpebral fissures, epicanthic folds, prominent pinnae, broad nasal bridge with a broad and large nasal tip and anteverted nares, prominent philtrum, prominent full lips, and pointed chin. Short stature may be found (16).

The lymphedema is restricted to the dorsal surfaces of the hands and feet. The lymphedema is nonpitting and firm to the touch. The digits appear somewhat shortened with persisting volar and plantar pads. There may be fingernail and toenail dysplasia (Fig. 25–43B).

Eye changes consist of large areas of reticulated choreoretinal atrophy in superior and inferior fundus. Mottled pigmentation is seen in the area of atrophy. Atrophic yellow spots occur in the inferior portion of the fundi. Mild optic atrophy may be noted.

Inheritance is autosomal dominant.

Familial microcephaly is usually autosomal recessive, but dominant examples have been cited. Perhaps some of these cases may represent the syndrome (6,13).

Various lymphedemas are discussed in *Hennekam syndrome*.

References (Microcephaly, distal lymphedema, and choreoretinal dysplasia with distinctive facies)

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2. Angle B et al: Microcephaly, lymphedema, and chorioretinal dysplasia. Report of two additional cases. Am J Med Genet 53:99–101, 1994.

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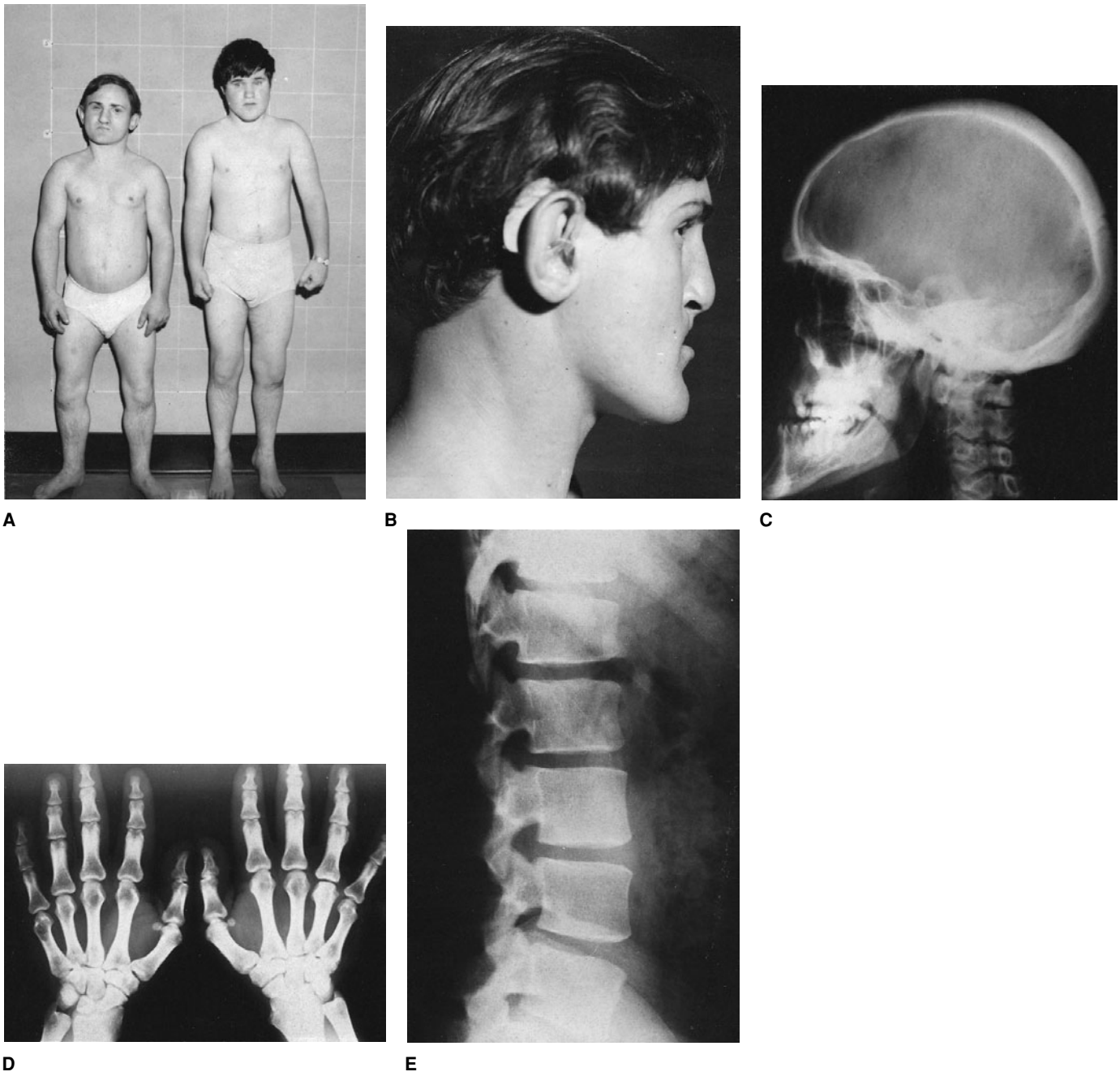

Fig. 25–42. *Mental and somatic retardation, generalized muscular hypertrophy, joint limitations, unusual facies, and mixed hearing loss (Myhre syndrome).* (A) Two unrelated males with short stature, decreased joint mobility, blepharophimosis. Note cleft lip in patient on the left. (B) Note midface hypoplasia, cleft lip, relative mandibular prognathism. Patient wears hearing aid. (C) Note thickened calvaria, midface hypoplasia, and relative mandibular prognathism. (D) Short tubular bones somewhat abbreviated. (E) Vertebrae, large, somewhat flattened with large, short pedicles. (From SA Myhre et al, Clin Genet 20:1, 1981).

9. Leroy JG et al: Familial distal lymphedema and microcephaly. 19th Annual David W. Smith Workshop on Malformations and Morphogenesis, Whistler BC, Canada, 1998.

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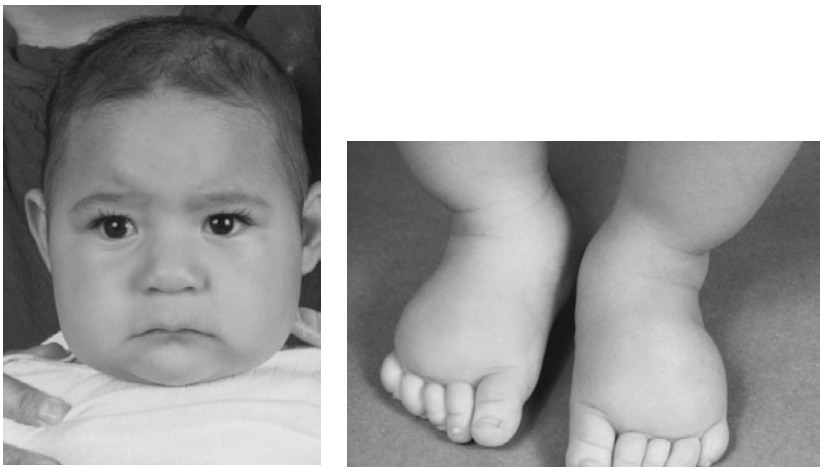

A B

Fig. 25–43. *Microcephaly, distal lymphedema, and chorioretinal dysplasia with distinctive facies*. (A) Microcephaly in 7-month-old male. (B) Lymphedema of feet. (From B Angle et al, Am J Med Genet 53:99, 1994.)

19. Young ID et al: Microcephaly, microphthalmos and retinal folds: Report of a family. J Med Genet 24:172–174, 1987.

Microcephaly, growth retardation, and facial anomalies

Partington and Anderson (1) described two sibs and a third unrelated child with the combination of pre- and postnatal growth retardation (average birthweight 2.6 kg), microcephaly, global developmental delay, thick curly hair, and minor facial anomalies. The facial appearance consisted of thick eyebrows with synophrys and short beaked nose with long columella. The personality was described as friendly.

Inheritance may be autosomal recessive.

Reference (Microcephaly, growth retardation, and facial anomalies)

1. Partington M, Anderson D: Mild growth retardation and developmental delay, microcephaly, and a distinctive facial appearance. Am J Med Genet 49: 247–250, 1994.

Microcephaly, mental retardation, Hirschsprung disease, and characteristic facies (Mowat-Wilson syndrome)

Mowat et al (3) reported six children with short stature, microcephaly, and marked mental retardation. Four had Hirschsprung disease and a distinct facies (Fig. 25–44). We suspect that this syndrome is identical to *Goldberg-Shprintzen syndrome*.

The facies was characterized by deep-set, large eyes, broad nasal bridge, rounded nasal tip, prominent columella, open mouth, prominent chin, and large uplifted ear lobes.

Postnatal short stature, slender tapered fingers, and bilateral calcaneovalgus were noted in all.

All exhibited severe developmental delay with absent or minimal speech and delayed gross motor skills, but a common feature was a happy smiling affect. Four developed seizures.

Five had Hirschsprung disease (most with short segment), and one has chronic constipation.

Three had congenital heart anomalies (pulmonary atresia, tetralogy of Fallot, patent ductus, peripheral pulmonary stenosis), and three had renal structural anomalies (duplex kidney, hydronephrosis, reflux).

Several other patients have had similar phenotype (1,2,4).

Inheritance has still not been determined. All have been isolated examples. Deletion at 2q22–q23 has been found.

References [Microcephaly, mental retardation, Hirschsprung disease, and characteristic facies (Mowat-Wilson syndrome)]

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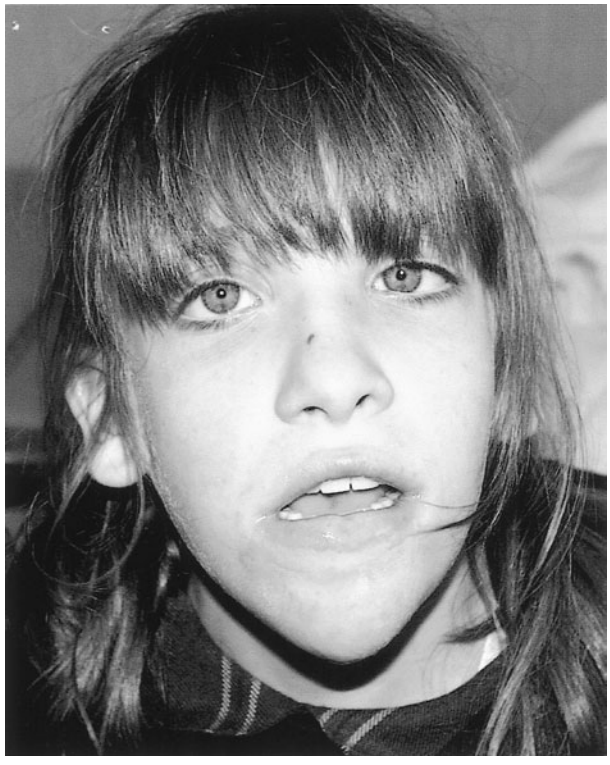
Fig. 25–44. *Mowat-Wilson syndrome*. Ten-year-old female with long face, prominent chin, and seizures. Patients often have Hirschsprung disease. We suspect that this disorder is the same as Goldberg-Shprintzen syndrome. (Courtesy of D Mowat, Sydney, Australia.)



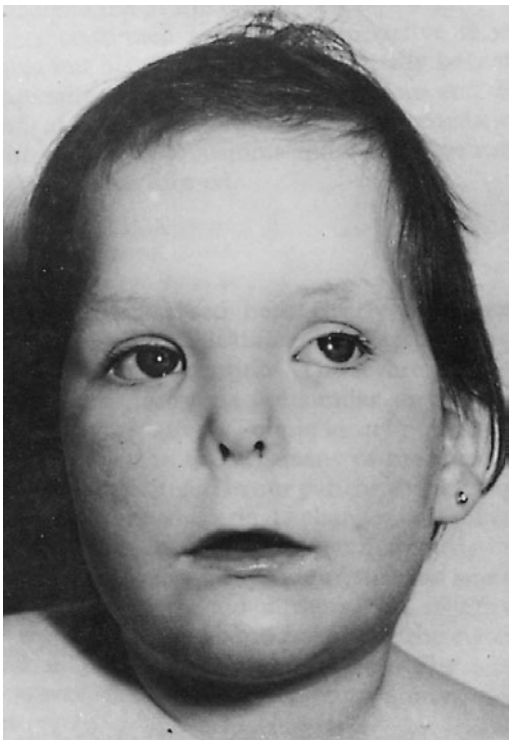


Fig. 25–45. *Nasal hypoplasia, sparse hair, truncal obesity, genital hypoplasia, and severe mental retardation*. Unusual facies characterized by ptosis, epicanthic folds, nasal hypoplasia, sparse scalp hair and eyebrows, long philtrum, and thin upper lip. (From JP Fryns et al, J Med Genet 29:676, 1992.)

Nasal hypoplasia, sparse hair, truncal obesity, genital hypoplasia, and severe mental retardation

Fryns et al (1) observed a female with unusual facies characterized by ptosis, nasal hypoplasia, epicanthic folds, and sparse scalp hair and eyebrows. The philtrum was long and the upper lip was thin (Fig. 25–45).

She was severely retarded with generalized hypotonia. In addition to truncal obesity, there were small hands and feet, puffy hands, syndactyly of toes 2–3, and hypoplastic labia majora and minora.

Reference (Nasal hypoplasia, sparse hair, truncal obesity, genital hypoplasia, and severe mental retardation)

1. Fryns JP et al: Nasal hypoplasia, sparse hair, truncal obesity, genital hypoplasia, and severe mental retardation. J Med Genet 29:676–677, 1992.

Pallister-Hall syndrome

In 1980, Hall, Pallister, and others (15) described a syndrome of hypothalamic hamartoblastoma, craniofacial anomalies, postaxial polydactyly, cardiac and renal defects, and endocrine dysfunction. To date, over 60 have been reported (1,2,6,7,12–19,23,29–36). Many cases have been sporadic, although there are several reports of autosomal dominant inheritance (14,19,24,28,31,32,34). Variable expressivity is common. The causative gene, mapped to 7p13, has recently been identified as the *GLI3* gene, the zinc finger transcription factor, which also causes Greig cephalopolysyndactyly syndrome, postaxial polydactyly type A and the PIV syndrome (polydactyly, imperforate anus, and vertebral anomalies) (19–21). It has been suggested by Biesecker and Graham (1) that frameshift mutations of *GLI3* cause PHS, whereas large deletions resulting in haploinsufficiency of *GLI3* cause Greig syndrome (19–21). However, Wild et al (38) have also described point mutations in individuals with Greig syndrome, so the reason for the different phenotypes has yet to be sorted out. There is no genotype-phenotype correlation (28a).

Table 25–1. *Pallister-Hall syndrome*: Clinical and pathological findings

Finding	%
Central nervous system	
Hypothalamic hamartoma	85
Holoprosencephaly	10
Hydrocephalus	25
Short/absent olfactory tracts	40
Craniofacial anomalies	
Flat nasal bridge	60
Short nose	60
Ear anomalies	90
Microglossia/micrognathia	25
Buccal frenula	50
Palatal anomalies	50
Bifid epiglottis-cleft larynx	50
Limb anomalies	
Postaxial polydactyly/oligodactyly	60
Nail dysplasia/hypoplasia	65
Short limbs	40
Syndactyly	50
Adducted forefoot	40
Pathological findings	
Renal ectopia/dysplasia	55
Congenital heart defects[a]	40
Imperforate/anteriorly placed anus	50
Lung segmentation anomalies	45
Endocrine findings[b]	
Adrenal hypoplasia/dysplasia causing hypoadrenalism	55
Pituitary aplasia/dysplasia causing panhypopituitarism	70
Testicular hypoplasia/cryptorchidism with micropenis in males	50
Thyroid aplasia/dysplasia hypothyroidism	65
Cryptorchidism	30

[a] PDA, VSD, endocardial cushion defect, mitral and aortic valve defects, and proximal aortic coarctation

[b] Endocrine findings reflect premorbid endocrinologic studies, and autopsy cases may be underreported.

Based on LG Biesecker et al, Am J Med Genet 65:76, 1996.

Diagnostic criteria were suggested by Biesecker et al (3), and include both hypothalamic hamartoma with characteristic MRI findings and central polydactyly.

Most patients were at or below the tenth centile for length and weight. Because the first reported children died during infancy, the condition was initially considered to be lethal. Over time, individuals with milder manifestations were described, and the prognosis can be quite good. Cheng et al (5) described an isolated example of hamartoblastoma and polysyndactyly in an asymptomatic adult. Biesecker and Graham (1) provide a good review of the evolution of the understanding of the phenotype. The major cause of death in the neonatal period is hypoadrenalism (13,18). Pulmonary anomalies undoubtedly contribute to neonatal respiratory distress. Clinical and pathologic findings on 13 examples are summarized in Table 25–1.

Craniofacial anomalies. Short midface, short nose with flat nasal bridge, anteverted nostrils, and asymmetric cranium with large fontanels are common. The ears are frequently low-set and posteriorly angulated. They protrude with small or absent lobules (7,13,15,17,18) (Fig. 25–46A,B).

Oral anomalies include micrognathia, microglossia, and multiple frenula between the alveolar ridge and buccal mucosa. Natal teeth, cysts of the gingiva, cleft palate, and cleft uvula have also been noted in some patients. Mandibular ridges are often hypoplastic. Two children with choanal atresia have been described (29,33).

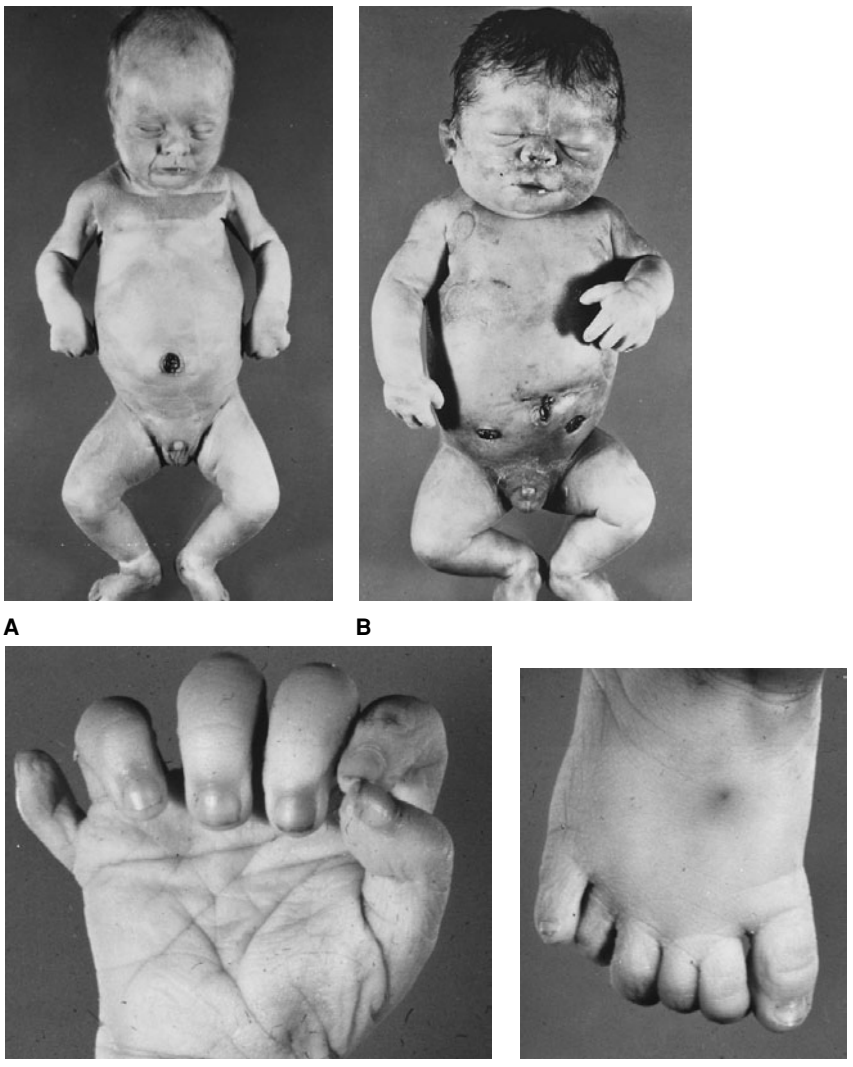


Fig. 25–46. *Pallister-Hall syndrome*. (A,B) Short midface, anteverted nostrils, long philtrum, short hands, microphallus, underdeveloped scrotum. (C) Postaxial polydactyly of hand. (D) Postaxial polydactyly of foot. (From JG Hall et al, Am J Med Genet 4:47, 1980.)

Limb abnormalities. Postaxial polydactyly, syndactyly, and nail dysplasia, involving both toes and fingers, are observed in most patients (Fig. 25–46C,D). The marked polydactyly, central or postaxial, is associated with short dysplastic fourth metacarpals, and small underdeveloped fourth fingers. Occasionally, a bifid third metacarpal is seen (Fig. 25–47). In the feet, the fourth and fifth digits are similarly involved. Subluxation of the radial head has been found in approximately half the patients (7,13,15,17,18,26) and mesomelic shortness of the long bones has been described as well (36). Encha-Razavi et al (8) described sibs with micromelia and short ribs, one of whom had hypothalamic hamartoma; it is uncertain whether they truly had Pallister–Hall syndrome.

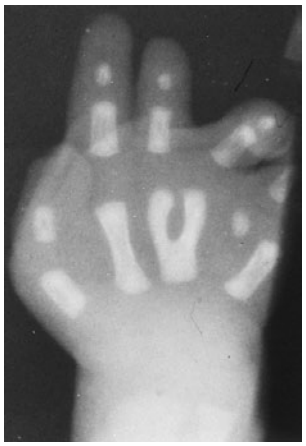
Congenital heart defects. A wide variety of congenital heart defects has been reported in some, including PDA, VSD, endocardial cushion defect, mitral and aortic valve defects, and proximal aortic coarctation (13,15,17). As more cases were described, it has become evident that cardiac defects are less frequent than originally thought (1).

Central nervous system. The most striking and unique abnormality is congenital hypothalamic tumor, which replaces the hypothalamus and nuclei and consists of normal neuronal elements in abnormal mixture (2,32) (Fig. 25–48). The tumor probably arises from the embryonic hypothalamic plate. While undifferentiated elements may be observed, mature neural tissue has been reported (18,32) lending credence to the hypothesis that such tumors retain the ability to mature over time (2,13). However, not all affected individuals have hypothalamic hamartomas (9,34).

Since facial anomalies are associated with hypothalamic hamartoblastoma, embryonic disruption by the tumor may upset stereotactic relationships, thereby altering migration of embryonic structures. This results in craniofacial anomalies. Variation in timing and degree of hamartoblastomatous disruption could result in a range of phenotypic expression. Early insult resulted in holoprosencephaly, noted in three cases (2,18). Disruption during the fifth week could lead to the milder craniofacial anomalies usually found in the Pallister–Hall syndrome. Instances of hypothalamic hamartoma and precocious puberty without facial anomalies (18) might represent a disruptive insult that occurred even later. Since solitary central maxillary incisor may be the mildest manifestation of holoprosencephaly, its association with precocious puberty and hypothalamic hamartoma (27) helps to bridge the gap between very early hypothalamic tumors with severe craniofacial anomalies and late hypothalamic tumors without associated anomalies. Hypothalamic hamartoblastoma and its associated disruptive craniofacial features may occur alone (10,18,25,27) or together with other embryonically noncontiguous anomalies making up a true malformation syndrome like the Pallister–Hall syndrome.

Lungs. Laryngeal cleft, aplastic, hypoplastic, or bifid epiglottis; dysplastic tracheal cartilages; and absence or hypoplasia of the lung and/or abnormal lung lobulation occur (1,7,13,15,17,18).

Endocrine findings. Severe multiple endocrine dysfunction usually includes hypopituitarism, hypothyroidism, hypoglycemia, and hypoadrenalism (13,15,30). These are not always present.



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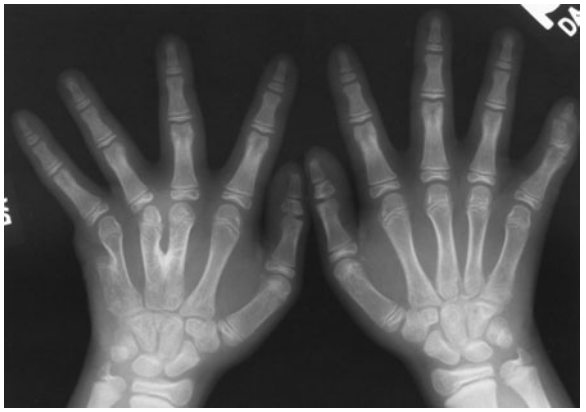

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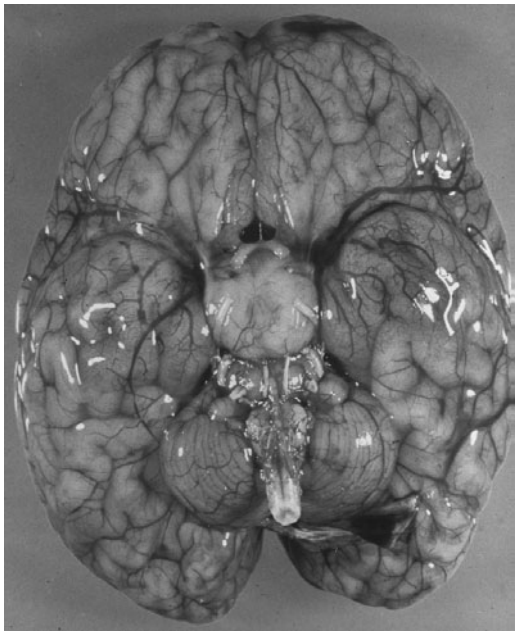
Fig. 25–47. *Pallister-Hall syndrome*. (A) Various bony anomalies of hands: fused metacarpals, hypoplastic metacarpals, fused proximal phalanges, agenesis of distal phalanges. (B) Asymmetric hand malformations: unilateral central or insertional polysyndactyly and contralateral postaxial polydactyly. (A from JG Hall et al, Am J Med Genet 4:47, 1980. B from LG Biesecker and JM Graham, Jr, J Med Genet 33:585, 1996.)

Fig. 25–48. *Pallister-Hall syndrome*. Hypothalamic hamartoblastoma. (From SK Clarren et al, Am J Med Genet 7:75, 1980.)



Other findings. Various genitourinary anomalies have been reported including absent, hypoplastic, dysplastic, or ectopic kidneys. Micropenis and cryptorchidism have also been noted. The anus is frequently imperforate or anteriorly placed. Squires et al (32) described a patient with vaginal atresia, and Unsinn et al (35) described a patient with hydrocolpos. Several patients have had narrow cervical vertebrae (7,13,15,17,18); others have laryngotracheal cleft or bifid epiglottis (26a).

Differential diagnosis. Natal teeth, multiple frenula, nail dysplasia, congenital heart defects, and postaxial polydactyly are observed in *Ellis-van Creveld syndrome*. Multiple frenula are also found in *Opitz trigonocephaly (C) syndrome*. Kaufman–McKusick syndrome, consisting of hydrometrocolpos, postaxial polydacytly, and congenital heart defect (11,23), should also be excluded. Marcuse et al (25), in a review of hypothalamic hamartoma unassociated with the syndrome, noted one patient with cleft palate and another with tetralogy of Fallot. Hennekam et al (16) reported congenital hypothalamic hamartoma, frontonasal malformation, frontal midline lipoma, and complex congenital heart defect. Gitlin and Behar (10) reported a patient with a large hypothalamic hamartoblastoma, agenesis of the corpus callosum, absent olfactory tracts and bulbs, and bilateral nasal proboscides. Verloes et al (37) described hypothalamic hamartoblastoma with holoprosencephaly, macrophthalmia, pulmonary malformations, radial hypoplasia, and Müllerian regression. Winter et al (39) reported a solitary central maxillary incisor with precocious puberty and hypothalamic hamartoma. The combination of holoprosencephaly and polydactyly may be seen in *pseudo-trisomy 13 syndrome* and *Meckel syndrome*. There is some overlap with the *oral-facial-digital syndromes* and *Smith-Lemli-Opitz syndrome*, although cholesterol levels are normal in Pallister–Hall syndrome (4). Kuller et al (22) described sibs with the presumptive diagnosis of Pallister-Hall syndrome; the younger was subsequently found to have an unbalanced translocation (46 XY, −7, +der(7),t(3;7)(p25.3;q36)pat).

Laboratory aids. Neuroradiological detection of hypothalamic hamartoblastoma can be difficult. Magnetic resonance imaging is the procedure of choice for evaluating suprasellar tumors but may be difficult to obtain in infants (18). Low maternal estriols prior to birth and large fontanels suggest endocrine hypofunction and should prompt immediate evaluation for hypoadrenalism and hypothyroidism.

Prenatal diagnosis may be possible by (*a*) measurement of maternal estriol levels, which are decreased in the presence of hypoplastic, fetal adrenals, (*b*) prenatal ultrasound for detection of renal, adrenal, and brain abnormalities, or presence of polydactyly, (*c*) measurement of disaccharidoses in amniotic fluid that may be decreased with imperforate anus (13,15) and (*d*) linkage analysis, and eventually direct mutation analysis.

References (Pallister-Hall syndrome).

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Enlarged parietal foramina, craniofacial anomalies, mental retardation, and multiple exostoses (Potocki-Shaffer syndrome, del11p11.2-p12 syndrome)

Gustavson et al (2), in 1984, reported two cases of what was described as 11p13 deletion. The female exhibited bilateral aniridia, persistent urogenital sinus, enlarged clitoris, and ovotestes. Intelligence was normal. The face was characterized by short somewhat everted upper lip exposing the maxillary incisor teeth (Fig. 25–49). An unrelated male had large fontanels, large pinnae, small penis, hypoplastic scrotum, and diaphragmatic hernia. Lorenz et al (5) reported a male with brachyturricephaly, biparietal foramina, multiple exostoses of metaphyses, micropenis, and mental retardation. Shaffer et al (10), in 1993, described interstitial deletion 11p11.12-p12 in a family in which two sibs and a maternal uncle exhibited Wormian bones, biparietal foramina, brachymicrocephaly, mental retardation, unusual facies, epicanthic folds, esotropia, micropenis, cryptorchidism, and multiple exostoses (Fig. 25–50). Potocki and Shaffer (7) and Potocki et al (8) and others (1,3–5) expanded the phenotype.

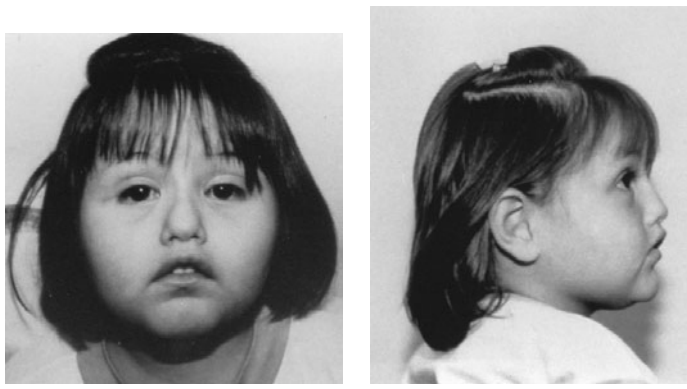
The syndrome has been shown to be a contiguous gene deletion involving the *EXT2* (multiple exostoses gene) at 11p11.2-p12 (1,4,7). The *EXT2* gene defines a family of putative tumor suppressor genes (10). Loss of functional mutations in the *ALX* homeobox gene has been shown to be responsible for the syndrome (5a,11,12). Wilkie showed that haploinsufficiency of *MSX2* causes parietal foramina.

Overlapping is the *WAGR syndrome* (Wilms tumor, aniridia, genital abnormalities, and mental retardation). A patient with WAGR and multiple exostoses and parietal ramus has been noted by McGaughran et al (6). We reject the pejorative term, DEFECT11 (8a).

Craniofacial findings. Large anterior fontanel, biparietal foramina, epicanthic folds, esotropia, downturned upper lip, and short underdeveloped philtrum have been noted in virtually all affected.

Central nervous system. Developmental delay and mental retardation have been constant features. Seizures have been noted by Shaffer et al (9).

Fig. 25–49. *Enlarged parietal foramina, craniofacial anomalies, mental retardation, and multiple exostoses (Potocki-Shaffer syndrome, del11p11.2-p12 syndrome).* (A,B) Short, somewhat everted upper lip exposing upper incisors. Downslanting corners of mouth. (From LG Shaffer et al, Am J Med Genet 45:581, 1993.)



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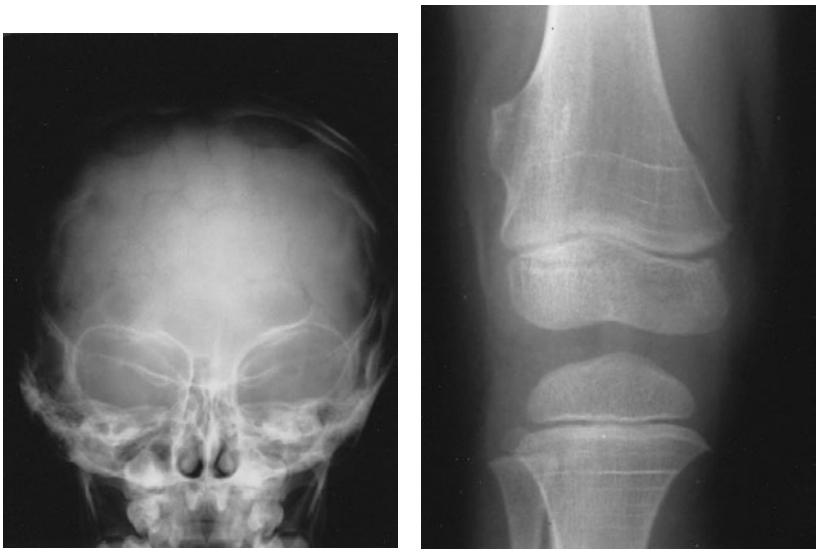

A B

Fig. 25–50. *Enlarged parietal foramina, craniofacial anomalies, mental retardation, and multiple exostoses (Potocki-Shaffer syndrome, del11p11.2p12 syndrome.)* (A) Biparietal foramina. (B) Exostoses of metaphysis. (From LG Shaffer et al, Am J Med Genet 45:581, 1993.)

Skeletal findings. Multiple cartilaginous exostoses have been noted in all patients.

Discussion. Hereditary multiple exostoses may be a solitary finding. They have autosomal dominant inheritance. Three loci have been identified: 8q24(*EXT1*), 11p12(*EXT2*), and 19p(*EXT3*) (3). *EXT1* deletions have been identified with *Langer–Giedion syndrome*. *EXT* deletions have been seen only with multiple exostoses. Enlarged parietal foramina have been seen with cleft lip and/or palate in a syndrome.

The parietal defects are much larger in those with the deletion than in those with *MSX2* haploinsufficiency. Wu et al (12) demonstrated haploinsufficiency of *ALX4* to be responsible for parietal foramina.

The facies resembles that of *Char syndrome*.

References [Enlarged parietal foramina, craniofacial anomalies, mental retardation, and multiple exostoses (Potocki-Shaffer syndrome, del11p11.2-p12 syndrome)]

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Speech delay, facial asymmetry, and strabismus

Mehes et al (1), in 1993, described a mother and two children with markedly delayed speech development (speech appeared at approximately 4 years), strabismus, and transverse ear crease. Facial asymmetry, hypertelorism, and highly arched palate were additional manifestations.

Autosomal dominant inheritance was proposed.

Reference (Speech delay, facial asymmetry, and strabismus)

1. Mehes K: Delayed speech development, facial asymmetry, strabismus, and transverse ear lobe creases: A new syndrome? J Med Genet 30:76–77, 1993.

Unusual facies, agonadism, and mental retardation

Kennerknecht et al (1), in 1995, described two sisters with agonadism, mental retardation, short stature, and unusual facies.

The parents were Turkish first cousins. Autosomal recessive inheritance appears likely. The karyotype was 46,XY.

Both exhibited short stature, central obesity, inverted nipples, and global developmental retardation. Bone age was severely retarded. Mild thoracolumbar scoliosis was evident as was dysplasia of the hips.

Characterizing the facies were low-set hairline, hypotelorism, sunken eyes, long eyelashes, broad nasal bridge, retracted nostrils, thin upper lip, and dysmorphic pinnae. Hypodontia was noted but not demonstrated in the photographs.

The external genitalia were female, but agonadism, blind-ended vagina, hypoplastic uterus, and rudimentary Müllerian structures were found.

Reference (Unusual facies, agonadism, and mental retardation)

1. Kennerknecht I et al: Agonadism in two sisters with XY gonosomal constitution, mental retardation, short stature, severely retarded bone age, and multiple extragenital malformations. Am J Med Genet 59:62–67, 1995.

Unusual facies and congenital hip dislocation

Collins et al (1) reported a mother and three daughters with unusual facies (hypertelorism, epicanthic folds, puffiness around eyes, flat midface, and downslanting mouth), ASD, short stature, and congenital hip dislocation.

In addition, all three girls had clinodactyly and hyperextensible joints, features seen in the father. A picture of the father resembles that of *trichorhino-phalangeal syndrome*.

Reference (Unusual facies and congenital hip dislocation)

1. Collins AL et al: A mother and three daughters with congenital dislocation of the hip and a characteristic facial appearance: A new syndrome? Clin Dysmorphol 4:277–282, 1995.

Unusual facies, hyperphalangism, hallux valgus, and bronchomalacia

Chitayat et al (1) reported a male infant with widow's peak, bushy eyebrows, synophrys, prominent eyes, hypertelorism, depressed nasal bridge and short pointed nose with anteverted nostrils, long philtrum, and full lips.

Hyperphalangism (resembling *Catel-Manzke syndrome*, only more extensive, involving digits 2 and 3) and hallux valgus were evident.

Congenital bronchomalacia and mild hypospadias were also noted.

Reference (Unusual facies, hyperphalangism, hallux valgus, and bronchomalacia)

1. Chitayat D et al: Hyperphalangism, facial anomalies, hallux valgus, and bronchomalacia: A new syndrome. Am J Med Genet 45:1–4, 1993.

Unusual facies, hirsutism, skeletal dysplasia, mental retardation, and uric acid metabolic disorder

Wiedemann et al (1) described a patient, the son of nonconsanguineous parents. He had strikingly generalized hirsutism, but especially marked on chin, neck, shoulders, and back, which turned somewhat gray early in life. Brachycephaly, long neck with downsloping shoulders, narrow thorax, prominent elbow joints, coxa valga with subluxation of hip joints, goutlike changes in the fingers, and pes excavatum with claw toes became evident (Fig. 25–51A).

From an early age, he had a deep voice. There were delayed milestones. Moderate mental retardation was established.

Facial appearance was characterized by relatively prominent nose with blunt nasal tip, malformed pinnae, and micrognathia (Fig. 25–51B).

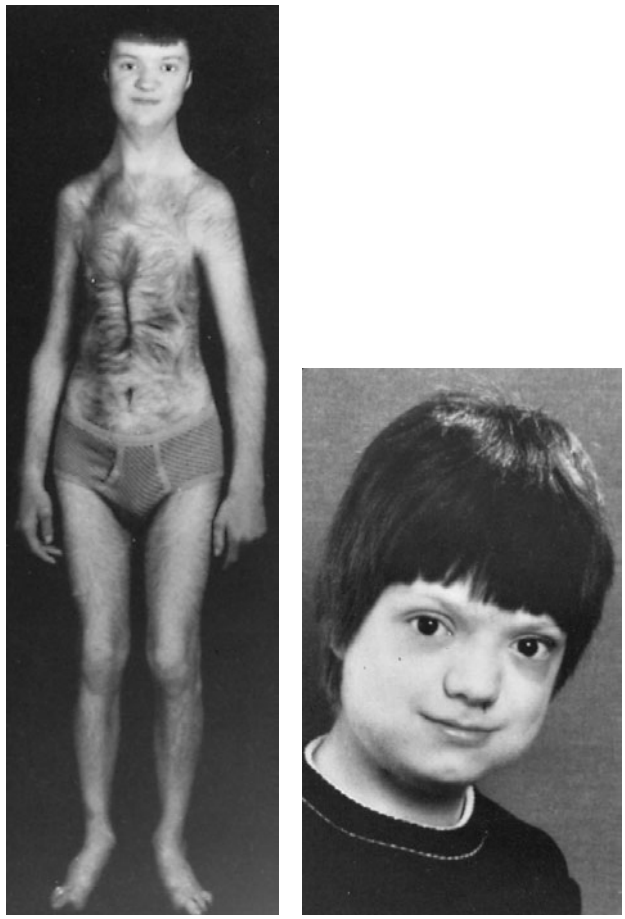
Elevated levels of uric acid were found in the plasma. Hypoexcretion of uric acid in the urine was suggested.

Reference (Unusual facies, hirsutism, skeletal dysplasia, mental retardation, and uric acid metabolic disorder)

1. Wiedemann H-R et al: Hirsutism-skeletal dysplasia-mental retardation syndrome with abnormal face and a uric acid metabolism disorder. Am J Med Genet 46:403–409, 1993.

Unusual facies, short stature, myopia, and mental retardation

Achermann et al (l), in 1999, described two brothers with short stature, microcephaly, myopia, retarded osseous maturation, and severe developmental delay. Facies was characterized by temporal narrowing, periorbital fullness, convergent squint, full cheeks during infancy, and wide mouth and protruding lower lip (Fig. 25–52).



A B

Fig. 25–51. *Unusual facies, hirsutism, skeletal dysplasia, mental retardation, and uric acid metabolic disorder*. (A) Fifteen-year-old male with narrow shoulders and marked hirsutism. (B) Face at 11 years showing relatively prominent nose with blunt tip and small mandible. (From H-R Wiedemann et al, Am J Med Genet 46:403, 1993.)

Inheritance may be autosomal or X-linked recessive.

Reference (Unusual facies, short stature, myopia, and mental retardation)

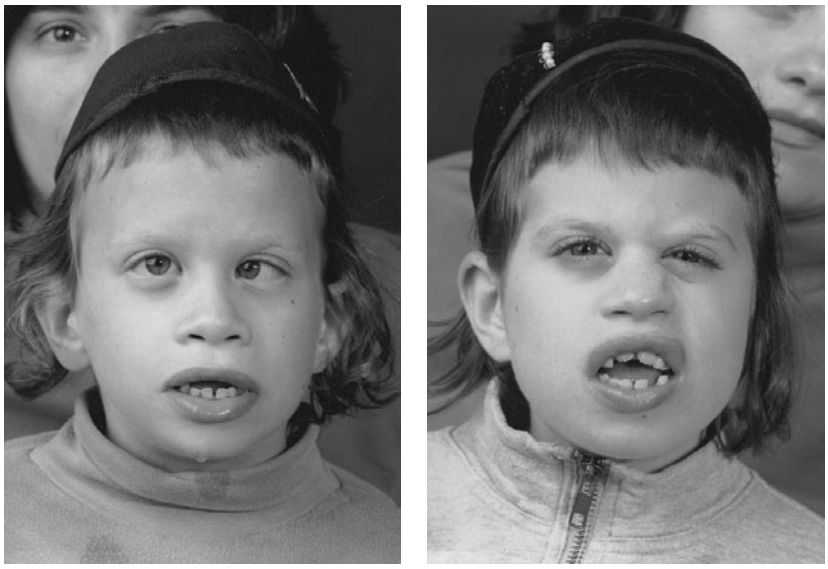
1. Achermann S et al: Short stature, myopia, severe developmental delay, and peculiar facial appearance in two brothers: A new syndrome? Am J Med Genet 86:486–491, 1999.

Unusual facies, hypertrichosis, and retinopathy

Pivnick et al (1) reported a boy with congenital hypertrichosis, pigmentary retinopathy, sunken cheeks, wide nasal bridge, and large downturned mouth. There was decreased fat over the buttocks, but not elsewhere. Development was delayed (Fig. 25–53).

Reference (Unusual facies, hypertrichosis, and retinopathy)

1. Pivnick EK et al: Hypertrichosis, pigmentary retinopathy, and facial anomalies: A new syndrome? Am J Med Genet 62:386–390, 1996.



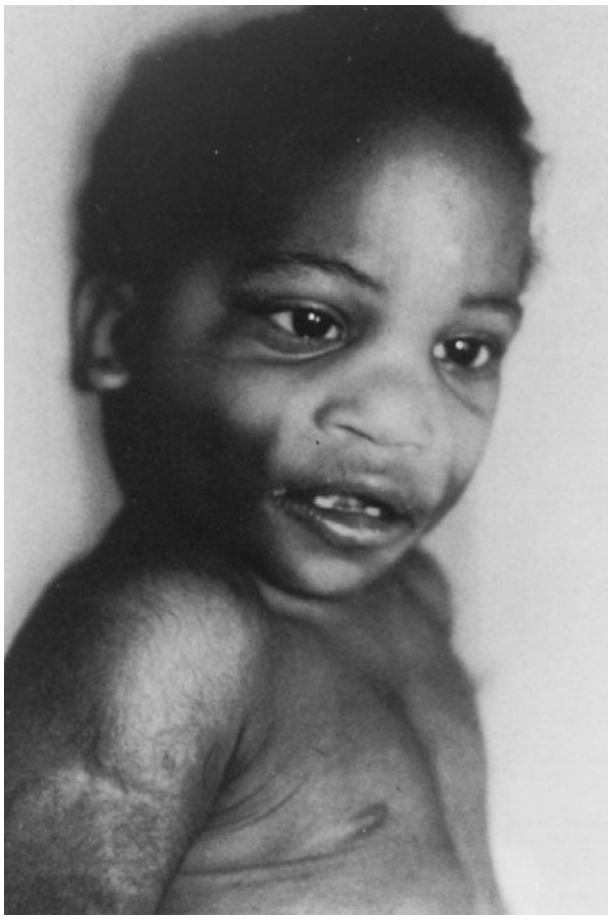
A B

Fig. 25–52. *Unusual facies, short stature, myopia, and mental retardation*. (A,B). Siblings with unusual facies, severe developmental delay, myopia and convergent squint. Note wide mouth, prominent lips, periorbital fullness. (From S Achermann et al, Am J Med Genet 86:486, 1999.)

Unusual facies, hypotonia, mental retardation, and radioulnar synostosis

Der Kaloustian et al (1) reported male and female sibs with unusual facies, generalized hypotonia, developmental retardation, and radioulnar synostosis.

Fig. 25–53. *Unusual facies, hypertrichosis, and retinopathy*. Boy with congenital hypertrichosis. Note wide nasal bridge and large downturned mouth. (From EK Pivnick et al, Am J Med Genet 62:386, 1996.)



Both exhibited dolichocephaly, long face, macrocephaly, esotropia or exotropia, prominent nose with high nasal bridge, outstanding simplified pinnae, pectus excavatum, generalized hypotonia, and type 2 radioulnar synostosis. This form is characterized by fusion just distal to the proximal radial epiphysis in association with congenital dislocation of the radial head (Fig. 25–54). One child also had unilateral polycystic kidney.

Inheritance is probably autosomal recessive.

Reference (Unusual facies, hypotonia, mental retardation, and radioulnar synostosis)

1. Der Kaloustian VM et al: Unilateral radio-ulnar synostosis, generalized hypotonia, developmental retardation, and a characteristic appearance in sibs: A new syndrome. Am J Med Genet 43:942–945, 1992.

Unusual facies, abnormal hair, camptodactyly, and caudal appendage (Teebi-Shaltout syndrome)

Teebi and Shaltout (2), in 1989, reported a kindred with unusual facies characterized by scaphocephaly with prominent occiput and bitemporal depression, thin, curly, sparse, slow-growing hair, hypertelorism, ptosis and blepharophimosis, bulbous nose with hypoplastic alae nasi, small pinnae, microstomia, camptodactyly, and caudal appendage (Fig. 25–55A). Froster et al (1) reported four affected siblings with microphthalmia, bulbous nose, hypoplastic alae nasi, microstomia, small pinnae, and mild cutis laxa.

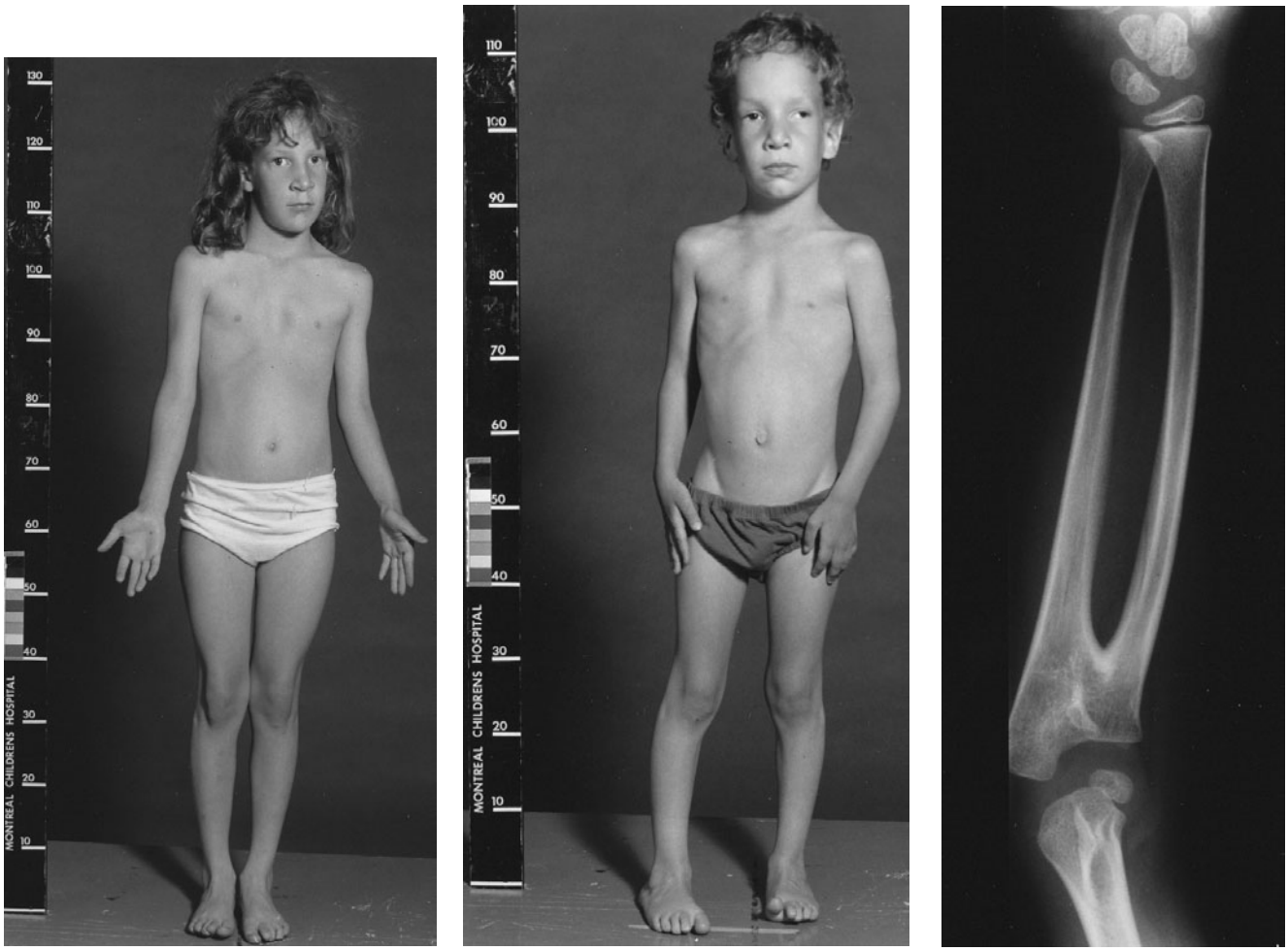
Camptodactyly, ulnar deviation of hands, abnormal skin creases, cutis laxa, and caudal appendix were found in both families (Fig. 25–55B,C). Froster et al (1) also noted unilateral microphthalmia, cleft palate, hydronephrosis, and diastasis recti.

Multiple sibs in one family and consanguinity in both families clearly suggest autosomal recessive inheritance (1,2).

References [Unusual facies, abnormal hair, camptodactyly, and caudal appendage (Teebi-Shaltout syndrome)]

1. Froster UG et al: Craniofacial anomalies, abnormal hair, camptodactyly, and caudal appendage (Teebi-Shaltout syndrome): Clinical and autopsy findings. Am J Med Genet 47:717–722, 1993.

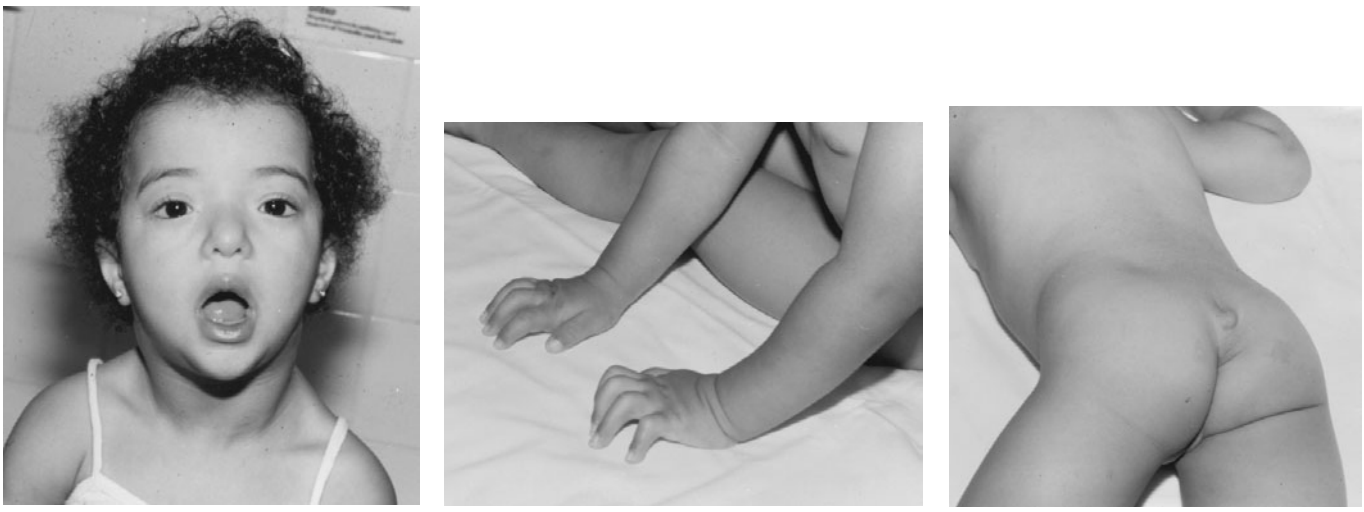
2. Teebi AS, Shaltout AA: Craniofacial anomalies, abnormal hair, camptodactyly, and caudal appendage. Am J Med Genet 33:58–60, 1989.



A B C

Fig. 25–54. *Unusual facies, hypotonia, mental retardation, and radioulnar synostosis*. (A,B) Sibs with dolichocephaly, long face, macrocephaly, exotropia, mild pectus excavatum. (C) Type 2 radioulnar synostosis. (From VM Der Kaloustian et al, Am J Med Genet 43:942, 1992.)

Fig. 25–55. *Unusual facies, abnormal hair, camptodactyly, and caudal appendage (Teebi-Shaltout syndrome*. (A) Thin, curly, sparse scalp hair, hypertelorism, ptosis/blepharophimosis, hypoplastic alae, microstomia. (B) Camptodactyly. (C) Caudal appendage. (From AS Teebi and AA Shaltout, Am J Med Genet 33:58, 1989.)



A B C

Unusual facies, elevated IgE level, and leukocyte dysfunction (Job syndrome, hyperimmunoglobulin E syndrome)

There are many syndromes in which there is defective neutrophil and monocyte chemotaxis (11,21). The most common of these syndromes was called Job syndrome by Davis et al (7) because of Job's affliction with "sore boils." About 250 patients have been described. Extensive reviews are those of Donabedian and Gallin (8), Belohradsky et al (1), Leung and Geha (18), and Grimbacher et al (12). There is no sex or race predilection. It has been estimated that Job syndrome constitutes about 1% of those with a primary immune defect (1). The classic triad of abscesses, pneumonia, and elevated IgE is seen in 75% of all patients and in 85% of those over 8 years (9).

Eczematous dermatitis, usually presenting during the first few weeks of life, often involves more than 50% of the body. There is a predilection for flexural surfaces such as popliteal and antecubital fossae and neck. From there on, nearly all patients exhibit increased susceptibility to recurrent pyogenic infections. There are abundant furuncles and carbuncles of the chest, back, and axillae. However, "cold" abscesses are found in only 30% and cellulitis occurs in only 10%.

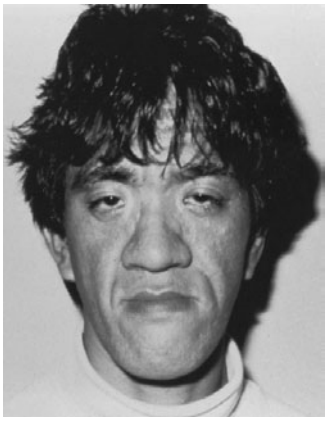
Sinopulmonary infections include otitis media (45%), otitis externa (10%), sinusitis (15%), tonsillitis (12%), mastoiditis (5%), pneumonia (70%), lung abscess (40%), and empyema (10%) (14,19). Gingivitis, periodontitis, aphthae, and oral abscesses have been noted in 70% (4,15). There is failure to shed deciduous teeth in 75%, owing to lack of root resorption (12, 19a). Conjunctivitis and/or corneal ulceration occur in 20%. Bones, joints, and viscera are involved in less than 5% of the cases. *Staphylococcus aureus* has been isolated in 90%. Oral and vaginal candidosis and candidal nail dystrophy are evident in about 40%. Perforation of the gut occurs rarely (5).

Joints are hyperextensible (70%) and recurrent fractures are noted in 50% (12).

Quie and Cates (20) first noted the coarse facies characterized by prominent forehead, deep-set eyes, hypoplastic midface, broad nasal bridge, prominent nose, thick pinnae, and prominent lower lip (2). It has been estimated that the facies is seen in 50%–60% (Fig. 25–56) and may be present at birth (17). Craniosynostosis has been occasionally reported (6,16,23), and these cases are discussed further in chapter 15 under *hyper-IgE syndrome*. Grimbacher et al (12) have suggested autosomal dominant inheritance with variable expressivity. The gene has been mapped to chromosome 4 (13).

The chemotactic defect, present at about 50% of the mean normal range, is variable and often intermittent. Most patients have a low grade eosinophilia (about 10%) (8). Serum IgE levels are at least 10 times normal, that is, greater than 2000 IU/ml, in some patients being as high as 100-fold normal values (1,3,10,22,24). Erythrocyte sedimentation rates are elevated in all patients. IgE levels tend to decline with time (12).

Fig. 25–56. *Unusual facies, elevated IgE levels, and leukocyte dysfunction (Job syndrome)*. Patient has coarse facies typical of patients with Job syndrome. The midface is hypoplastic and there is hypertelorism. (Courtesy of PG Quie, Minneapolis, Minnesota.)



References [Unusual facies, elevated IgE level, and leukocyte dysfunction (Job syndrome, hyperimmunoglobulin E syndrome)]

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22. Shuttleworth D et al: Hyperimmunoglobulin E syndrome (treatment with isotretinoin). Br J Dermatol 119:93–99, 1988.
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Unusual facies, microcephaly, normal intelligence, immunodeficiency, and lymphoreticular malignancy

Seemanová et al (1) described a disorder in nine patients characterized by microcephaly with normal intelligence, cellular and humoral immune defects, increased risk for lymphoreticular malignancy, and a facies similar to that of primordial dwarfism.

Inheritance is clearly autosomal recessive.

Reference (Unusual facies, microcephaly, normal intelligence, immunodeficiency, and lymphoreticular malignancy)

1. Seemanová E et al: Familial microcephaly with normal intelligence, immunodeficiency, and risk for lymphoreticular malignancies: A new autosomal recessive disorder. Am J Med Genet 20:639–648, 1985.

Unusual facies and familial intestinal malrotation

Stalker and Chitayat (1) reported a brother and sister with boxy head, high forehead, frontal bossing, long palpebral fissures, epicanthic folds, and micrognathia.

Both had congenital midgut volvulus.

Inheritance, if any, may be autosomal recessive.

Reference (Unusual facies and familial intestinal malrotation)

1. Stalker HJ, Chitayat D: Familial intestinal malrotation with midgut volvulus and facial anomalies: A disorder involving a gene controlling the normal gut rotation. Am J Med Genet 44:46–47, 1992.

Unusual facies, cerebellar hypoplasia, and heart and lung abnormalities

Seller et al (1) described three female sibs with unusual facies characterized by high forehead, low posteriorly rotated pinnae, prominent upper lip, and micrognathia.

All had cerebellar hypoplasia and contractures (flexed fingers, talipes). Two have ASD and two had deficient lobulation of lungs

Inheritance is likely autosomal recessive.

Reference (Unusual facies, cerebellar hypoplasia, and heart and lung abnormalities)

1. Seller MJ et al: Cerebellar hypoplasia, facial dysmorphism, and internal abnormalities. A new recessive syndrome? Clin Dysmorphol 7:41–44, 1994.

Unusual facies, congenital hypothyroidism, and severe mental retardation (Young-Simpson syndrome)

Young and Simpson (6), in 1987, reported a syndrome of unusual facies, congenital hypothyroidism, asphyxia, hypotonia, and severe global and growth retardation. Similar examples have subsequently been described (1–5). The craniofacies was characterized by microcephaly, blepharophimosis, bulbous nose, long philtrum, thin upper lip, downturned mouth, low-set posteriorly rotated pinnae, and micrognathia (Fig. 25–57). All males have had cryptorchidism. Less constant features have been congenital heart anomaly (ASD, VSD, AV canal, PDA) (1,4–6), and postaxial polydactyly of hands and feet (2). Cleft palate was found by Fryns and Moerman (3).

Polyhydramnios has been noted in a few cases (3,4).

Although autosomal recessive inheritance was proposed on the basis of parental consanguinity (1), all examples have been sporadic.

References [Unusual facies, congenital hypothyroidism, and severe mental retardation (Young-Simpson syndrome)]

1. Bonthron DT et al: Parental consanguinity in the blepharophimosis, heart defect, hypothyroidism, mental retardation syndrome (Young-Simpson syndrome). J Med Genet 30:255–256, 1993.
2. Cavalcanti DP: Unknown syndrome: Abnormal facies, hypothyroidism, postaxial polydactyly and severe retardation: A third patient. J Med Genet 26:785–786, 1989.
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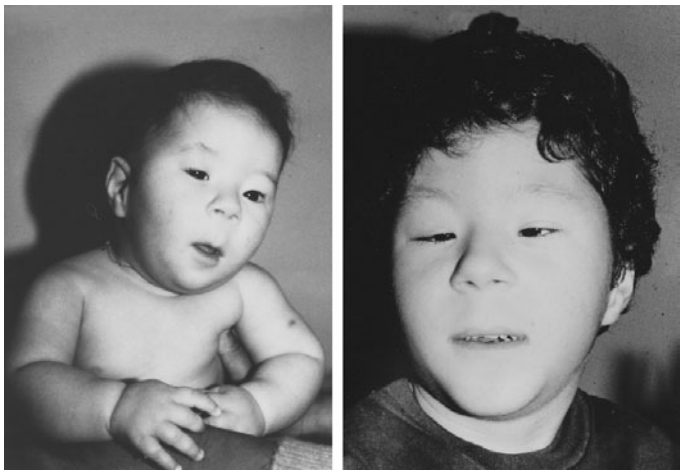


A **B**

Fig. 25–57. *Unusual facies, congenital hypothyroidism, and severe mental retardation (Young-Simpson syndrome).* (A,B) Note microcephaly, blepharophimosis, bulbous nose, long philtrum, and micrognathia in child seen at one year and six years of age. (From DP Cavalcanti, J Med Genet 26:785, 1989.)

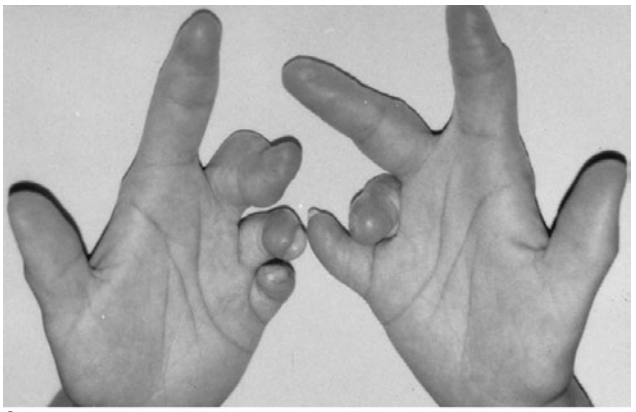
4. Masuno M et al: Young-Simpson syndrome: Further delineation of a distinct syndrome with congenital hypothyroidism, congenital heart defects, facial dysmorphism, and mental retardation. Am J Med Genet 84:8–11, 1999.
5. Nakamura T, Noma S: A Japanese boy with Young-Simpson syndrome. Acta Paediatr Jpn 39:472–474, 1997.
6. Young ID, Simpson K: Unknown syndrome: Abnormal facies, congenital heart defects, hypothyroidism, and severe retardation. J Med Genet 24:715–716, 1987.

Digital fibromas, metacarpal and metatarsal disorganization, and facial pigmentary dysplasia (digito-cutaneous dysplasia, terminal osseous dysplasia, and pigmentary defects)

Bloem et al (2), in 1974, described a syndrome consisting of recurring digital fibromas of infancy in a female infant. There were wide linear pigmented marks over the temporal regions and abundance of the vermilion of the lower lip. Two editors (RJG, RCMH) had an occasion in Amsterdam in 1995 to see this affected woman and her more severely affected child. In addition to multiple digital fibromas, the hands and feet were dysplastic (Fig. 25–58A–C). Toriello (personal communication, 1995) indicated that she had seen a similar example in a female patient. Horii et al (5), in 1998, and Dabney et al (4) described females with skeletal changes in the hands and feet including digital fibromas, joint contractures, brachymesophalangy with cone-shaped epiphyses, variable brachydactyly and deformity of the metacarpals and metatarsals, unusual brachydactyly, hypertelorism, and midface hypoplasia with punched out pigmentary anomalies of the face and scalp. A similar case was shown to one of the authors (RJG) in 1992. A large kindred was reported by Zhang et al (6,7) and the clinical features reviewed by Bacino et al (1) who demonstrated the cutaneous and bony changes (Figs. 25–58A–C and 25–59). Bacino et al (1) suggested the term "terminal osseous dysplasia with pigmentary defects." We prefer *digito-cutaneous dysplasia*.

Facial abnormalities included upslanting palpebral fissures, primary telecanthus with epicanthic folds, depressed nasal tip, and small fibrous tumor of left eyelid. There were also patchy brownish facial discolorations (Fig. 25–58D). Multiple oral frenula were reported in three of nine patients.

The condition clearly has X-linked dominant inheritance, lethal in the male. It has been mapped to Xq28 (1,6).



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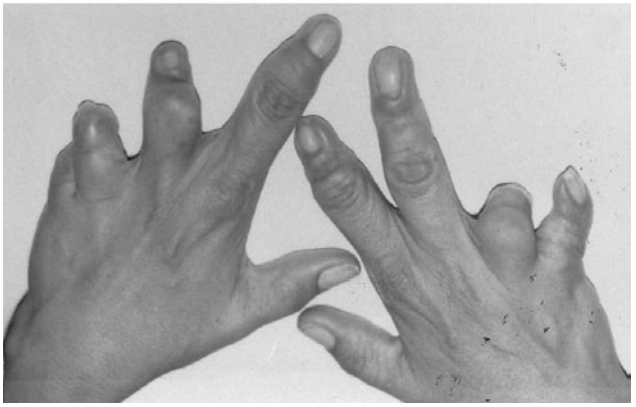

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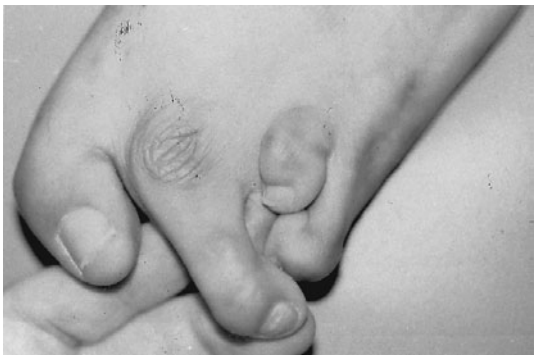

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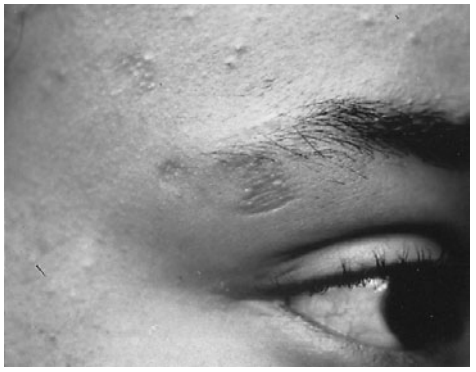
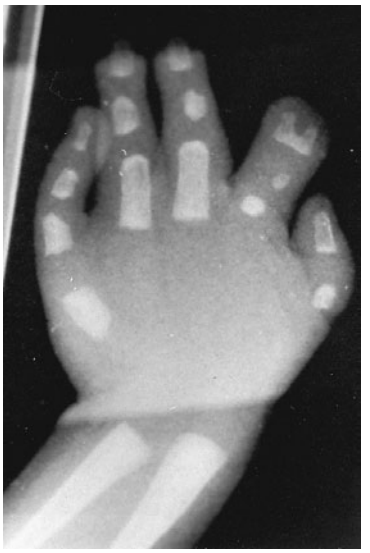


D

Fig. 25–58. *Digital fibromas, metacarpal and metatarsal disorganization, and facial pigmentary dysplasia (digito-cutaneous dysplasia)*. (A–C) Digital shortening and deformities, digital fibromas. (D) Punched-out pigmented lesions of skin above and lateral to eye. (From C Bacino et al, Am J Med Genet 94:102, 2000.)



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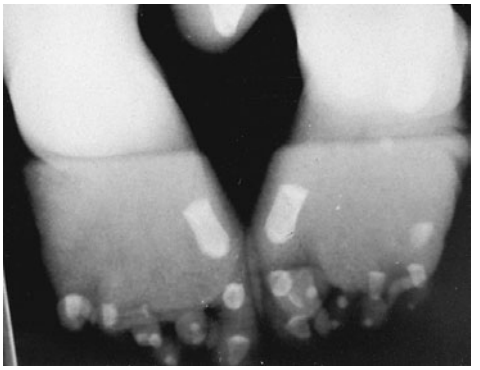


B

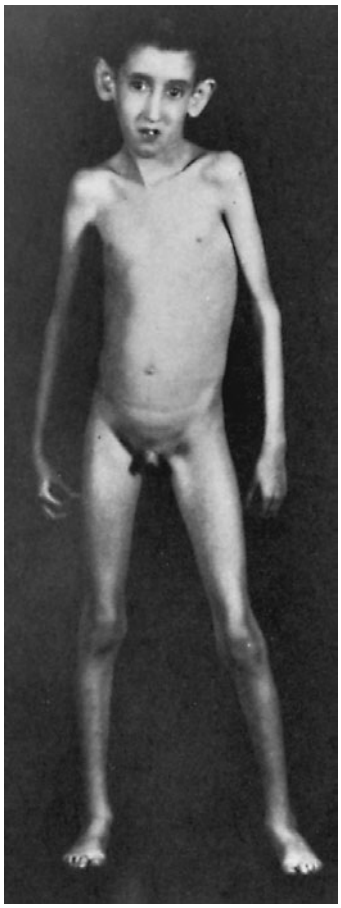
Fig. 25–59. *Digital fibromas, metacarpal and metatarsal disorganization, and facial pigmentary dysplasia (digito-cutaneous dysplasia)*. (A) Delayed metacarpal ossification, generalized brachydactyly. Split terminal phalanx of second digit. (B) Delayed ossification of most metatarsals. (From C Bacino et al, Am J Med Genet 94:102, 2000.)

References [Digital fibromas, metacarpal and metatarsal disorganization, and facial pigmentary dysplasia (digito-cutaneous dysplasia, terminal osseous dysplasia, and pigmentary defects)]

1. Bacino CA et al: Terminal osseous dysplasia and pigmentary defects: Clinical characterization of a novel male lethal X-linked syndrome. Am J Med Genet 94:102–112, 2000.
2. Bloem JJ et al: Recurring digital fibroma of infancy. J Bone Joint Surg Br 56:746–751, 1974.
3. Breuning MH et al: New syndrome? Recurrent digital fibroma, focal dermal hypoplasia, and limb malformations. Am J Med Genet 94:91–101, 2000.
4. Dabney KW et al: Recurring digital fibrous tumor of childhood: Case report with long term follow-up and review of the literature. J Pediatr Orthop 6:612–617, 1986.
5. Horii E et al: A syndrome of digital fibromas, facial pigmentary dysplasia, and metacarpal and metatarsal disorganization. Am J Med Genet 80:1–5, 1998.
6. Zhang W et al: Terminal osseous dysplasia with pigmentary defects maps to human chromosome Xq27.3-Xqter. Am J Hum Genet 66:1461–1464, 2000.

Unusual facies, arachnodactyly, hypogenitalism, and failure to thrive

Harrod et al (2) reported two brothers with small size at birth, microcephaly, mental retardation, long thin face, unusually large anteverted pinnae, long thin nose, hypotelorism, small mouth, and pointed chin



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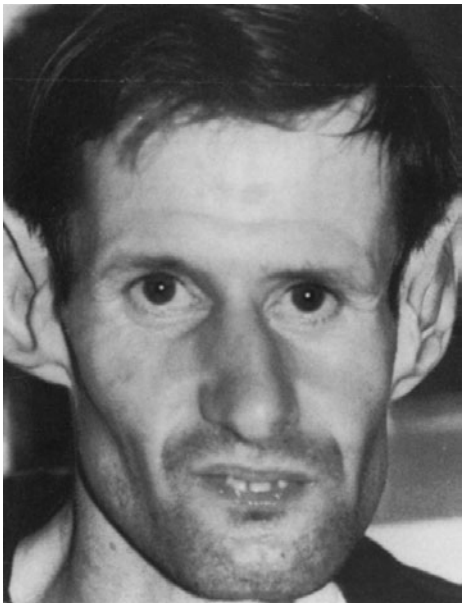


B

Fig. 25–60. *Unusual facies, arachnodactyly, hypogenitalism and failure to thrive*. (A) Child with microcephaly, mental retardation, long thin face, large ears. (B) Microcephaly, long thin face, unusually large anteverted pinnae, long thin nose, hypotelorism, small mouth, and pointed chin in male with severe mental retardation. Note resemblance to that of fragile X syndrome. [A from MJ Harrod et al, Birth Defects 13(3B):111, 1977. B from SB Jurenka and MI Van Allen, Am J Med Genet 61:168, 1996.]

(Fig. 25–60). The facies resembled that of typical *fragile X syndrome*. Both exhibited pectus, arachnodactyly, hypospadias, cryptorchidism, and aberrant subclavian artery. Malrotation of the bowel and pyloric stenosis as well as multiple microcysts of the renal cortex were found in one brother. An additional example of an affected male was reported by Jurenka and Van Allen (3). In addition, their patient had scoliosis, cataracts, megacolon, and varicose veins.

Inheritance may be X-linked recessive.

A similar phenotype was reported in *unusual facies, arachnodactyly, and mental retardation* by de Die-Smulders et al (1). One must exclude other X-linked mental retardation syndromes such as Allan–Harndon–Dudley syndrome (4) and others cited by Stevenson et al (5).

References (Unusual facies, arachnodactyly, hypogenitalism, and failure to thrive)

1. de Die-Smulders C et al: Characteristic facial dysmorphism, arachnodactyly and mental handicap in two unrelated girls. A distinct MCA/MR syndrome? Genet Couns 4:165–167, 1993.

2. Harrod MJ et al: A syndrome of craniofacial, digital, and genital anomalies. Birth Defects 13(3B):111–115, 1977.

3. Jurenka SB, Van Allen MI: Additional case of craniofacial and digital anomalies as reported by Harrod et al. Am J Med Genet 61:168–170, 1996.

4. Neri G et al: XLMR genes: Update 1994. Am J Med Genet 51:542–549, 1994.

5. Stevenson RE et al: X-Linked Mental Retardation. Oxford University Press, 2000.

Unusual facies, hypopituitarism, distal arthrogryposis, and mental retardation

Chitayat et al (1) described a brother and sister with unusual facial features, mental retardation, hypopituitarism, and distal arthrogryposis.

The head was somewhat square with a small anterior fontanel and ridging of the coronal, sagittal, and metopic sutures. There was frontal bossing, high narrow forehead, prominent supraorbital ridges, small upturned nose with depressed bridge, small mouth, prominent pinnae, and small mandible.

Seizures and severe developmental delay were noted in both sibs. Partial growth hormone deficiency was ascertained. Low serum gonadotropin and testosterone concentrations combined with microphallus, cryptorchidism, and small adrenals suggested hypopituitarism. Further findings indicated hypothalamic origin.

The distal arthrogryposis resembled the hand changes seen in *trisomy 18*.

Reference (Unusual facies, hypopituitarism, distal arthrogryposis, and mental retardation)

1. Chitayat D et al: Syndrome of mental retardation, facial anomalies, hypopituitarism, and distal arthrogryposis. Am J Med Genet 37:65–70, 1990.

Unusual facies and microcephaly with normal intelligence

Teebi et al (1) reported a large highly inbred kindred of Palestinian Arabs with eight affected.

All were microcephalic but with normal intelligence.

There were low receding forehead, prominent eyes, upslanting palpebral fissures, epicanthic folds, long straight nose with high nasal bridge, widely spaced teeth, and receding chin.

Inheritance is autosomal recessive.

Reference (Unusual facies and microcephaly with normal intelligence)

1. Teebi AS et al: Autosomal recessive microcephaly with normal intelligence. Am J Med Genet 26:355–359, 1987.

Unusual facies and partial alopecia

Feinstein et al (1) and Straussberg et al (2) reported a male patient and his female first cousin from a highly inbred family of Oriental Jews. They exhibited partial alopecia (sparse light scalp hair, eyebrows, eyelashes), smooth skin, and an unusual facies characterized by long philtrum, thick earlobes, and microcephaly. Both had a harsh deep voice and very similar personality (mischievous, hyperactive, affable, etc.).

Inheritance may be autosomal recessive.

References (Unusual facies and partial alopecia)

1. Feinstein A et al: Genetic disorders associated with severe alopecia in children: A report of two unusual cases and a review. J Craniofac Genet Dev Biol 7:301–310, 1987.

2. Straussberg R et al: A newly recognized alopecia syndrome associated with distinct personality traits. J Craniofac Genet Dev Biol 11:3–6, 1991.

Unusual facies, hooked clavicles, supernumerary ribs, widened metaphyses, and square-shaped vertebral bodies

Kozlowski et al (1) noted dizygotic twins with long narrow head, midface hypoplasia, hypertelorism, small upturned nose, downslanting palpebral fissures, small chin, large hands and feet, and long slender fingers.

Radiographic changes included large anterior fontanel, hypertelorism, 13 pairs of ribs, hypoplastic hooked clavicles, widened metaphyses, and square-shaped vertebral bodies.

Inheritance may be autosomal recessive.

Reference (Unusual facies, hooked clavicles, supernumerary ribs, widened metaphyses, and square-shaped vertebral bodies)

1. Kozlowski K et al: Unusual facies, hooked clavicles, 13 pairs of ribs, widened metaphyses, square shaped vertebral bodies and communicating hydrocephalus. Pediatr Radiol 22:328–330, 1992.

Unusual facies, lipodystrophy, and joint contractures (Werner-like syndrome)

Hoepffner et al (1) described a Werner syndrome-like disorder in three male siblings (Fig. 25–61). They had been described earlier by Mensing et al (2). Sclerodermatous alterations of the skin, sharp facies, and joint contractures were noted. One had insulin-resistant diabetes mellitus. Impaired function of three related peptide growth factors was found at the post-receptor level. The related peptides were insulin, insulinlike growth factor, and epidermal growth factor.

Various syndromes of insulin-resistant diabetes mellitus must be excluded: *leprechaunism*, severe insulin resistance A–E, *lipodystrophic diabetes*, and Rabson–Mendenhall syndrome. *Werner syndrome* was excluded because the patients' fibroblasts had normal life and redoubling spans. We believe the sibs have *mandibuloacral dysplasia*.

References [Unusual facies, lipodystrophy, and joint contractures (Werner-like syndrome)]

1. Hoepffner HJ et al: A new familial syndrome with impaired function of three related peptide growth factors. Hum Genet 83:209–216, 1989.

2. Mensing H et al: Werner-Syndrom-artige Erkrankung bei drei Brüdern. Hautarzt 33:542–547, 1982.

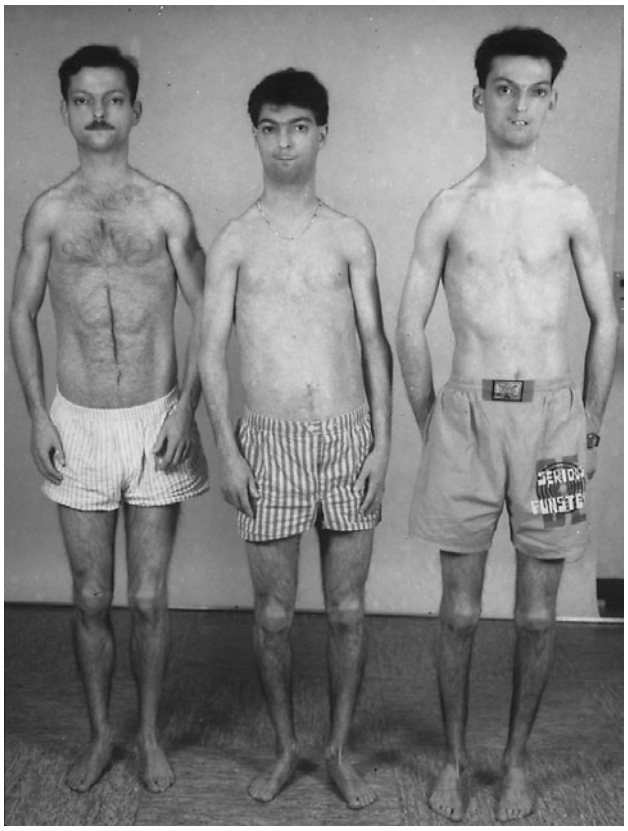


Fig. 25–61. *Unusual facies, lipodystrophy, and joint contractures (Werner-like syndrome)*. Note small mandible, long neck, sloping shoulders, genu varum. We suspect that these brothers have *mandibuloacral dysplasia*. (From HJ Hoepffner et al, Hum Genet 83:209, 1989.)

Unusual facies, lymphedema, intestinal lymphangiectasia, and mental retardation (Hennekam syndrome)

Hennekam et al (5), in 1988, described three sibs and their cousin with mental retardation, lymphedematous facies, marked edema of the lower extremities, and gastrointestinal lymphangiectasia. Gabrielli et al (4) confirmed the syndrome. About 25 examples have since been reported (1,2,13).

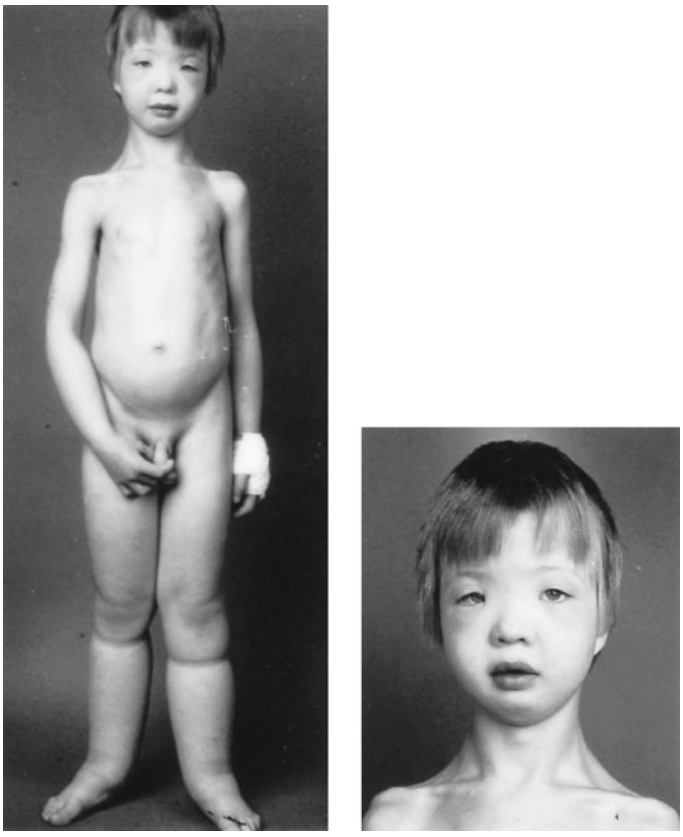
Inheritance is autosomal recessive, there being multiple sibs (4) and parental consanguinity in 25% (2,4). The gene is probably involved in lymphangiogenesis.

The facies appears Oriental due to periorbital edema. Hypertelorism, frontal upsweep, heavy eyebrows, epicanthic folds, and depressed nasal bridge give the face a flat appearance. Some had dysmorphic pinnae, microstomia, narrow palate, retrognathia, and unusual teeth: oligodontia and incisors with conical crown form (Fig. 25–62).

Lymphedema, present before birth, causes the characteristic facies. After birth, the swelling progresses and causes asymmetric massive enlargement of the lower extremities and genitalia. Lymph may ooze from the swollen area and become infected, resulting in erysipelas. Intestinal lymphangiectasia of the small bowel was demonstrated in all affected, causing protein-losing enteropathy and attendant complications, such as mild growth retardation (1,5).

Talipes equinovarus and cryptorchidism were noted as well as mild cutaneous syndactyly of fingers 2–5 (4). The distal thumbs were hypoplastic. MRI showed focal parietal pachygyria (4). Bone age may be retarded (13). Coronal craniosynostosis has been reported as well as ectopic kidney (2). Other findings include rectal prolapse and VSD (1) and ectopic pelvic kidney (2). Death rarely occurs during the first year of life (11).

Mental retardation was mild to moderate in nearly all affected. Most have exhibited seizures. Sensorineural and conductive hearing loss have been described (1).



A B

Fig. 25–62. *Unusual facies, lymphedema, intestinal lymphangiectasia, and mental retardation*. (A) This boy shows congenital generalized edema especially of the lower extremities. (B) Hypertelorism, periorbital edema, epicanthal folds, and depressed nasal bridge impart a flat appearance to the face. (Courtesy of RCM Hennekam, Amsterdam, The Netherlands.)

There is some overlap with the autosomal recessive disorder described by Mücke et al (8). Unrelated is the syndrome in two brothers reported by Irons et al (7). This involved lymphedema of the lower limbs, atrial septal defect, and a somewhat unusual facies (upslanting palpebral fissures, prominent forehead, flat nasal bridge). An affected sister had severe hydrops fetalis, omphalocele, ASD, round face, wide nasal bridge, and horizontal chin cleft. The two boys had speech delay.

Among the other cases of congenital lymphedema, there are Nonne–Milroy syndrome, *Turner syndrome, Noonan syndrome*, distichiasis and lymphedema (9,10), microcephaly and lymphedema (3), lymphedema of legs and conjunctivae (12), and cerebellar hypoplasia and lymphedema (6). Distichiasis-lymphedema-cleft palate maps to 16q24.3 (1a). Mutations in *FOXC2(MFH-1)*, a forkhead family transcription factor, are responsible for the condition (3a).

References [Unusual facies, lymphedema, intestinal lymphangiectasia, and mental retardation (Hennekam syndrome)]

1. Angle B, Hersh JH: Expansion of the phenotype in Hennekam syndrome. Am J Med Genet 71:211–214, 1997.

1a. Bahuau N et al: Co-localization of distichiasis-lymphedema-cleft palate (DLC) with distichiasis-lymphedema syndrome in 16q24.3. Am J Hum Genet 67:Abst 600, 2000.

2. Cormier-Daire V et al: Craniosynostosis and kidney malformation in a case of Hennekam syndrome. Am J Med Genet 57:66–68, 1994.

3. Crowe CA, Dickerman LH: A genetic association between microcephaly and lymphedema. Am J Med Genet 24:131–135, 1986.

3a. Fang J et al: Mutations in FOX2C(MFH-1), a forkhead family transciption factor, are responsible for the hereditary lymphedema-distichiasis syndrome. Am J Hum Genet 67:1382–1388, 2000.

4. Gabrielli O et al: Intestinal lymphangiectasia, lymphedema, mental retardation, and typical face. Confirmation of the Hennekam syndrome. Am J Med Genet 40:244–247, 1991.

5. Hennekam RCM et al: Autosomal recessive intestinal lymphangiectasia and lymphedema with facial anomalies and mental retardation. Am J Med Genet 34:593–600, 1989.

6. Hourihane J et al: A sibship with a neuronal migration defect, cerebellar hypoplasia, and congenital lymphedema. Neuropediatrics 24:43–46, 1993.

7. Irons MB et al: Possible new autosomal recessive syndrome of lymphedema, hydroceles, atrial septal defect, and characteristic facial changes. Am J Med Genet 66:69–71, 1996.

8. Mücke J et al: Early onset lymphoedema, recessive form—a new form of genetic lymphoedema syndrome. Eur J Pediatr 145:195–198, 1986.

9. Robinow M et al: Distichiasis-lymphedema. Am J Dis Child 119:343–347, 1970.

10. Rosbotham JL et al: Distichiasis-lymphoedema. Clinical features, venous function and lymphoscintigraphy. Br J Dermatol 142:148–152, 2000.

11. Scarcella A et al: Early death in two sisters with Hennekam syndrome. Am J Med Genet 93:181–183, 2000.

12. Tabbara KF, Baghdassarian SA: Chronic hereditary lymphedema of the legs with congenital conjunctival lymphedema. Am J Ophthalmol 73:531–532, 1972.

13. Yasunaga M et al: Protein-losing gastroenteropathy with facial anomaly and growth retardation: A mild case of Hennekam syndrome. Am J Med Genet 45:477–480, 1993.

Unusual facies, ectodermal dysplasia, and polycystic brain (dilated Virchow-Robin spaces) (Sener syndrome)

Sener (2) reported a 9-year-old girl with progressive learning difficulties. Lynch et al (1) described two additional examples.

The facies somewhat resembled that of *Noonan syndrome* (Fig. 25–63A). The maxilla was prominent. A broad nasal bridge, hypertelorism, and low hairline somewhat resemble mild *frontonasal malformation*. Dystrophic nails, hypodontia, and multiple buccal frenula were evident. Ophthalmologic examination revealed irregular retinal pigment epithelium and prominent excavation of the optic discs. Inguinal hernia was also documented.

CT and MRI studies of the brain showed numerous small hypodense lesions scattered throughout the cerebral hemispheres, predominantly within the white matter (Fig. 25–63B). The authors suggested that they may have been derived from the normal perivascular spaces of Virchow–Robin.

References [Unusual facies, ectodermal dysplasia, and polycystic brain (dilated Virchow-Robin spaces) (Sener syndrome)]

1. Lynch SA et al: Two further cases of Sener syndrome: Frontonasal dysplasia and dilated Virchow-Robin spaces. J Med Genet 37:466–470, 2000.

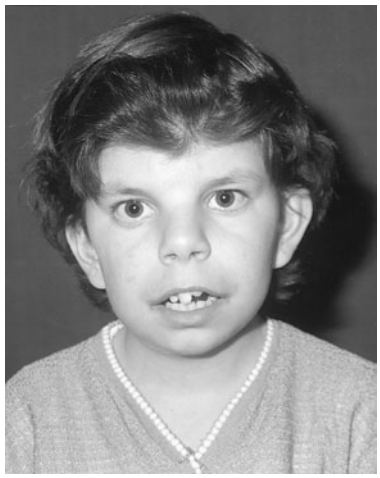
2. Sener RN: Polycystic brain (cerebrum polycystica vera) associated with ectodermal dysplasia: A new neurocutaneous syndrome. Pediatr Radiol 24: 116–118, 1994.

Unusual facies, mental retardation, and intrauterine and postnatal growth retardation (Pitt-Rogers-Danks syndrome, microdeletion 4p16)

Pitt et al (10), in 1984, reported two sibs and two isolated children with intrauterine and postnatal growth retardation and unusual facies. An additional nine cases were reported by a number of authors (1,2,4,6–9,12). In 1996, the syndrome was found to be due to a microdeletion of 4p16 by FISH technique (2,5,6).

Microcephaly is a constant feature as are intrauterine growth retardation, mental retardation (IQ 35–49), and short stature. About 50% have seizures and hyperactivity.

The forehead is high, and usually there is moderate telecanthus. The eyes appear prominent due to maxillary hypoplasia. The nose is usually beaked with a prominent glabella. The columella is low, the philtrum



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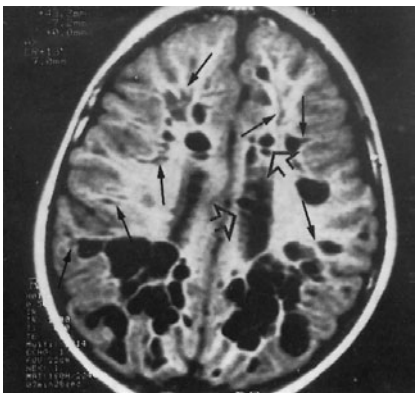

B

Fig. 25–63. *Unusual facies, ectodermal dysplasia, and polycystic brain (dilated Virchow-Robin spaces) (Sener syndrome).* (A) Facies somewhat resembling that of Noonan syndrome. (B) Numerous small hypodense lesions scattered throughout cerebral hemisphere. Arrows point to larger Virchow-Robin spaces. (From RN Sener, Pediatr Radiol 24:116, 1994.)

short, and the mouth always wide. The pinnae are simplified and often outstanding. The corners of the mouth are downturned (Fig. 25–64).

The joints are hyperextensible. Extra palmar or digital creases are very common. Some patients have had a wide space between the hallux and the second toe (6).

There is some resemblance to del(4p) (Wolf–Hirschhorn) syndrome (2,5,6) and overlapping deletions have been demonstrated (11). Pitt–Rogers–Danks syndrome lies just outside the critical region for del(4p) syndrome. It should be pointed out that not all patients with a Pitt–Rogers–Danks phenotype exhibit the microdeletion (4,5,12). In one case, dup(11q) was noted (3).

Partington et al (9) noted overgrowth and mental retardation in duplication of the 4p16.3 area. There were macrocephaly, bushy eyebrows and synophrys, prominent supraorbital ridges, and short nose and philtrum. Height was increased and the hands were enlarged.

References [Unusual facies, mental retardation, and intrauterine and postnatal growth retardation (Pitt-Rogers-Danks syndrome, microdeletion 4p16)]

1. Battaglia A, Carey JC: Wolf-Hirschhorn syndrome and Pitt-Rogers-Danks syndrome. Am J Med Genet 75:541, 1998.

2. Clemens M et al: Pitt-Rogers-Danks syndrome. The result of a 4p microdeletion. Am J Med Genet 66:95–100, 1996.

3. de Die-Smulders CEM, Engelen JJM: 11q duplication in a patient with Pitt-Rogers-Danks phenotype. Am J Med Genet 66:116–117, 1996.

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6. Lindeman-Kusse MC et al: Cytogenetic abnormalities in two new patients with Pitt-Rogers-Danks phenotype. Am J Med Genet 66:104–112, 1996.

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8. Oorthuys JWE, Bleeker-Wagemakers EM: A girl with the Pitt-Rogers-Danks syndrome. Am J Med Genet 32:140–141, 1989.

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10. Pitt DB et al: Mental retardation, unusual facies and intrauterine growth retardation—a new recessive syndrome? Am J Med Genet 19:307–313, 1984.

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12. Zollino M et al: Pitt-Rogers-Danks syndrome to Wolf-Hirschhorn syndrome and back? Am J Med Genet 66:113–115, 1996.

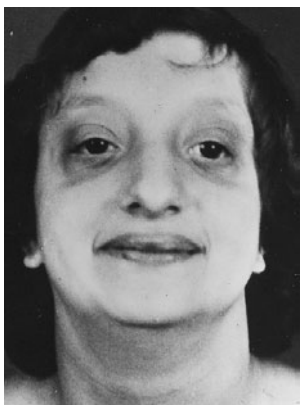
Unusual facies, macrocephaly, aplasia of corpus callosum, seizures, hypertrichosis, claw hands, and overlapping fingers

Müller et al (1) described female and male sibs with a distinct syndrome of macrocephaly.

Both sibs exhibited macrocephaly, aplasia of the corpus callosum, septum pellucidum cyst, cavum vergae, hypertrichosis with synophrys, dysplastic pinnae, overlapping digits, transverse palmar creases, widespaced nipples, lack of sucking, swallowing, and vomiting reflexes, hypertonia of limbs, and tonic seizures.

Inheritance is probably autosomal recessive.

Various syndromes such as *Toriello–Carey, Lin–Gettig*, and *FG* were excluded.



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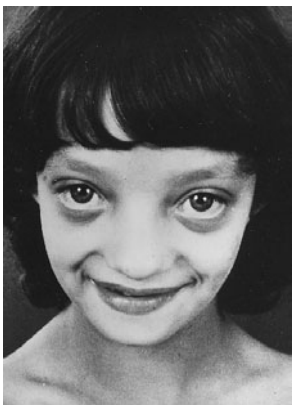

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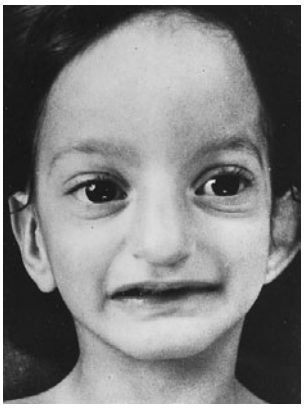

C

Fig. 25–64. *Unusual facies, mental retardation, and intrauterine growth retardation.* (A–C) Two sibs and isolated child with reduced head circumference, beaked nose, wide mouth, short upper lip with flat philtrum, and prominent eyes. Intelligence quotients ranged from 35 to 49. (From DB Pitt et al, Am J Med Genet 19:307, 1984.)

Reference (Unusual facies, macrocephaly, aplasia of corpus callosum, seizures, hypertrichosis, claw hands, and overlapping fingers)

1. Müller FM et al: Cerebral malformation, seizures, hypertrichosis, distinct face, claw hands, and overlapping fingers in sibs of both sexes. Am J Med Genet 47:698–701, 1993.

Unusual facies, microcephaly, abnormal gyri, contractural arachnodactyly, and glomerulopathy (Galloway-Mowat syndrome)

Galloway and Mowat (2), in 1968, described a syndrome in sibs which consisted of microcephaly, developmental delay, abnormal gyri, glomerulopathy, and contractural arachnodactyly. Other examples have been noted (1,3–5).

Receding forehead, large pinnae, and micrognathia are striking.

Onset of proteinuria often occurs in the first 3 months of life. Various renal changes lead to the development of nephrotic syndrome with marked proteinuria and microscopic hematuria.

References [Unusual facies, microcephaly, abnormal gyri, contractural arachnodactyly, and glomerulopathy (Galloway-Mowat syndrome)]

1. Cooperstone BG et al: Galloway-Mowat syndrome of abnormal gyral patterns and glomerulopathy. Am J Med Genet 47:250–254, 1993.

2. Galloway WH, Mowat AP: Congenital microcephaly with hiatus hernia and nephrotic syndrome in two sibs. J Med Genet 5:319–321, 1968.

3. Hou J-W, Wang TR: Galloway-Mowat syndrome in Taiwan. Am J Med Genet 58:245–248, 1995.

4. Roos RAC et al: Congenital microcephaly, infantile spasms, psychomotor retardation and nephrotic syndrome in two sibs. Eur J Pediatr 146:532–536, 1987.

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Unusual facies, microcephaly, and large ears (Lambotte syndrome)

Verloes et al (2) described four Moroccan Arabic sibs (one had been described earlier in abstract form by Lambotte et al). The sublethal condition included mental retardation, intrauterine growth retardation, hypotonia, microcephaly, hypertelorism, large floppy pinnae, hooked nose, flat face, narrow mouth, small chin, severe neurologic impairment, delayed bone age, wide anterior fontanel, and 13 ribs. Herens et al (1) noted that a subtle translocation which results in 2q trisomy/4p monosomy is responsible for the phenotype.

References [Unusual facies, microcephaly, and large ears (Lambotte syndrome)]

1. Herens C et al: Private multiple congenital anomaly syndromes may result from unbalanced subtle translocations: t(2q:4p) explains the Lambotte syndrome. Am J Med Genet 73:127–131, 1997.

2. Verloes A et al: Lambotte syndrome: Microcephaly, holoprosencephaly, intrauterine growth retardation, facial anomalies and early lethality—a new sublethal multiple congenital anomaly/mental retardation syndrome in four sibs. Am J Med Genet 37:119–123, 1990.

Multicentric osteolysis with arthritis, short stature, and unusual facies

There are several disorders of multicentric osteolysis which have recessive inheritance. The syndromes of Torg, Thieffry-Kohler, Winchester, and François principally affect the carpal, tarsal, and interphalangeal joints. There is progressive bone loss. The crippling arthritic deformities mimic severe juvenile rheumatoid arthritis. Al-Mayouf et al (2) and Al Aqeel et al (1) collectively described twelve patients from seven unrelated Saudi Arabian families. Similarly affected patients have been reported by others (3–7).

All patients had nodulosis and distal arthropathy. Ten patients presented with deformed hands, and approximately half exhibited pain in the hands.

Radiographically, osteopenia and undertubulation of bones affecting the distal areas more than the proximal areas and the upper limbs more severely than the lower limbs were apparent in all patients. Osteolysis was also seen in carpal and tarsal bones. Other common findings were sclerotic cranial sutures, brachycephaly, and broad medial clavicles. Stature is short. Involvement of the extremities begins in the first few months of life and eventuates in a crippling ankylosis.

Facial changes include high forehead, proptosis, narrow high nasal bridge, flat nasofrontal angle, short nose with bulbous tip, flat philtrum, and micrognathia.

Large painful fibrocollagenous palmar and plantar pads are evident as well as mild hirsutism of the body.

Normal intelligence and normal renal function mark this form of multicentric osteolysis. A dominantly-inherited form with nephropathy has been described (8).

References (Multicentric osteolysis with arthritis, short stature, and unusual facies)

1. Al Aqeel A et al: Inherited multicentric osteolysis with arthritis: Variant resembling Torg syndrome in a Saudi family. Am J Med Genet 93:11–18, 2000.

2. Al-Mayouf SM et al: Two forms of idiopathic osteolysis: Nodulosis [arthropathy and osteolysis (NAO syndrome)]. Am J Med Genet 93:5–10, 2000.

3. Carnevale A et al: Idiopathic multicentric osteolysis with facial anomalies and nephropathy. Am J Med Genet 26:877–886, 1987.

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5. Petit P, Fryns J-P: Distal osteolysis, short stature, mental retardation and characteristic facial appearance: Delineation of an autosomal recessive subtype of essential osteolysis. Am J Med Genet 25:537–541, 1986.

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8. Urlus M et al: Carpo-tarsal osteolysis: Case report and review of the literature. Genet Couns 4:25–36, 1993.

Unusual facies, mental retardation, early balding, patellar subluxation, acromicria, and hypogonadism

Scholte et al (1) noted an isolated male with unusual facies, mental retardation, hypogonadism, small hands, and subluxation of the kneecaps.

His facies was characterized by a narrow cranium, pronounced frontal balding, pale blue irides, upslanting palpebral fissures, thin nose with bulbous tip, and short philtrum with thin upper vermilion. The frontal balding began at puberty.

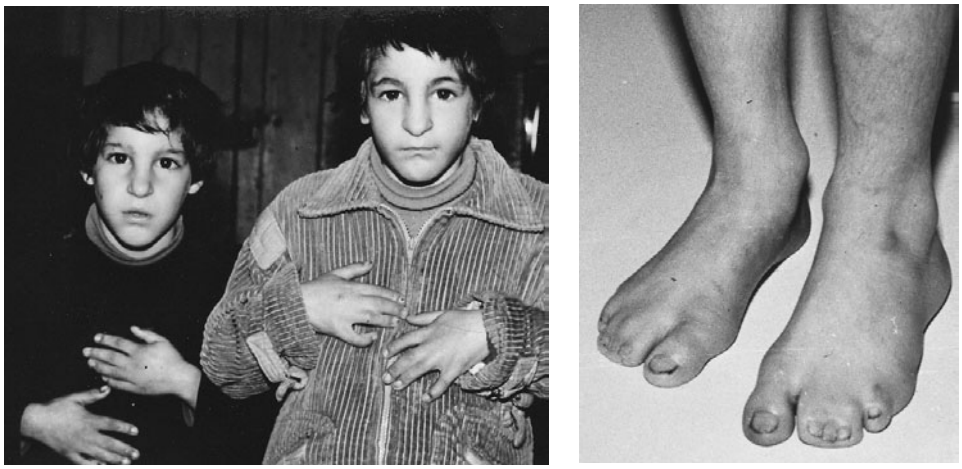
The hands and feet are small. In addition, there is kypholordosis. Flexion of the metacarpophalangeal joints is limited. The proximal interphalangeal joints are hyperextensible. The knee caps frequently subluxate. Pes cavus is evident.

Intelligence is severely retarded. Speech was never attained.

The penis and testes are small.

Reference (Unusual facies, mental retardation, early balding, patellar subluxation, acromicria, and hypogonadism)

1. Scholte FA et al: Unknown syndrome: Mental retardation with dysmorphic features, early balding, patella luxations, acromicria and hypogonadism. J Med Genet 28:140–142, 1991.



A B

Fig. 25–65. *Unusual facies, microcephaly, syndactyly, and growth and mental retardation*. (A) In addition to microcephaly and moderate mental retardation, the sibs have similar facies. Note broad nasal root, lack of alar flare, and syndactyly. (B) Both brothers had syndactyly of fingers 3–4 and toes 2–3–4. (From G Filippi, Am J Med Genet 22:821, 1985.)

Unusual facies, microcephaly, syndactyly, and growth and mental retardation (Filippi syndrome, craniodigital syndrome of Filippi)

Filippi (1), in 1985, reported two male and one female sib with unusual facies, retarded somatic development, severe mental retardation with inability to speak, and syndactyly of the fingers and toes. Additional examples have been described (3,5,8,10). Possible examples are those of Fryer (2) and Orrico and Hayek (6). All had low birthweight. Nearly all have retarded stature (9).

The facies was characterized by microcephaly, high forehead, prominent broad nasal root and diminished alar flare, long philtrum, and thin vermilion. Optic atrophy has also been noted (10) (Fig. 25–65A)

Bilateral syndactyly of fingers 2–3 or 3–4 and toes 2–4 or 2–3, 4–5 is a constant feature. There was clinodactyly of the fifth fingers, single palmar crease, and long great toes (Fig. 25–65B).

Cryptorchidism was a constant feature. Other features have included delayed bone age (1,8), cleft palate (8), and dislocated elbow (3).

Inheritance is clearly autosomal recessive (3,5,10).

Differential diagnosis would include *craniodigital syndrome, blepharo-naso-facial syndrome, Chitayat syndrome* (normal mental development), Kelly syndrome (microcephaly, normal birthweight, digital anomalies, mental retardation) (4), Zerres syndrome (postnatal short stature, microcephaly, dysmorphic face, syndactyly of hands and feet, and mental retardation (11), and Pfeiffer–Kapferer syndrome (synostosis of metacarpals and metatarsals 4–5, sensorineural hearing loss, hypospadias, and mental retardation) (7). Woods et al (10) reported three sibs, offspring of consanguineous Pakistani parents. Growth and head circumference were grossly retarded. Other findings included brachyclinodactyly of fifth toes, 3–4 syndactyly of fingers, single palmar creases, restricted elbow extension, mild spastic paraplegia, and dystonic movements.

References [Unusual facies, microcephaly, syndactyly, and growth and mental retardation (Filippi syndrome, craniodigital syndrome of Filippi)]

1. Filippi G: Unusual facial appearance, microcephaly, growth and mental retardation, and syndactyly. Am J Med Genet 22:821–824, 1985.

2. Fryer A: Filippi syndrome with mild learning difficulties. Clin Dysmorphol 5:35–39, 1996.

3. Héron D et al: Filippi syndrome: A new case with skeletal abnormalities. J Med Genet 32:659–661, 1995.

4. Kelly TE et al: Microcephaly and digital anomalies. A newly recognized syndrome of recessively inherited mental retardation. Am J Med Genet 45:353–355, 1993.

5. Meinecke P: Short stature, microcephaly, characteristic face, syndactyly, and mental retardation. The Filippi syndrome. Report on second family. Genet Couns 4:147–151, 1993.

6. Orrico A, Hayek G: An additional case of craniodigital syndrome: Variable expression of the Filippi syndrome? Clin Genet 52:177–179, 1997.

7. Pfeiffer RA, Kapferer L: Sensorineural deafness, hypospadias, and synostosis of metacarpals and metatarsals 4 and 5: A previously apparently undescribed MCA/MR syndrome. Am J Med Genet 31:5–8, 1988.

8. Toriello HV, Higgins JV: Craniodigital syndromes: Report of a child with Filippi syndrome and discussion of differential diagnosis. Am J Med Genet 55: 200–204, 1995.

9. Williams MS et al: Filippi syndrome: Report of three additional cases. Am J Med Genet 87:128–133, 1999.

10. Woods CG et al: Three sibs with phalangeal anomalies, microcephaly, severe mental retardation, and neurological abnormalities. J Med Genet 29:500–502, 1992.

11. Zerres K et al: Postnatal short stature, microcephaly, severe syndactyly of hands and feet, dysmorphic face and mental retardation. J Med Genet 29:269–271, 1992.

Unusual facies, short stature, enamel hypoplasia, stiff joints, and high-pitched voice

Pfeiffer et al (1) reported male and female sibs with short stature, unusual facies, lack of enamel, stiff joints, and high- pitched voice. Gait was stiff and movements slow, characterized as "puppetlike." Intelligence was normal.

The facies was characterized by narrow palpebral fissures, epicanthic folds, and cup-shaped pinnae.

Inheritance is probably autosomal recessive.

Reference (Unusual facies, short stature, enamel hypoplasia, stiff joints, and high-pitched voice)

1. Pfeiffer RA et al: A syndrome of short stature, amimic facies, enamel hypoplasia, slowly progressive stiffness of the joints, and high-pitched voice in two siblings. J Pediatr 91:955–957, 1977.

Unusual facies, short webbed neck, mental retardation, and short stature

There are a number of autosomal recessive Noonan-like syndromes which have various degrees of overlap which we cannot easily separate into distinct conditions. Neuhauser and Opitz (4), in 1975, described three sibs with dysmorphic facies, mental retardation, and congenital heart anomalies that they termed McDonough syndrome. Garcia-Segredo et al (2), in 1984, added two cases. Siblings described by Maximilian et al (3) also exhibited a Noonan-like phenotype.

Al-Gazali et al (1), in 1996, noted four sibs with consanguineous parents who, in addition, had webbed neck and somewhat eczematous skin and dystrophic nail changes. The face was long and the forehead high with hypoplastic supraorbital ridges. The eyebrows were highly arched

with downslanting palpebral fissures. The nose was large. The neck was short and webbed, the chest resembling that of *Noonan syndrome* with pectus excavatum or carinatum and widely spaced nipples. Umbilical hernia was commonly noted. The abdomen was distended. Congenital heart anomalies (ASD, VSD) were found in two of the four children.

References (Unusual facies, short webbed neck, mental retardation, and short stature)

1. Al-Gazali LI et al: A syndrome of short stature, mental retardation, facial dysmorphism, short webbed neck, skin changes and congenital heart disease. Clin Dysmorphol 5:321–327, 1996.
2. Garcia-Sagredo JM et al: Mentally retarded siblings with congenital heart defect, peculiar facies, and cryptorchidism in a male: Possible McDonough syndrome with coincidental (X;20) translocation. Clin Genet 26:117–126, 1984.
3. Maximilian C et al: A syndrome of mental retardation, short stature, craniofacial anomalies with palpebral ptosis and pulmonary stenosis in three siblings with normal parents. Genet Couns 3:115–118, 1992.
4. Neuhauser G, Opitz JM: Multiple congenital anomalies/mental retardation syndrome as variant familial developmental pattern: Differential diagnosis and descriptions of the McDonough syndrome. Z Kinderheilkd 120:231–242, 1975.

Unusual facies, arachnodactyly, and mental retardation

In 1993, de Die-Smulders et al (1) reported two unrelated females with mental retardation, absent speech, microcephaly, long face with flat upper jaw, hypertelorism, divergent strabismus, thin upper lip, and hyperextensible finger joints (Fig. 25–66). Another example was reported by Van Buggenhout et al (3). A similar phenotype was observed in *unusual facies, arachnodactyly, hypogenitalism, and failure to thrive* by Harrod et al (2).

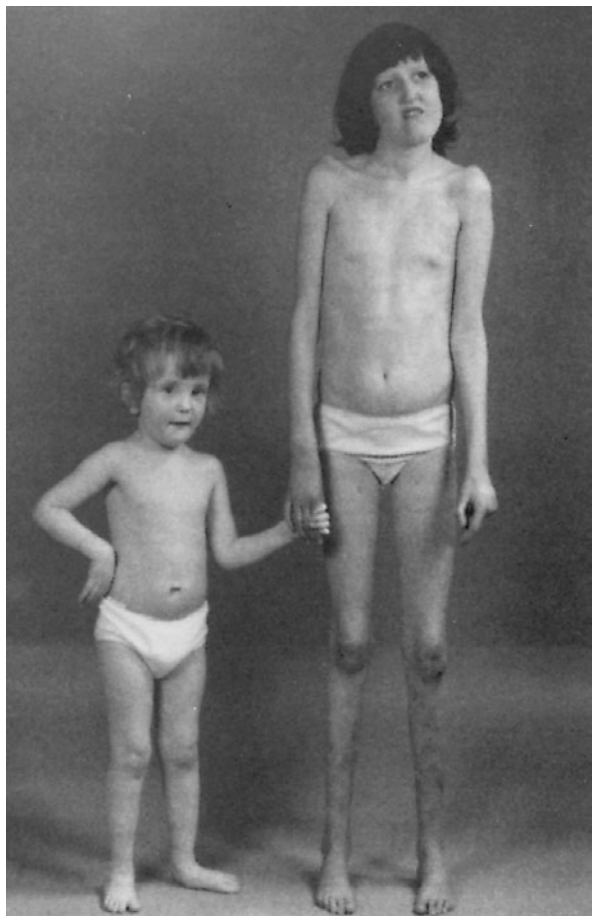


Fig. 25–66. *Unusual facies, arachnodactyly, and mental retardation.* Unrelated females with absent speech, mental retardation, microcephaly, long face with flat upper jaw, thin upper lip, and hyperextensible finger joints. [From C de Die-Smulders et al, Genet Couns 4(2): 165, 1993.]

References (Unusual facies, arachnodactyly, and mental retardation)

1. de Die-Smulders C et al: Characteristic facial dysmorphism, arachnodactyly and mental handicap in two unrelated girls. A distinct MCA/MR syndrome? Genet Couns 4:165–167, 1993.
2. Harrod MJ et al: A syndrome of craniofacial, digital, and genital anomalies. Birth Defects 13(3B):111–115, 1977.
3. Van Buggenhout GJCM et al: Characteristic facial dysmorphism, arachnodactyly and mental retardation: Another case. Genet Couns 6:61–63, 1995.

Unusual facies, preauricular pits, fifth finger clinodactyly, and tetralogy of Fallot (Jones-Waldman syndrome)

Jones and Waldman (1) noted six related individuals.

All had low birthweight but normal postnatal growth.

Frequent facial features included broad forehead, proptosis in infancy, prominent nasal tip, and preauricular pits.

The hands had short or clinodactylous fifth fingers and thenar crease hypoplasia. Two of the four males had cryptorchidism. Three had tetralogy of Fallot.

Schuler et al (2) described a male child with tetralogy of Fallot, somewhat prominent eyes, wide nasal bridge, thin vermilion of upper lip, and cleft palate. We are not convinced that this child had the same condition as that described by Jones and Waldman (1).

References [Unusual facies, preauricular pits, fifth finger clinodactyly, and tetralogy of Fallot (Jones-Waldman syndrome)]

1. Jones MC, Waldman D: An autosomal dominant syndrome of characteristic facial appearance, preauricular pits, fifth finger clinodactyly, and tetralogy of Fallot. Am J Med Genet 22:135–141, 1985.
2. Schuler L et al: Jones-Waldman syndrome: Another report? Am J Med Genet 51:83, 1994.

Unusual facies, uncombable hair, mental retardation, postaxial polydactyly, phalangeal hypoplasia, and 2–3 toe syndactyly

Kozlowski and Krajewski (1), in 1997, described a syndrome comprising unusual facies, uncombable hair, mental retardation, postaxial manual polydactyly, phalangeal hypoplasia, and 2–3 toe syndactyly.

Height, weight, and head circumference were all below the third centile. The facies was characterized by frontal bossing, hypotelorism, narrow mildly upslanting palpebral fissures, prominent nasal root with narrow bridge, thin lips, micrognathia, outstanding pinnae with prominent anthelix and poorly folded helix, underdeveloped lobule and antitragus. Conductive hearing loss was noted. I.Q. was between 60 and 70. The hair was uncombable. The neck exhibited decreased mobility. There was pectus carinatum, widely spaced nipples, inguinal hernia, dysplastic scrotum, cryptorchidism, and small bowed penis.

The hands were small with short fingers and clinodactyly V. Talipes equinovarus and syndactyly of toes 2–3 were noted. The hallux was large and broad. Radiographically, the phalanges were short, especially the middle phalanges of the hand. The ribs were thin, curved in the posterior part, and obliquely positioned. The sternal ends of the clavicles were widened. The proximal femoral epiphyses were large, the knee epiphyses flattened, and the distal tibia epiphyses wedge shaped. A similarly affected brother died at 4 months. Inheritance is presumably X-linked or autosomal recessive.

Reference (Unusual facies, uncombable hair, mental retardation, postaxial polydactyly, phalangeal hypoplasia, and 2–3 toe syndactyly)

1. Kozlowski K, Krajewska M: Mental retardation, postaxial polydactyly, phalangeal hypoplasia, 2–3 toe syndactyly, unusual face, uncombable hair: New syndrome? Am J Med Genet 68:142–146, 1997.

Unusual facies, trigonobrachycephaly, and hand and foot anomalies

Male and female Kuwaiti sibs with trigonobrachycephaly, narrow forehead, upslanting palpebral fissures, thin eyebrows, long eyelashes, broad nasal root, bulbous nose with mildly bifid tip, thick nasal septum, short philtrum, macrostomia, thin vermilion, and small chin were noted by Teebi et al (1). One had cleft palate.

Other findings included bulbous fingertips, fifth finger clinodactyly, short stature, hypotonia, pectus excavatum, and severe psychomotor retardation.

Inheritance is autosomal recessive.

Reference (Unusual facies, trigonobrachycephaly, and hand and foot anomalies)

1. Teebi AS: Trigonobrachycephaly, bulbous bifid nose, macrostomia, acral anomalies, and hypotonia in sibs: New syndrome. Am J Med Genet 38:529–531, 1991.

Unusual facies, osteochondrodysplasia, and short stature, Brussels type

Mievis et al (1) reported two brothers with extreme intrauterine and postnatal growth retardation, short stature, osteochondrodysplasia, and unusual facies.

The facies is characterized by a relatively large head, small triangular face, frontal bossing, broad forehead with prominent veins, deep-set eyes, narrow palpebral fissures, poorly formed philtrum, wide mouth with thin vermilion, and microretrognathia.

Radiographic changes included delayed bone age, narrow thorax, short iliac bones, unusually-shaped humeral and femoral metaphyses, short broad metacarpals and phalanges, and short fourth metacarpals.

X-linked or autosomal recessive inheritance is possible.

Various short stature disorders including *Silver-Russell syndrome, 3-M syndrome*, and *mulibrey nanism* must be excluded.

Reference (Unusual facies, osteochondrodysplasia, and short stature, Brussels type)

1. Mievis C et al: A new familial short stature syndrome: Brussels type. Clin Dysmorphol 5:9–16, 1996.

Unusual facies, multiple pterygia, hypogonadism, and somatic and mental retardation (Haspeslagh syndrome)

Haspeslagh et al (2) described severe mental retardation, postnatal growth retardation, multiple pterygia with distal muscle wasting, hypogonadism, and unusual facies. Other examples or possible examples are those of Schrander-Stumpel et al (4) and van Bever and Hennekam (5).

De Vriendt et al (1) noted that the syndrome results from an unbalanced reciprocal 6q/9p translocation.

The facies is characterized by trigonocephaly, frontal bossing, hypertelorism, dysmorphic pinnae, and microretrognathia. Two patients had cleft palate (1–3).

Pterygia of the neck and other pterygia, arachnodactyly, camptodactyly, long toes, and scoliosis are other musculoskeletal problems.

References [Unusual facies, multiple pterygia, hypogonadism, and somatic and mental retardation (Haspeslagh syndrome)]

1. De Vriendt K et al: The Haspeslagh syndrome is caused by an unbalanced reciprocal 6q/9p translocation. Clin Genet 57:83–85, 2000.
2. Haspeslagh M et al: Mental retardation with pterygia, shortness and distinct facial appearance: A new MCA/MR syndrome. Clin Genet 28:550–555, 1985.
3. Schrander-Stumpel C: Clinical follow up of a girl with "mental retardation with pterygia, shortness, and distinct facial appearance" (Haspeslagh syndrome). Clin Genet 47:332–334, 1995.
4. Schrander-Stumpel C et al: Mental retardation with pterygia, shortness and distinct facial appearance. Confirmation of a new MCA/MR syndrome. Clin Genet 34:279–281, 1988.
5. van Bever Y, Hennekam RCM: Haspeslagh syndrome without severe retardation and pterygia? Clin Genet 47:263–266, 1995.

Floating-Harbor syndrome (unusual facies, short stature, delayed bone age, and hypoplastic penis)

The name *Floating-Harbor syndrome* is derived from one patient seen at Boston Floating Hospital, and another being reported from Harbor General Hospital.

Pelletier and Feingold (14) and Leisti et al (8,9) independently described males with strikingly similar phenotype. Approximately 20 cases have been reported (1–9,11–15,17). We cannot accept as an example the patient noted by Zabransky (17). Affected sibs have been reported (4).

There is no sex or racial predilection. D Donnai (personal communication, 1989) informed us that paternal age is advanced, suggesting autosomal dominant inheritance. In one family, a mother was stated to be affected as well as her child (7), but we remain skeptical. There has been only one instance of parental consanguinity (15).

Birthweight in 50% and birth length in 70% are below the third centile, and stature in childhood is lower than −4 SD in 95% (5,7). Adult height is 130–140 cm (15). Head circumference is normal.

The face is triangular in about 50%. The eyes, which are prominent in infancy, become deep-set. The nose is outstanding or bulbous with a broad prominent bridge and wide columella. The eyelashes are long and the pinnae posteriorly angulated. Thin upper and lower lips, significantly short philtrum, wide mouth, and short neck with low posterior hairline are evident (Fig. 25–67).

Although motor development is retarded in only 25%, expressive speech delay is marked in 100% (3). Nasal speech and high-pitched voice have been reported (1,13). Mild mental retardation has been noted in about 50% (5).

Skeletal changes include delayed bone age (100%), brachydactyly (50%), clinodactyly V (75%), finger clubbing (45%), and joint laxity (50%). Pseudoarthrosis of the right clavicle has been noted in a few cases (5,7,8,13).

Celiac disease has been found in several patients (1,2,6,15).

Miscellaneous findings have included hirsutism (5,6,13), hypoplastic penis (8,9), high-pitched voice, and supernumerary upper incisor (1).

The facies is somewhat reminiscent of *Shprintzen syndrome* (10,16). One must also exclude *Silver-Russell syndrome, 3-M syndrome*, and *Dubowitz syndrome*.

References [Floating-Harbor syndrome (unusual facies, short stature, delayed bone age, and hypoplastic penis)]

1. Ala-Mello S, Peippo M: Two more diagnostic signs in the Floating-Harbor syndrome. Clin Dysmorphol 5:85–88, 1996.
2. Chudley AE, Moroz SP: Floating-Harbor syndrome and celiac disease. Am J Med Genet 38:562–564, 1991.
3. Davalos IP et al: Floating-Harbor syndrome. A neuropsychological approach. Genet Couns 7:283–288, 1996.
4. Fryns JP et al: The Floating-Harbor syndrome: Two affected siblings in a family. Clin Genet 50:217–219, 1996.
5. Hersh JH et al: Changing phenotype in Floating-Harbor syndrome. Am J Med Genet 76:58–61, 1998.

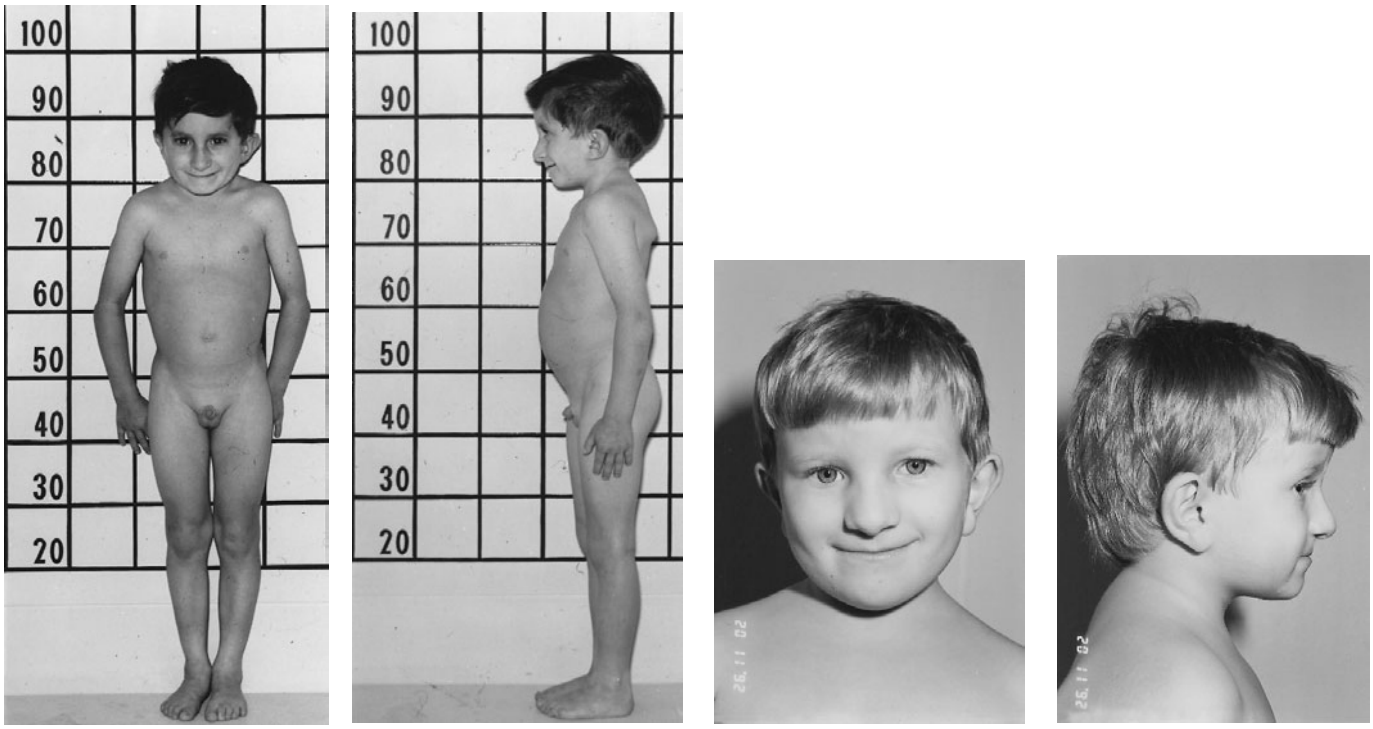


Fig. 25–67. *Floating-Harbor syndrome (unusual facies, short stature, delayed bone age, and hypoplastic penis*). (A,B) Patient at 6 years, 8 months. Notice proportionate short stature, dolichocephaly, triangular facies, deep-set eyes, large nose, thin lips, short philtrum, low hairline, short neck, large and wide nose, low-set and posteriorly rotated ears, small penis, and short fingers. (C,D) Nose is prominent with broad nasal bridge and wide columella. Lips are thin with significantly shortened philtrum. Note wide mouth and short neck. [A,B from J Leisti et al, Syndrome Ident 2(1):3, 1974. C,D from S Ala-Mello and M Peippo, Clin Dysmorphol 5:85, 1996.]

6. Houlston RS et al: Further observations on the Floating-Harbor syndrome. Clin Dysmorphol 3:143–149, 1994.
7. Lacombe D et al: Floating-Harbor syndrome: Description of a further patient, review of the literature, and suggestion of autosomal dominant inheritance. Eur J Pediatr 154:658–661, 1995.
8. Leisti J et al: Case report 12. Syndrome Ident 2(1):3–5, 1974.
9. Leisti J et al: The Floating-Harbor syndrome. Birth Defects 11(5):305–309, 1975.
10. Lipson A: Floating-Harbor and the good ship Shprintzen. J Med Genet 28:807–808, 1991.
11. Majewski F, Lenard H-G: The Floating-Harbor syndrome and differential diagnosis with Shprintzen syndrome. Eur J Pediatr 150:250–252, 1991.
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13. Patton MA et al: Floating-Harbor syndrome. In: Congenital Malformation Syndromes, Donnai D, Winter RM (eds), Chapman & Hall Medical, London, 1995.
14. Pelletier G, Feingold M: Case report 1. Syndrome Ident 1(1):8–9, 1973.
15. Robinson PL et al: A unique association of short stature, dysmorphic features, and speech impairment (Floating-Harbor syndrome). J Pediatr 113:703–706, 1988.
16. Smeets E et al: The Floating-Harbor syndrome and differential diagnosis with Shprintzen syndrome. Genet Couns 7:143–146, 1996.
17. Zabransky S: Das Floating-Harbor-Homburg Syndrom. Akt Endokr Stoffw 6:25–29, 1985.

Unusual facies, renal and Müllerian hypoplasia, and severe somatic and mental retardation

Davee et al (1), in 1992, documented a brother and sister with renal hypoplasia in both, Müllerian hypoplasia in the sister, and severe somatic and mental retardation and seizures. Both had similar craniofacial anomalies (open metopic suture, large anterior fontanel, high forehead, frontal bossing, hypertelorism, strabismus, short nose, low-set posteriorly angulated pinnae, and mild micrognathia). Large flat dimples were found at each elbow and wrist.

Inheritance is probably autosomal recessive.

Reference (Unusual facies, renal and Müllerian hypoplasia, and severe somatic and mental retardation)

1. Davee MA et al: Familial occurrence of renal and Müllerian duct hypoplasia, craniofacial anomalies, severe growth and developmental delay. Am J Med Genet 44:293–296, 1992.

Unusual facies, vitiligo, canities, and progressive spastic paraplegia

Lison et al (1) reported three affected sibs, the product of healthy consanguineous Arab parents. There were distinct facies, premature graying, vitiligo, and progressive spastic paraplegia. Mukamel et al (2) described an additional four Arab children.

The cutaneous findings included diffuse lentigines, graying of scalp and body hair, vitiligo, and hyperpigmentation of exposed areas (Fig. 25–68).

Microcephaly and mental retardation were evident in the family described by Mukamel et al (2). The face tended to be small and thin, producing moderately sharp features including pointed nose, small chin, and high cheek bones.

All exhibited decreased tendon reflexes, positive Babinski reflex, foot drop, and spastic gait. Thoracic scoliosis, lumbar lordosis, and loss of muscle mass of the lower limbs were evident (Fig. 25–69).

Inheritance is autosomal recessive.

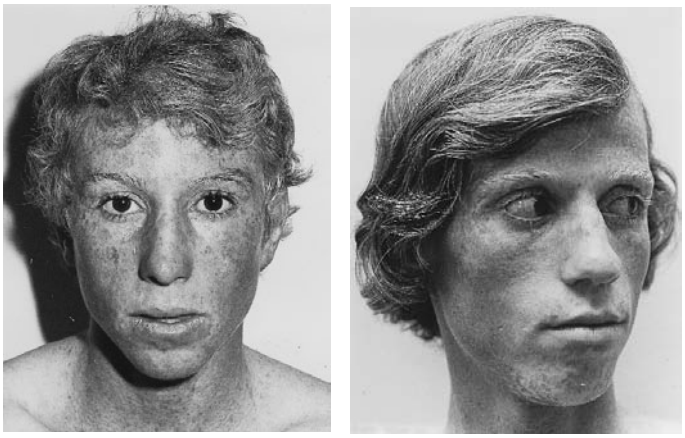

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Fig. 25–68. *Unusual facies, vitiligo, canities, and progressive spastic paraplegia*. (A,B) Premature graying of scalp hair, eyebrows, eyelashes. Note midfacial vitiligo, sharpened features. (From M Lison et al, Am J Med Genet 9:351, 1981.)

References (Unusual facies, vitiligo, canities, and progressive spastic paraplegia)

1. Lison M et al: Progressive spastic paraparesis, vitiligo, premature graying, and distinct facial appearance: A new genetic syndrome in 3 sibs. Am J Med Genet 9:351–357, 1981.

2. Mukamel M et al: Spastic paraplegia, mental retardation and cutaneous pigmentation disorder: A new syndrome. Am J Dis Child 139:1090–1092, 1985.

Unusual facies-serpentine fibula-polycystic kidney syndrome (ter Haar syndrome)

Exner (2), in 1988, was the first to employ the name serpentine fibula–polycystic kidney syndrome. Earlier examples were classified as autosomal recessive Melnick–Needles patients (1,7). Since then, other examples have been documented (3,5,6,8). Löhr and Wiedemann (4) reported a male with many similar features. R Hennekam has seen another patient of Turkish descent in The Netherlands.

Inheritance is clearly autosomal recessive (6,7). Consanguinity has been found in four of five examples.

Intelligence is normal.

The syndrome is characterized by short stature, coarse hair, hirsutism of forehead and neck, arched heavy eyebrows, congenital glaucoma, hypertelorism, prominent eyes, large cornea, full cheeks, and marked micrognathia. The neck is short and the voice is hoarse (Fig. 25–70). Sensorineural hearing loss has been noted (2,7).

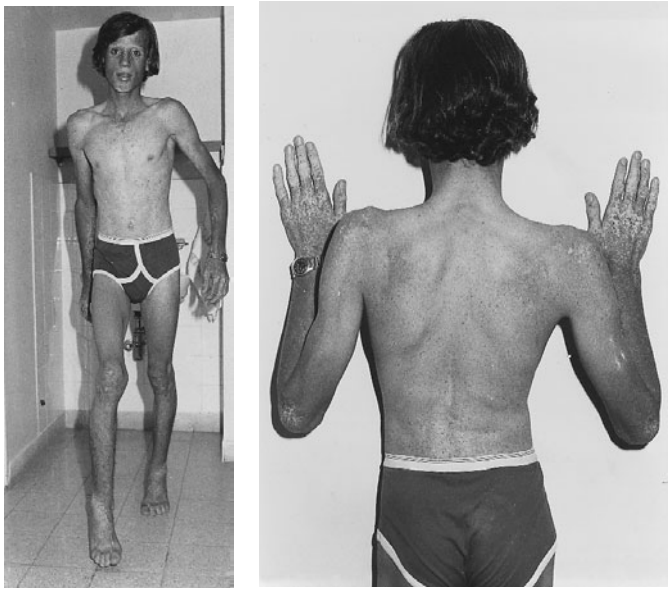
Skeletal changes include wormian bones in lambdoidal sutures, irregular serpentine fibulae, ulnar bowing, curved radius, joint limitation, scoliosis, flared iliac crest, metaphyseal flaring, acroosteolysis, bilateral pes valgus, and metatarsus adductus. Prominent anterior tibiae have been described (2). Other muscular-skeletal findings have been flaring of clavicles, lateral subluxation of talus, pes planus, prominent coccyx with skin fold (3,6), large anterior fontanel, scalloping of anterior surface of anterior vertebrae, and inguinal hernia.

All but one (8) has died at an early age from cardiovascular problems: double outlet right ventricle, VSD, tricuspid insufficiency.

Polycystic kidneys have been documented (2,7).

One must exclude *Melnick–Needles syndrome, megalocornea–mental retardation syndrome type 2*, and *Hajdu–Cheney syndrome*.

Fig. 25–69. *Unusual facies, vitiligo, canities, and progressive spastic paraplegia*. (A,B) Vitiligo, lentigines, mild scoliosis, muscle wasting, and tip-toe gait. (From M Lison et al, Am J Med Genet 9:351, 1981.)



A B

References [Unusual facies-serpentine fibula-polycystic kidney syndrome (ter Haar syndrome)]

1. Dereymaeker AM et al: Melnick-Needles syndrome (osteodysplasty). Helv Paediatr Acta 41:339–351, 1986 (Case 1).

2. Exner GU: Serpentine fibula-polycystic kidney syndrome. A variant of the Melnick-Needles syndrome or a distinct entity? Eur J Pediatr 147:544–546, 1988.

3. Hamel B et al: Autosomal recessive Melnick-Needles syndrome or ter Haar syndrome? Report of a patient and reappraisal of an earlier report. Am J Med Genet 56:312–316, 1995.

4. Löhr H, Wiedemann H-R: Mesomelic dysplasia-associated with other abnormalities. Eur J Pediatr 137:313–316, 1981.

5. Majewski F et al: Serpentine fibula-polycystic kidney disease and Melnick-Needles syndrome are different disorders. Eur J Pediatr 152:916–921, 1993.

6. Rosser EM et al: Serpentine fibula syndrome: Expansion of the phenotype with three affected siblings. Clin Dysmorphol 5:105–113, 1996.

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8. Wallerstein R et al: Extended survival in a new case of ter Haar syndrome: Further delineation of the syndrome. Am J Med Genet 70:267–272, 1997.

Unusual facies, microcephaly, polycystic kidneys, brachymelia, Potter sequence, and congenital heart anomalies (Gillessen-Kaesbach syndrome)

In 1993, Gillessen-Kaesbach et al (1) reported a new lethal syndrome consisting of polycystic kidney, microbrachycephaly, brachymelia, and congenital heart disease. They described six patients, sibs from three unrelated families.

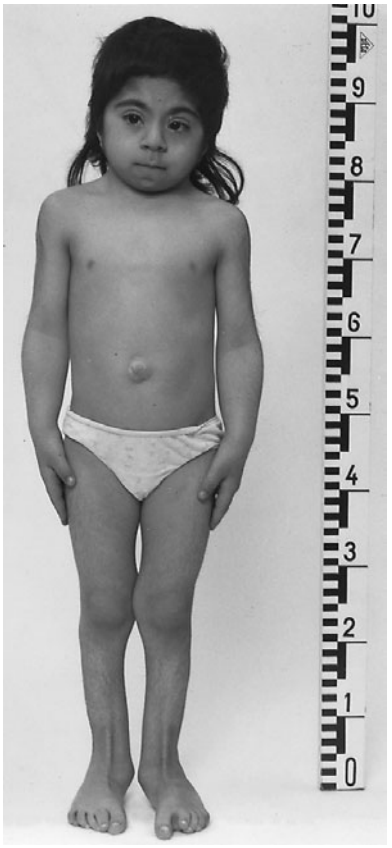
Inheritance is clearly recessive. Two of the sibships were Turkish with consanguineous parents.

The infants, after full term, have birthweights and lengths 4 SD below the mean Head circumference is even more reduced (−5 SD). All the infants died within the first few hours of life.

Craniofacial changes included microbrachycephaly, prominent forehead, hypertelorism, upslanting palpebral fissures, short beaked nose with wide bridge, cleft palate, flat philtrum, large deeply set posteriorly rotated pinnae, and loose neck skin (Fig. 25–71).

The abdomen was protuberant.

Autopsy showed hypoplastic genitalia, micro- and polycystic spongy kidneys (Potter I type) with smooth surface and ectasia of the collecting tubules, bile duct and pancreatic duct proliferation, and lung hypoplasia.



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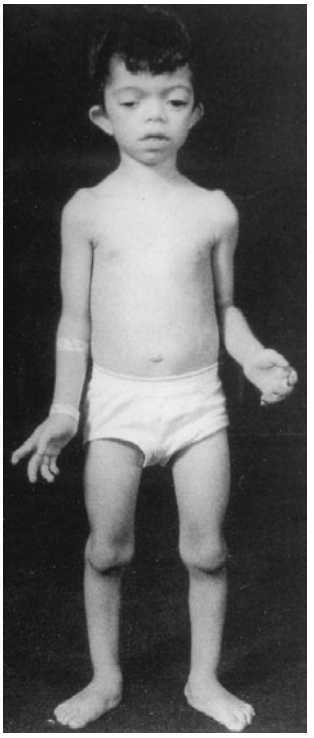

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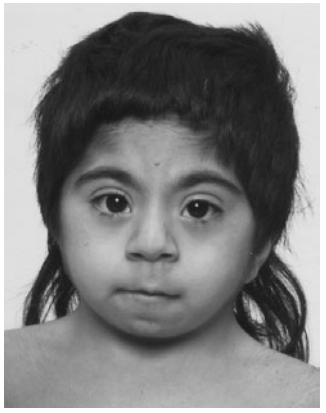

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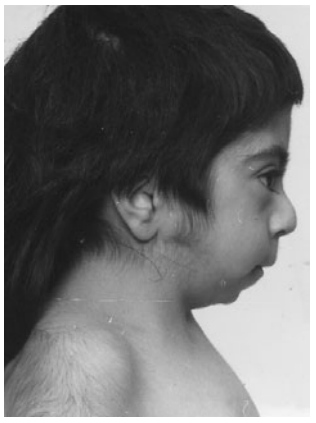

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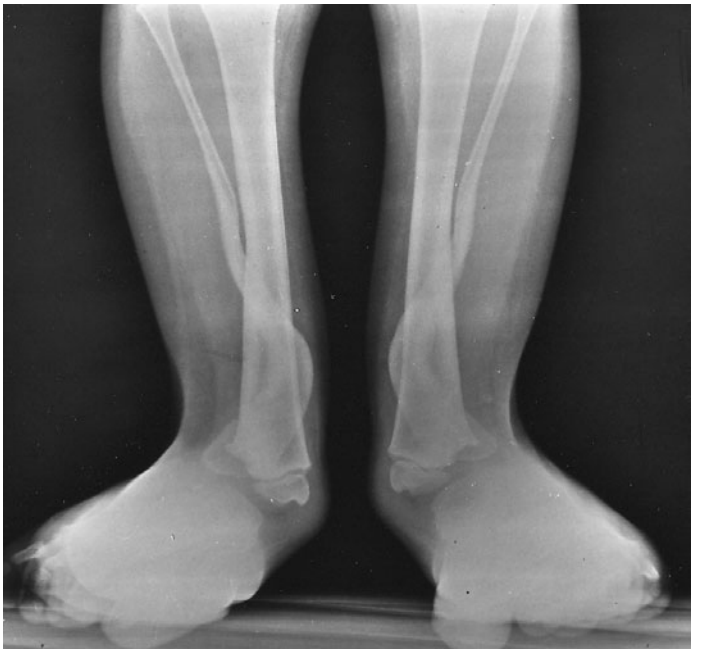

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Fig. 25–70. *Unusual facies–serpentine fibula–polycystic kidney syndrome (ter Haar syndrome)*. (A,C,D) Five-year-old female with unusual facial appearance characterized by short neck, hirsute forehead and neck, thick eyebrows, micrognathia, pes valgus, metatarsus adductus, and prominent tibialis anterior tendon. (B) Outstanding ears, megalocornea, broad mouth with full lips, hyperextension of finger joints, flat feet. Compare with A. (E) Bilateral serpentine fibulae. (A,C–E from GU Exner, Eur J Pediatr 147:544, 1988. B from R Wallerstein et al, Am J Med Genet 70:267, 1997.)

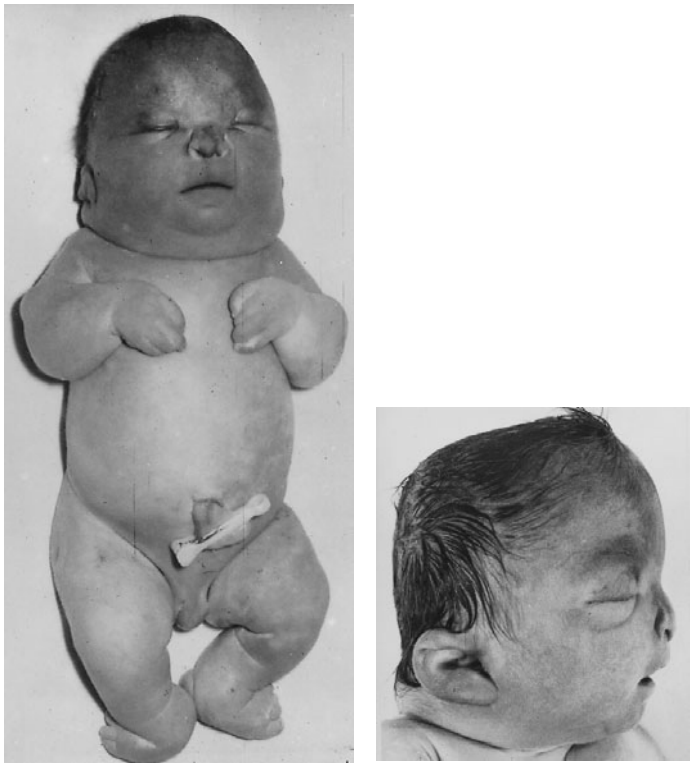

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Fig. 25–71. *Unusual facies, microcephaly, polycystic kidneys, brachymelia, Potter sequence, and congenital heart anomalies (Gillessen-Kaesbach syndrome).* (A,B) Microbrachycephaly, short beaked nose with wide nasal bridge, flat philtrum, low-set posteriorly rotated pinnae. Loose neck skin, protuberant abdomen, brachymelia, extreme talipes, extreme ulnar deviation of hands, rocker-bottom feet. Note Potter facies. (From G Gillessen-Kaesbach et al, Am J Med Genet 45:511, 1993.)

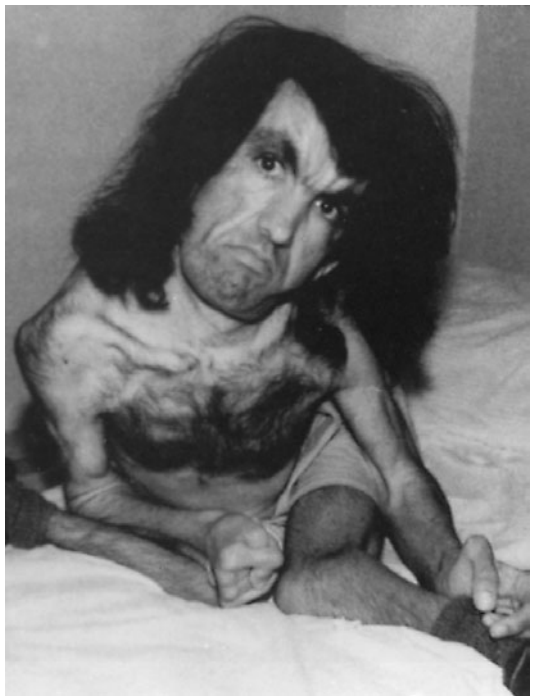

Fig. 25–72. *Unusual facies, musculoskeletal abnormalities and sensory defects*. Ridged triangular skin extends from glabella to anterior fontanel. Elevation of medial eyebrows, widow's peak, and short neck. Marked hirsutism, winged scapulae, kyphoscoliosis, dislocated hips, and joint contractures. (From LT Middleton et al, Am J Med Genet 44:757, 1992.)

Various heart anomalies were found in four of six patients including VSD, dextraposition of aorta, complex heart malformations, and transposition of great vessels.

The extremities exhibited ulnar deviation of the hands, microbrachydactyly, and rocker bottom feet.

Miscellaneous findings included one case each of omphalocele, myelomeningocoele, diaphragmatic hernia, bicornuate uterus, and situs inversus.

All males exhibited cryptorchidism.

Pathologic studies on the brain of one infant showed temporal lobe and cerebellar hypoplasia, irregular gyrations of the cortex, and internal hydrocephalus.

One should exclude other syndromes or association of Potter sequence, especially *Holzgreve–Wagner–Rehder syndrome* and *Thomas syndrome*.

Reference [Unusual facies, microcephaly, polycystic kidneys, brachymelia, Potter sequence, and congenital heart anomalies (Gillessen-Kaesbach syndrome)]

1. Gillessen-Kaesbach G et al: New autosomal recessive lethal disorder with polycystic kidneys type Potter I, characteristic face, microcephaly, brachymelia, and congenital heart defects. Am J Med Genet 45:511–518, 1993.

Unusual facies, musculoskeletal abnormalities, and sensory defects

Middleton et al (1) described a syndrome of unusual facies, musculoskeletal abnormalities, and sensory defects in three generations of a Greek Cypriot family (Fig. 25–72).

The facies is striking. There is a thickened, ridged triangular skin fold extending from the glabella to the anterior fontanel, elevation of medial eyebrows, widow's peak, low hair line, hypertelorism, exotropia, ptosis, and short neck. Hirsutism is marked. Cataracts were noted in a few members of the family.

Musculoskeletal anomalies included winged scapulae, kyphoscoliosis, dislocated hips, talipes, wasting of muscles in both arms and legs, and joint contractures.

Inheritance is autosomal dominant with very variable expressivity.

Reference (Unusual facies, musculoskeletal abnormalities, and sensory defects)

1. Middleton LT et al: New hereditary malformation syndrome of unusual facial appearance, skeletal deformities, and musculoskeletal and sensory defects. Am J Med Genet 44:757–761, 1992.

Unusual facies, polysyndactyly of fingers and toes, and congenital heart disease

Bonneau et al (1), in 1983, reported three affected sibs. The polysyndactyly involved digits 3–4 leading to a mitten-shaped hand. In the feet, the hallux was duplicated. Complex cyanotic congenital heart disease with AV septal defects led to death. The nose was bulbous. A similar condition in sibs was found in Oman (2).

References (Unusual facies, polysyndactyly of fingers and toes, and congenital heart disease)

1. Bonneau JC et al: Polysyndactylie avec cardiopatie complexe à propos de trois cas dans une meme fratrie. J Genet Hum 31:93–105, 1983.

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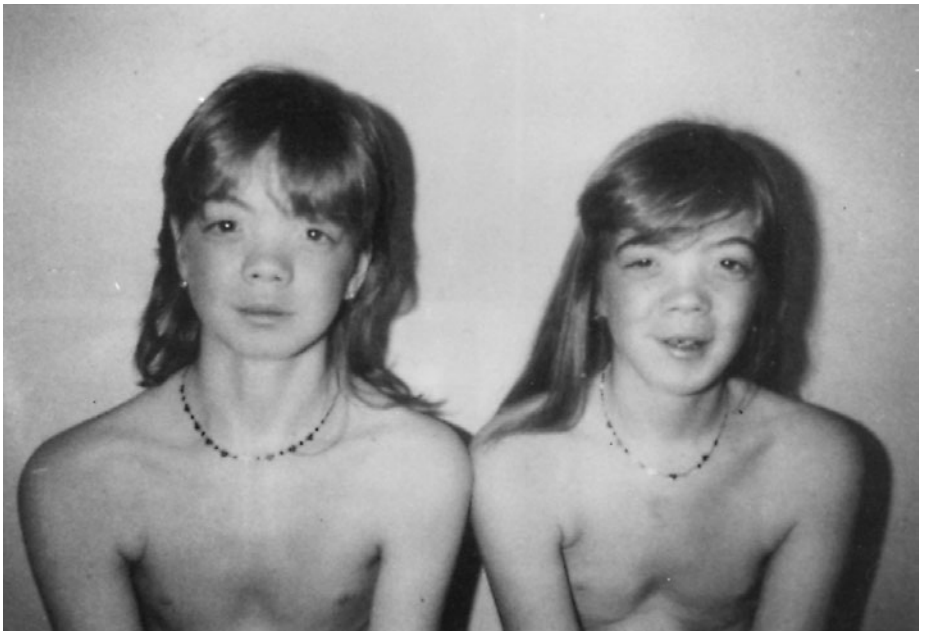


Fig. 25–73. *Unusual facies, oligodontia, and precocious choroid calcifications*. Identical twin daughters with inner telecanthus, downslanting palpebral fissures, flat nasal bridge, small nose with anteverted nares. (From R Pallotta and P Fusilli, J Med Genet 35:435, 1998.)

Unusual facies, oligodontia, and precocious choroid calcifications

Pallotta and Fusilli (1), in 1998, reported a mother and her identical twin daughters.

The facies was characterized by inner telecanthus, downslanting palpebral fissures, mild ocular proptosis, wide flat nasal bridge, small nose with anteverted nares, hypoplastic nasal septum, and full lips (Fig. 25–73).

Other concordant findings included pectus carinatum, clinodactyly of fifth fingers, hypoplastic distal second toes, hypoplastic sphenoid, and bilateral choroid plexus calcification.

All permanent teeth were missing save those of the maxillary central incisors and first maxillary and mandibular molars (Fig. 25–74). The deciduous precursors were not shed.

Reference (Unusual facies, oligodontia, and precocious choroid calcifications)

1. Pallotta R, Fusilli P: Unknown syndrome: Peculiar face, severe hypodontia of permanent teeth, and precocious choroid calcifications. J Med Genet 35:435–437, 1998.

Unusual facies, myelodysplasia, and immunodeficiency

Stoll et al (1) described three siblings born to first cousin parents. These sibs had neutropenia, immunodeficiency, steatorrhea, short stature, microcephaly, mild mental retardation, and characteristic facial appearance. The facial phenotype consisted of prominent forehead, narrow palpebral fissures, depressed nasal bridge, large nose, thick lips, and prominent chin. Two children also had cardiac defects and two had vesicoureteral reflux. One developed leukemia at age 14 years.

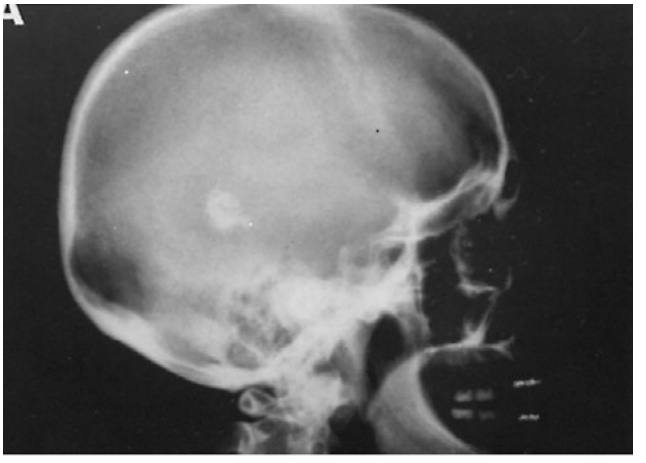
Reference (Unusual facies, myelodysplasia, and immunodeficiency)

1. Stoll C et al: A syndrome of facial dysmorphism, birth defects, myelodysplasia and immunodeficiency in three sibs of consanguineous parents. Genet Couns 5:161–165, 1994.

Unusual facies, retinal pigment abnormalities, short stature, radioulnar synostosis, and mental retardation

Buntinx et al (1), in 1991, reported two severely mentally retarded sibs with microbrachycephaly, zygomatico-maxillary hypoplasia, malformed

Fig. 25–74. *Unusual facies, oligodontia, and precocious choroid calcifications*. (A,B) Note bilateral choroid plexus calcification and absence of teeth. (From R Pallotta and P Fusilli, J Med Genet 35:435, 1998.)



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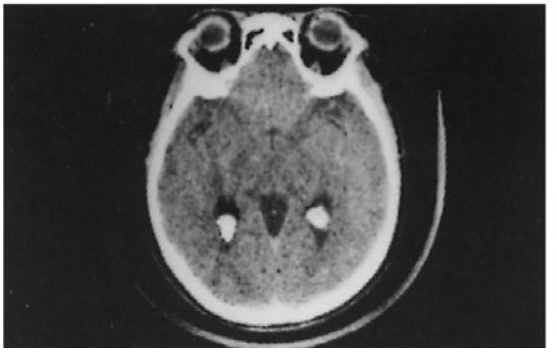

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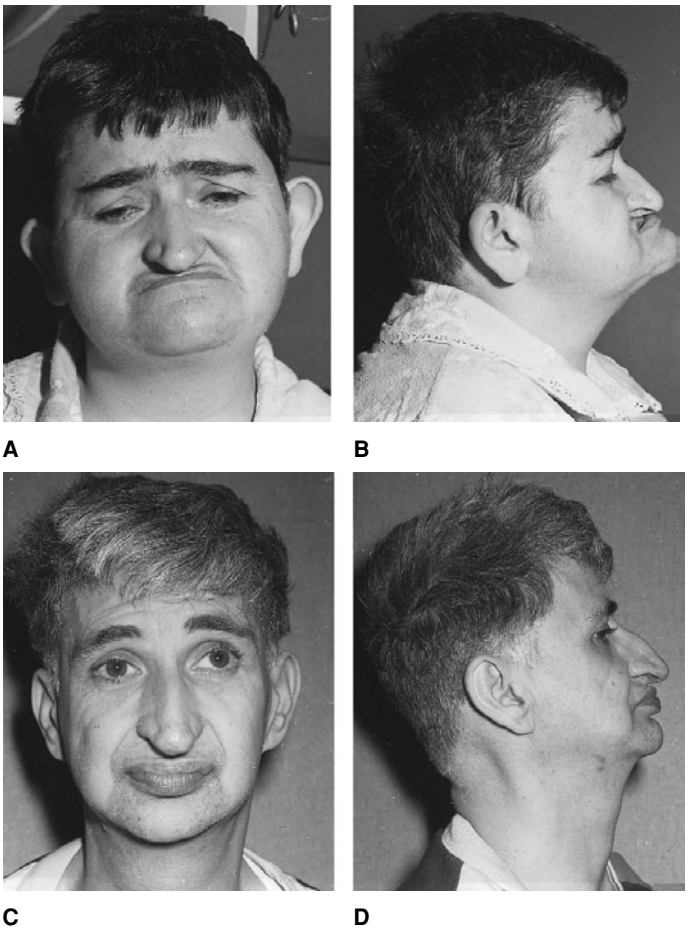

Fig. 25–75. *Unusual facies, retinal pigment abnormalities, short stature, radioulnar synostosis, and mental retardation*. (A–D) Two severely mentally retarded sibs with microbrachycephaly, short forehead with lower anterior hairline, depressed nasal tips, and short philtrum. (From IM Buntinx et al, Genet Couns 2:237, 1991.)

pinnae, short forehead with low anterior hairline, synophrys, depressed nasal tip, short philtrum, full lips, retinal pigmentary abnormalities, kyphoscoliosis, short stature, radioulnar synostosis, small hands and feet, and cryptorchidism (Fig. 25–75).

Inheritance is probably autosomal recessive. The parents were first cousins.

Reference (Unusual facies, retinal pigment abnormalities, short stature, radioulnar synostosis, and mental retardation)

1. Buntinx IM et al: A new association of mental retardation, short stature, unusual face, radioulnar synostosis, and retinal pigment abnormalities. Genet Couns 2:237–240, 1991.

Unusual facies, Müllerian hypoplasia, and limb anomalies (Al-Awadi–Raas-Rothschild syndrome)

Al-Awadi et al (1), studying an inbred Jordanian Arab kindred, reported male and female sibs with unusual facies, limb anomalies, thoracic dysplasia, and normal intelligence. Similar examples have been found in Bedouins (3), Brazilians (5), Italians (2), and Iranian Jews (4).

The face is long with a broad nasal bridge that is almost as wide as the alae. The pinnae are dysplastic. The chin is pointed. The chest is barrel

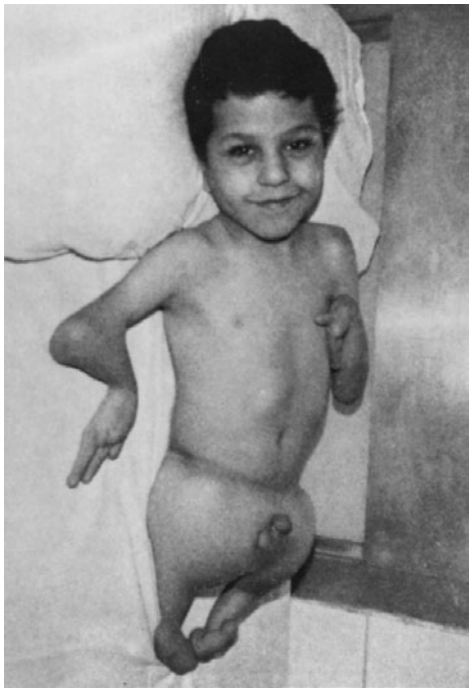

Fig. 25–76. *Unusual facies, Müllerian hypoplasia, and limb anomalies (Al-Awadi–Raas-Rothschild syndrome)*. Note absence of joints at elbows, short radii, absent ulnae. Malformed pelvis with one lower limb bone and reduced number of rays in feet. (From SA Al-Awadi et al, J Med Genet 22:36, 1985.)

shaped with prominent sternum. There are no joints at the elbows, but a contraction is evident. The radii are short, the ulnae absent. The hands have three or four digits, the fifth and/or fourth rays being missing. Some carpal bones are fused. The nails are vestigial. The pelvis is malformed with one lower limb bone and one tarsal bone. The feet have only two rays (Fig. 25–76).

The genitalia are displaced, the testes undescended. The anal pit is deep. The uterus is absent in females (1).

Inheritance is autosomal recessive (1-5).

References [Unusual facies, Müllerian hypoplasia, and limb anomalies (Al-Awadi–Raas-Rothschild syndrome)]

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3. Farag TI et al: The newly recognized limb/pelvis hypoplasia/aplasia syndrome: Report of a Bedouin patient and review. J Med Genet 30:62–64, 1993.

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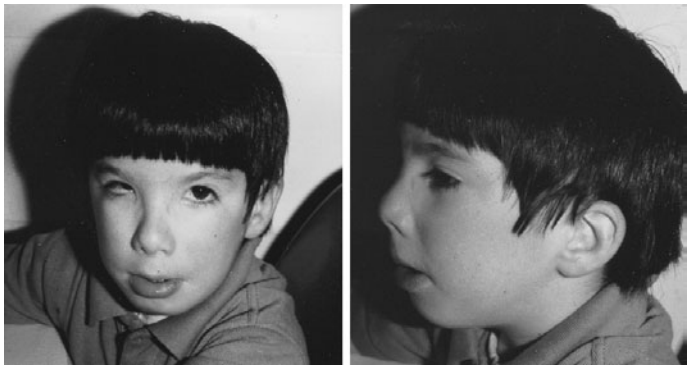
Unusual facies, hepatic fibrosis, renal cysts, and mental retardation

Hunter et al (1), in 1974, and Thompson and Baraitser (3), in 1986, described affected sibs with a syndrome of unusual facies, hepatic fibrosis,



A B

Fig. 25–77. *Unusual facies, hepatic fibrosis, renal cysts, and mental retardation*. (A,B) Note ptosis, marked strabismus, anteverted nares, everted lower lip. (Courtesy of P Labrune, Paris, France.)

renal anomalies, and mental retardation. Labrune et al (2) added another example.

The renal anomalies included cortical cysts, medullary cystic dilatation, and enlarged kidneys.

The facies was characterized by strabismus, nystagmus, ptosis, anteverted nares, and drooping mouth (Fig. 25–77). Ocular coloboma was found in two sibs (1).

References (Unusual facies, hepatic fibrosis, renal cysts, and mental retardation)

1. Hunter AGW et al: Hepatic fibrosis, polycystic kidney, colobomata, and encephalopathy in siblings. Clin Genet 6:82–89, 1974.

2. Labrune P et al: Congenital hepatic fibrosis, cystic kidneys, mental retardation facial dysmorphy: A new report of an autosomal recessive syndrome. J Pediatr Gastroenterol Nutr 10:540–543, 1990.

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Unusual facies, sparse hair, and mental retardation

Nicolaides and Baraitser (2) and Krajewska-Walasek et al (1) described patients with mild mental retardation, postnatal growth retardation, advanced bone age, sparse scalp hair, somewhat coarse facies, deeply-set eyes, narrow palpebral fissures, upturned nose with thick nares, prominent lower lip, brachydactyly, swelling of interphalangeal joints, and drumstick fingers.

References (Unusual facies, sparse hair, and mental retardation)

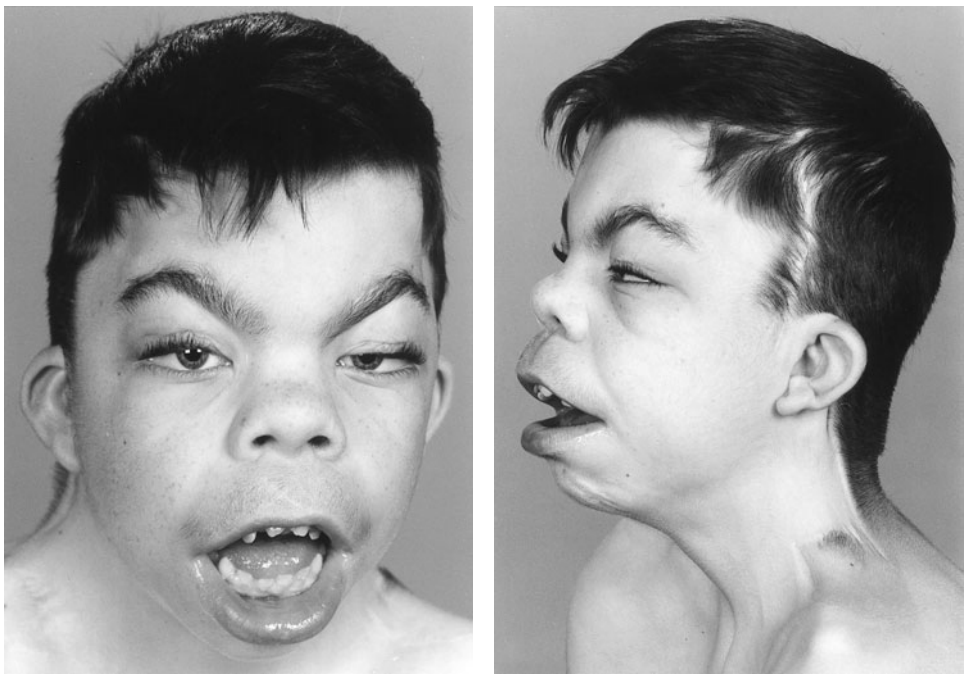
1. Krajewska-Walasek M et al: Another patient with an unusual syndrome of mental retardation and sparse hair? Clin Dysmorphol 5:183–186, 1996.

2. Nicolaides P, Baraitser M: An unusual syndrome with mental retardation and sparse hair. Clin Dysmorphol 2:232–236, 1993.

Unusual facies, broad webbed neck, inverted nipples, epilepsy, and pachygyria of frontal lobes (cerebro-fronto-facial syndrome)

Fryns and Aftimos (2), in 2000, described two unrelated boys with postnatal weight loss, short stature, unusual facies, broad webbed neck, broad thorax, hypoplastic and inverted nipples, seizures, and pachygyria of frontal lobes. Similarly affected patients were noted by der Kaloustian et al (1) and Guion-Almeida and Richieri-Costa (3). The latter child, a girl, also exhibited callosal agenesis, cleft lip/palate, grooved chin, and bifid thumbs. Winter (4) avers there is heterogeneity.

Microcephaly, trigonocephaly, facial edema, ptosis of upper eyelids, temporal flattening, posteriorly rotated pinnae with hypoplastic anthelix, broad nasal root, arched shaggy eyebrows, hypertelorism, long flat philtrum, and large mouth with thin upper lip and everted lower lip, at times with a central groove, were seen (Fig. 25–78). The upper dental incisors were prominent. The posterior hair line was low. The shoulders were downslanting. The hands were broad and short with permanent edema of the dorsum and tapering fingers. Extension deficit of the knees and elbows was evident. Hypertonia of the lower limbs resulted in toe walking. Scoliosis has been noted.



A B

Fig. 25–78. *Unusual facies, broad webbed neck, inverted nipples, epilepsy, and pachygyria of frontal lobes*. (A) Highly arched bushy eyebrows, broad nasal root, short upturned nostrils, low-set and posteriorly-rotated auricles, somewhat widened palpebral fissures. (B) Broad, flat philtrum, large mouth, thin upper lip, everted lower lip, pterygium colli. The child had poorly controlled seizures and inverted nipples. (Courtesy of V Der Kaloustian et al, Montreal, Quebec, Canada.)

The skin of the arms was especially loose and hyperextensible. Axillary pterygia were present in one case (1). The testes were undescended, and the scrotum was shallow.

Seizures of grand mal, petit mal, and myoclonic type began at about 3 to 5 years. Psychomotor retardation, at first mild, became more marked with age and following onset of seizures. Diffuse pachygyria, especially marked in the frontal area, was found on MRI. Mild spastic paraparesis appeared at about 6 years.

Vesicouteral reflux with hydronephrosis was observed (1,2) as well as inguinal herniae (1).

Such conditions as *frontonasal malformation* and *acrofrontofacionasal dysostosis* must be excluded.

References [Unusual facies, broad webbed neck, inverted nipples, epilepsy, and pachygyria of frontal lobes (cerebro-fronto-facial syndrome)]

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Chapter 26
Syndromes with Gingival/Periodontal Components

Gingival fibromatosis and its syndromes

Gingival fibromatosis may exist as an isolated abnormality due to genetic or environmental causes or as part of a syndrome (19,25,40). As an isolated finding, it is often sporadic but may exhibit autosomal dominant inheritance (34,37) or rarely autosomal recessive inheritance (21,25,35,37). There appear to be two genes on chromosome 2, one in the 2p21→p22 region and the other at 2p13–p16, that can be mutated (20,23,23a,36).

Generalized gingival enlargement may occur as a result of inflammation, pregnancy, leukemia, *I-cell disease* and as a response to various medications [phenytoin (Dilantin), diltiazem, cyclosporin A, verapamil, and nifedipine] (6,8,30). In these disorders, the gingiva is usually not as enlarged or as fibrotic as in gingival fibromatosis where it may be so severe that the affected individual may appear to have no teeth. History and physical examination will serve to distinguish these disorders from gingival fibromatosis. Gingival fibromatosis with hypertrichosis is the most common of the syndromes.

Hirsutism may result from many causes (29). There are various forms of regional hypertrichosis with dominant and recessive patterns: hairy elbows (11–13), elbows and knees (11), and anterior neck with or without neuropathy and hallux valgus (7). Acquired lanuginous hypertrichosis may be associated with endocrine or metabolic disturbances or rarely may be a sign of internal malignancy (24).

Extreme hypertrichosis (hypertrichosis universalis congenita) may represent a heterogeneity. Some examples may have association with anodontia or oligodontia, manifesting X-linked dominant inheritance (4,18,27,31,33). Baumeister et al (3) proposed a subgroup, known as *Ambras syndrome*, characterized by abnormal hair distribution (forehead, eyelids, nose, cheeks, preauricular region and external auditory canals as well as the rest of the body, except for the palms and soles). The hair may grow to several decimeters if not cut. Baumeister (2) noted that the facial hair of the patient reported by Balducci et al (1) was not uniformly distributed. It was principally located on the face and in the frontal, temporal, and preauricular regions, the nose and ears being largely spared. Hence, he categorized the case of Balducci et al (1) as hypertrichosis universalis congenita. Since they both map to 8q22 (1,3), we doubt that the clinical variation is based on different disorders. Early examples have been elegantly illustrated by Baumeister et al (2) and Nowakowski and Scholz (31). The hair has been so profuse that some individuals have been exhibited in carnivals (9,15,17,38) (Fig. 26–1). With rare exceptions, Juliana Pastrana and a few others (5,16,26,28), these persons have not had gingival enlargement. Pastrana had congenital generalized hypertrichosis terminalis and four normal but unerupted teeth, according to Bondeson and Miles (5).

The pathogenesis of gingival fibromatosis is unknown, but the fibroblasts appear to have abnormal cellular properties (36) and there is altered postranslational modification of collagen (32). Occasionally calcifications or marked fibroblastic activity in the gingiva are found (14,16,31).

Gingival fibromatosis has been reported with prune belly, but we suspect that the association is aleatory (22). Wiedemann et al (39) reported an unusual syndrome of *hirsutism, mental retardation, skeletal abnormalities, and uric acid dysmetabolism*.

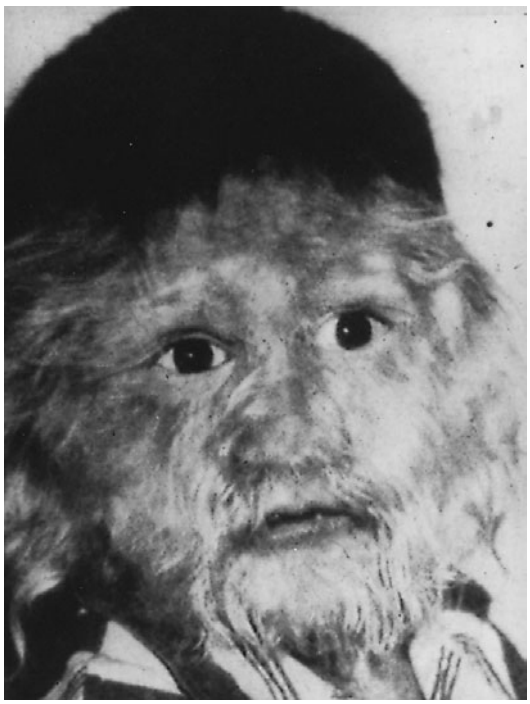

Fig. 26–1. *Hypertrichosis universalis congenita* or *Ambras syndrome*. Total face covered by lanugolike hair. (From IJ Lee et al, Pediatr Dermatol 10:263, 1993.)

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Gingival fibromatosis, hypertrichosis, epilepsy, and mental retardation

This is the most commonly reported syndrome in which gingival fibromatosis is but one of the manifestations of a single gene mutation. The hypertrichosis is usually generalized, involving the eyebrows, face, ears, extremities, and sacral areas (12,13) (Fig. 26–2). Epilepsy and mental retardation are variable features. The binary combination of gingival enlargement and hypertrichosis (5,8,9,12–14,17,21–23) is probably much less common than is isolated gingival fibromatosis. The syndrome appears to have autosomal dominant inheritance (5,21,23). Two proximate genes have been mapped to 2p21 (6,7,15,24).

Associated mental retardation and/or epilepsy have been noted in some cases (1–3,6a,16,18,19,23). It is likely that this combination has genetic heterogeneity, some examples possibly having autosomal recessive inheritance (1,6a,9). Other possible aleatory skeletal alterations, such as narrow second cervical vertebra, long odontoid process, and abnormal first ribs, were described by Anderson et al (2). The gingival enlargement usually occurs at less than 5 years of age (18).

Affected female children of first cousin parents were described with gingival fibromatosis, hirsutism, mental retardation, and brachymetacarpalia (6a).

An unusual case reported by Vontobel (19) cannot be classified. Features included acromegaloid features, marked hypertrichosis, hyperconvex nails, and gingival fibromatosis. Nevin et al (11) reported male and female sibs with gingival fibromatosis, epilepsy, mental retardation, and bilateral camptodactyly of the third, fourth, and fifth fingers. Hypertrichosis was specifically denied. Inheritance was presumed autosomal recessive. Another unusual case described by Cohen et al (4) concerns a child with hirsutism, gingival fibromatosis, prominent frontal bone, soft alar and auricular cartilages, unilateral axillary pterygium, hepatomegaly, broad ribs, and metacarpal alterations. Intelligence was normal as were fingers and toes, and there was no seizure activity.

The reader is referred to the discussion of Ambras syndrome in the section above and in Chapter 13.

References (Gingival fibromatosis, hypertrichosis, epilepsy, and mental retardation)

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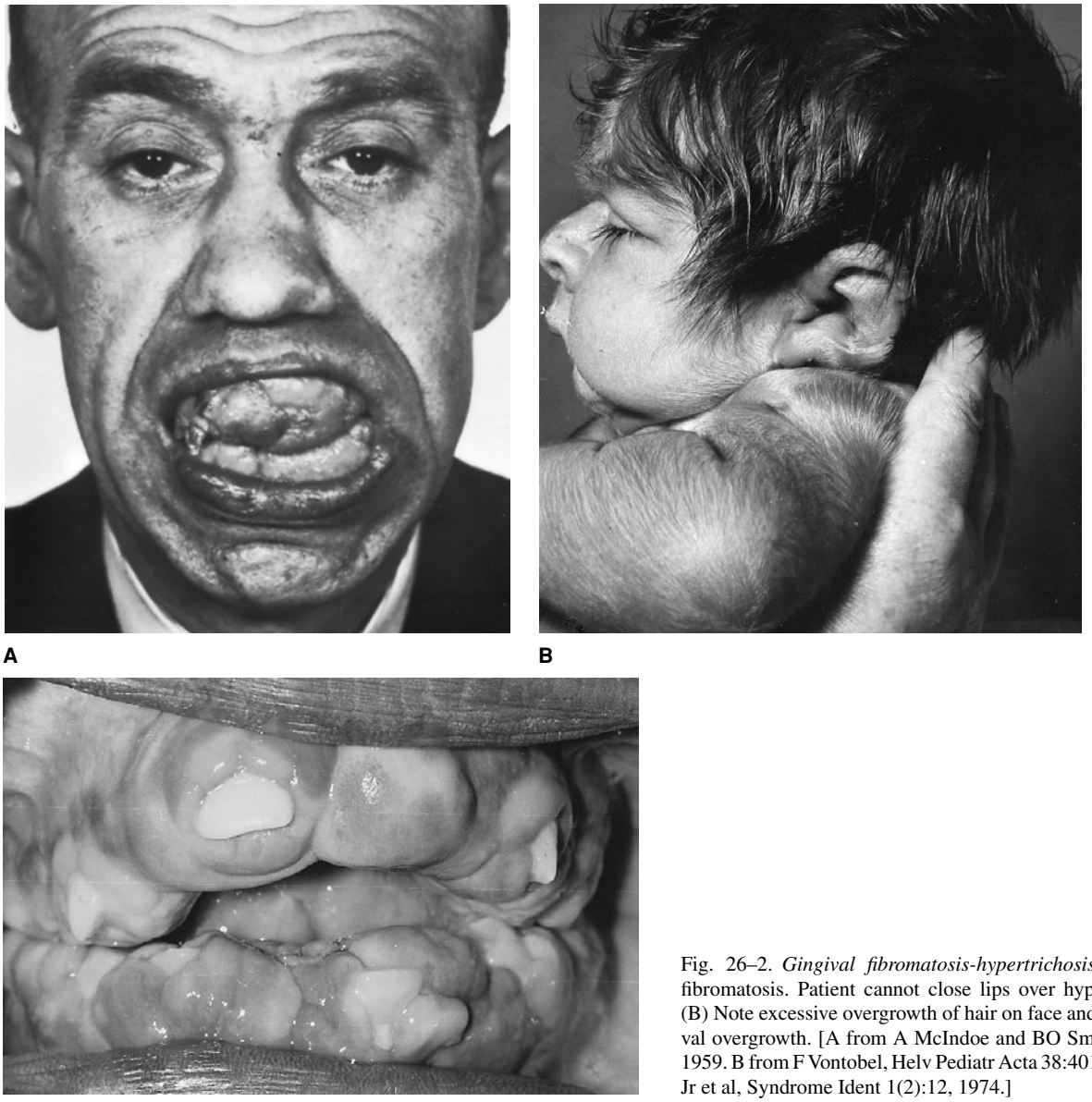

Fig. 26–2. *Gingival fibromatosis-hypertrichosis*. (A) Extensive gingival fibromatosis. Patient cannot close lips over hyperplastic gingival masses. (B) Note excessive overgrowth of hair on face and limbs. (C) Massive gingival overgrowth. [A from A McIndoe and BO Smith, Br J Plast Surg 11:62, 1959. B from F Vontobel, Helv Pediatr Acta 38:401, 1973. C from MM Cohen Jr et al, Syndrome Ident 1(2):12, 1974.]

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Gingival fibromatosis with juvenile hyaline fibromatosis (Murray-Puretić-Drescher syndrome)

This condition, first reported by Murray (22), in 1873, is characterized by multiple hyaline fibromas, white papules on the skin, flexion contractures, osteolytic bone lesions, and gingival fibromatosis (6,22,25,34). Affected sibs born to normal parents (50%) and parental consanguinity in at least 30% (6,8,13,16,18,22,23,29,30,36,37) indicate that inheritance is autosomal recessive. At least 40 patients have been described (11,28).

Skin. Multiple painless, freely movable, subcutaneous hyaline, fibrous tumors of the scalp, face, chin, ears, back, digits, thighs, and legs appear between 2 months and 4 years of age (31). They slowly enlarge, sometimes to the size of a small orange, and may ulcerate (6,15). Perianal lesions have also been noted (3,10,13,18–20). With puberty, masses may regress, and the number of new tumors decrease (Fig. 26–3A–C). There appears to be a marked tendency to suppurative infections of the skin and mucous membranes (25). The skin undergoes poikilodermatous and sclerodermatous changes. In addition, white papules are found on the neck, pinnae, nose, nasal septum, upper lip, and behind the ears (9,13, 16,30). The same material has been found in the tongue, esophagus, stomach, intestine, spleen, thymus, and lymph nodes (31).

On light microscopic examination, the tumors contain a homogeneous, amorphous, eosinophilic, PAS-positive ground substance that is sometimes chondroid in appearance (6,16,30,35). Spindle-shaped fibroblasts are present in this matrix in a streaklike pattern. The proportion of cells to ground substance varies from one tumor to another. Between the cells, argyrophilic fibers are sometimes found (Fig. 26–3H). Collagen fibers are thicker than normal. Ultrastructural studies have indicated excessive proliferation of fibroblasts, their organelles, and secretory products (16,20,30,35). Abnormalities in the Golgi apparatus have also been found (27,35). Ishikawa and co-workers (15,16) and Iwata et al (17) found an increased amount of chondroitin-6-sulfate in these tumors. Electrophoretically, it has been shown that an increased amount of acid mucopolysaccharides such as hyaluronic acid and dermatan sulfate is present in the urine (27,31).

Musculoskeletal. Painful progressive flexion contractures of the knees, elbows, hips, ankles, and shoulders appear within the first year of life in 75% (13,15,19,20,25,27). The temporomandibular joint may

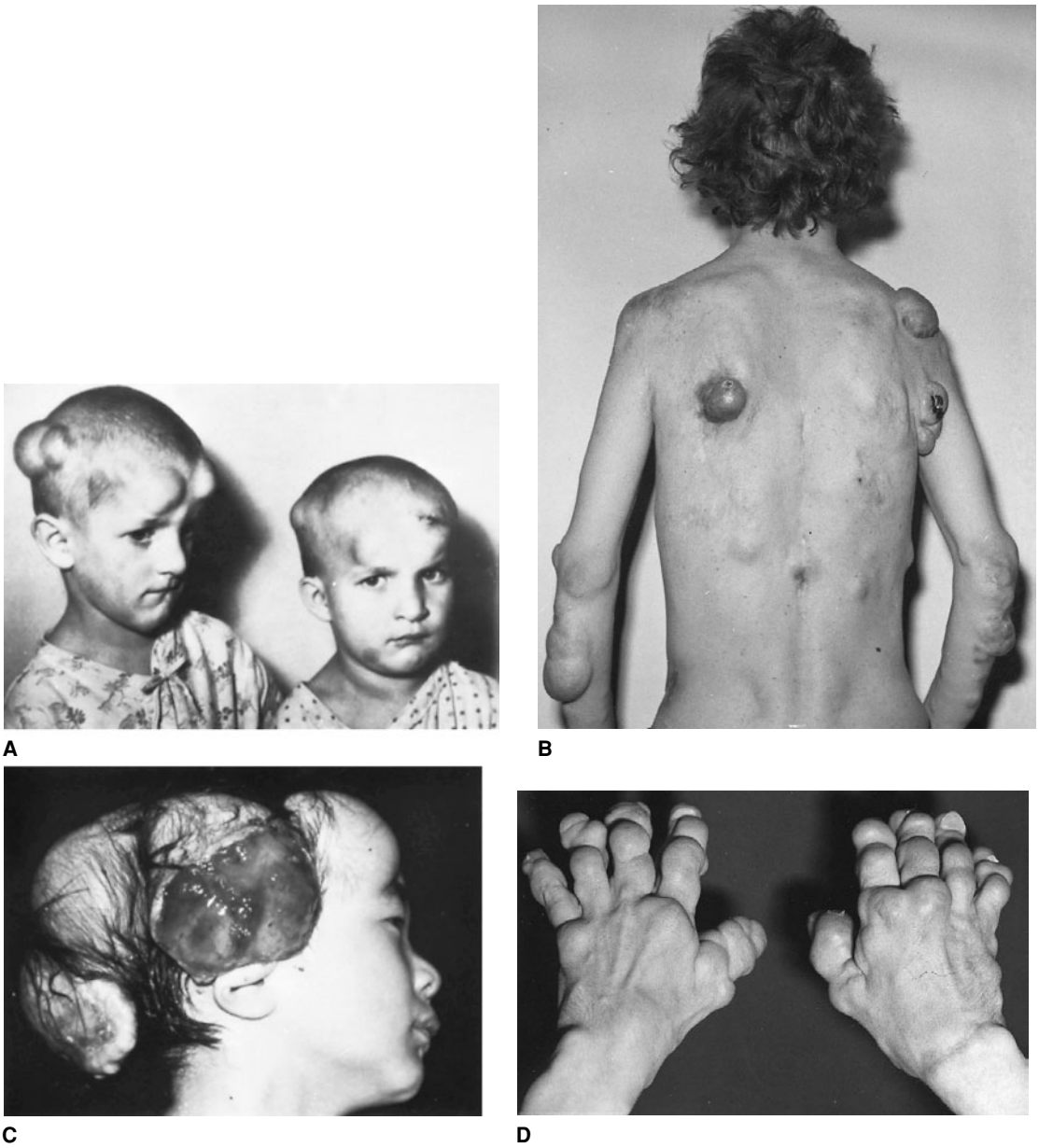


Fig. 26–3. *Gingival fibromatosis with juvenile hyaline fibromatosis (Murray-Puretić-Drescher syndrome)*. (A) Tumors of the head in 5-year-old male and 4-year-old female sibs. Tumors first appeared when children were 2 years of age. (B) Note tumors of trunk and forearms. (C) Tumors of head of 7-year-old boy. (D) Extensive involvement of hands. (E) Gingival hyperplasia of tumor mass of lower lip. (F) Gingival enlargement. (G) Radiograph showing bone cysts and calcification of skin tumorous masses. (H) Microscopic sections showing cells lying in amorphous stroma. (A from E Drescher et al, J Pediatr Surg 3:427, 1957. B,D courtesy of S Woyke, Szczecin, Poland. C,F from Y Kitano et al, Arch Dermatol 106:877, 19973. H from H Ishikawa and S Mori, Acta Derm Venereol 53:185 1973.)

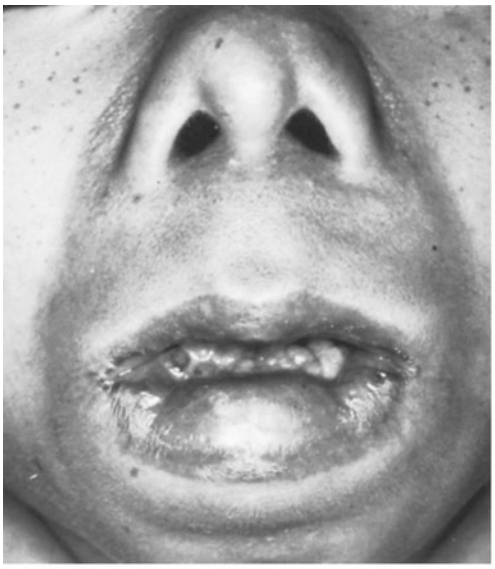
also be affected (13). Contractures were absent in a few patients (26,32). Digital tumors, osteolysis of the terminal phalanges (2,13,27,30,31), and small cystic lesions of long bones, phalanges, and scapulae (9,28) have been noted in over 65% of the patients, as well as generalized osteoporosis and thoracolumbar scoliosis (25) (Fig. 26–3D,G). These lesions progress throughout life (4,9,26). Height and weight are reduced, and skeletal and sexual maturation are delayed (18).

Psychomotor development. Mental development is normal (9,13, 15,19,20,22,27).

Oral findings. Generalized gingival enlargement begins during the first year or so of life (8) and can extend onto the occlusal surfaces of the teeth (22) (Fig. 26–3E,F). Gingival biopsy has demonstrated findings similar to those of the skin (9). Patients with juvenile hyaline fibromas who do not have gingival enlargement (26,32) have been reported. The patient observed by Woyke et al (36) had skin lesions and gingival hyperplasia, but no flexion contractures.

Differential diagnosis includes *infantile systemic hyalinosis* (21), *neurofibromatosis*, and *Winchester syndrome* (7).

Infantile systemic hyalinosis, a disorder of collagen, is an autosomal recessive disorder which presents in infancy with hard diffusely thickened skin, persistent diarrhea, recurrent severe infections, and failure to thrive. Patients also have painful limitation of joints, hypoproteinemia, and papular lesions of the face, mouth, and abdomen. Life expectancy is less than 20 months. There is striking histologic similarity to juvenile hyaline fibromatosis (21). Type VI collagen accumulates in the tissues. It is possible that the infantile and juvenile forms of hyaline fibromatosis are allelic (5,12). *Winchester syndrome* lacks hyaline matrix.



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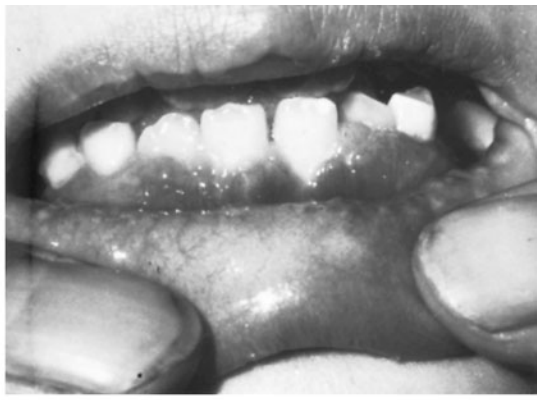

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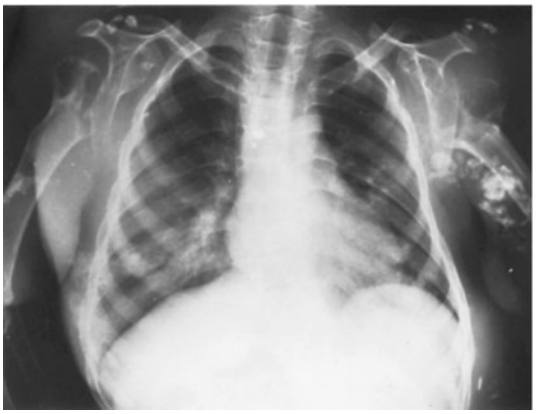

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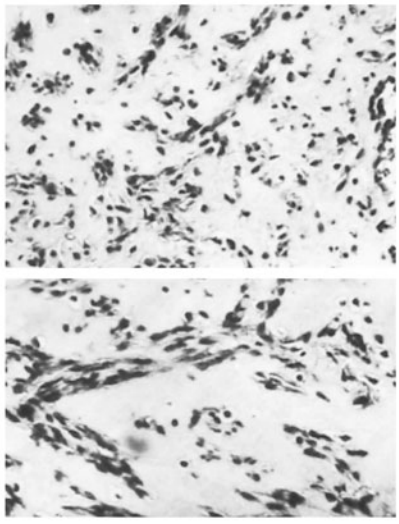

H

Fig. 26–3. (*Continued*)

References [Gingival fibromatosis with juvenile hyaline fibromatosis (Murray-Puretić-Drescher syndrome)]

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Gingival fibromatosis and corneal dystrophy (Rutherfurd syndrome)

Relatively mild gingival enlargement, failure of tooth eruption, and corneal opacities were described in three generations as an autosomal dominant syndrome by Rutherfurd (2). This family was followed up and reported on again in 1966 by Houston and Shotts (1), who described the corneal opacities as curtainlike, involving the superior part of the cornea (Fig. 26–4). Although mental retardation and aggressive behavior have been noted, it is not certain whether these abnormalities are manifestations of the syndrome or are segregating independently.

References [Gingival fibromatosis and corneal dystrophy (Rutherfurd syndrome)]

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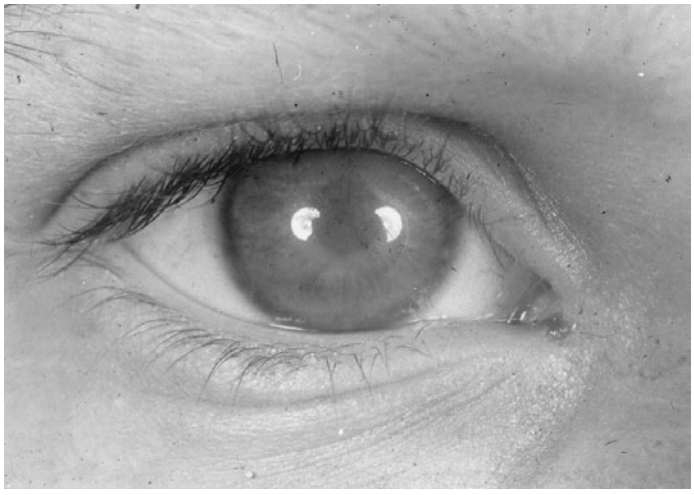
Fig. 26–4. *Gingival fibromatosis and corneal dystrophy (Rutherfurd syndrome)*. Curtain-like corneal opacities. (From I Houston and N Shotts, Acta Paediatr Scand 55:233, 1966.)



Gingival fibromatosis; ear, nose, bone, and nail defects; and hepatosplenomegaly (Laband syndrome, Zimmermann-Laband syndrome)

Zimmermann (20), in 1928, and Laband et al (12), in 1964, described gingival fibromatosis manifested at birth or within the first few months of life, abnormalities of the nose and ears, and striking hypoplastic changes in the terminal phalanges of the fingers and toes. Although most are isolated examples, the syndrome has autosomal dominant inheritance (1,12). However, male and female sibs, the offspring of consanguineous parents, have been reported (2). Henefer and Kay (7) reported a patient with gingival fibromatosis and nasal and ear abnormalities, but the hands and feet were not described. Lacombe et al (13) noted the overlap with *gingival fibromatosis, hypertrichosis, epilepsy, and mental retardation*. About 35 patients have been described (1–15,17–20). We are not convinced that the patient reported by Pfeiffer et al (16) has the syndrome.

Facies. Mild hirsutism in the form of synophrys, hairy arms, back, and legs, thick eyebrows, and increased sacral hair has been noted (9,10,15,17,20) (Fig. 26–5A). Severe hirsutism was noted by Lacombe et al (13).

Skeletal alterations. The thumb nails are hypoplastic or absent. The nails and terminal phalanges on the fingers are usually rudimentary or missing. In most cases, all toes lack terminal phalanges; the first and second toes often have only one phalanx each (9,12,20). Toenails are usually absent (Fig. 26–5B). Pes cavus was noted in about half the kindred described by Laband et al (12). Joint hypermobility, especially involving the metacarpophalangeal, shoulder, and knee joints (1,12), is common. Spina bifida occulta of the fifth lumbar vertebra was described in a few cases (9,20). The third thoracic vertebra has been reported to be divided sagittally into two segments, with the fourth thoracic vertebra flattened (9).

Hepatosplenomegaly. Hepatomegaly (1,15) and splenomegaly (12) have been noted. Laband et al (12) suggested that splenomegaly might become more marked with age. On the other hand, enlargement of the liver and spleen has been specifically denied (15,20).

Other findings. Mental retardation has been reported in several cases (5,6,12,15,17–20). Seizures have also been documented (17) as has retinitis pigmentosa (11).

Oral manifestations. Gingival fibromatosis is a constant feature (Fig. 26–5C).

References [Gingival fibromatosis; ear, nose, bone, and nail defects; and hepatosplenomegaly (Laband syndrome, Zimmermann-Laband syndrome)]

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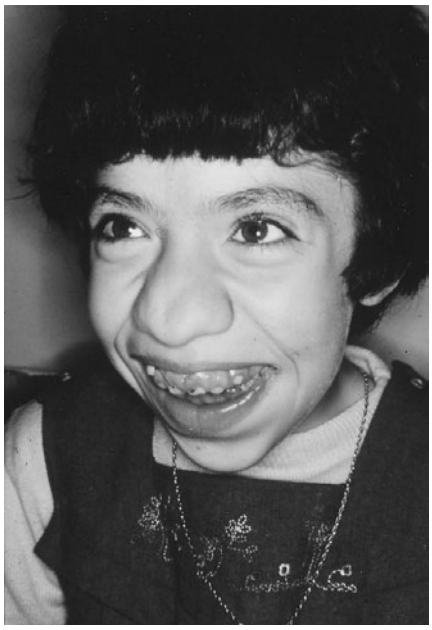

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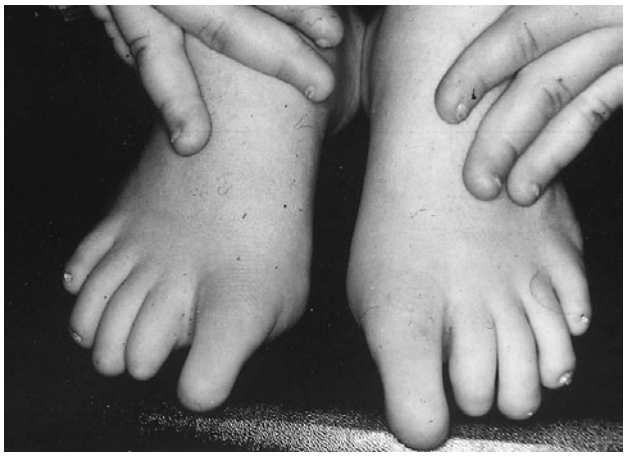

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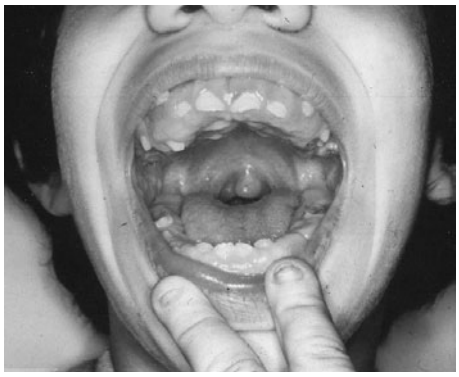

C

Fig. 26–5. *Gingival fibromatosis; ear, nose, bone, and nail defects; and hepatosplenomegaly (Laband syndrome)*. (A) Nose large and poorly formed because of soft cartilage. Note marked gingival enlargement. (B) Hypoplastic nails and terminal phalanges of toes. (C) Hyperplastic gingiva. (From E Bazopoulou-Kyrkanidou et al, J Oral Pathol Med 19:385, 1990.)

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Gingival fibromatosis and sensorineural hearing loss (Jones syndrome)

Jones et al (4), in 1977, Hartsfield et al (3), in 1985, and Wynne et al (6), in 1995, reported autosomal dominant inheritance of generalized gingival fibromatosis and sensorineural hearing loss. Jorgenson and Crocker (5) described a family with gingival fibromatosis, hearing deficiency, and allergy.

Dental eruption was described as delayed in one family (1), with the first primary tooth erupting at 13 months in the proband. Eruption of permanent teeth was delayed as well. The proband in another family (3) had only eight permanent teeth at 12 years. The gingivae were described as hypertrophied, with stippled and nodular areas (Fig. 26–6).

In two of five patients, Wynne et al (6) noted supernumerary teeth.

Hearing loss became evident in the second decade. Audiometric testing revealed a sloping, moderate (30–70 dB) sensorineural hearing loss, which was greater for the higher frequencies. This loss was usually bilateral but varied between ears.

A gene for sensorineural hearing loss (1) and one for gingival fibromatosis (2) have been mapped to chromosome 2p21–p22. Could this represent a contiguous gene syndrome?

References [Gingival fibromatosis and sensorineural hearing loss (Jones syndrome)]

1. Chaib H et al: A gene responsible for a sensorineural nonsyndromic recessive deafness maps to chromosome 2p22–23. Hum Mol Genet 5:155–158, 1996.

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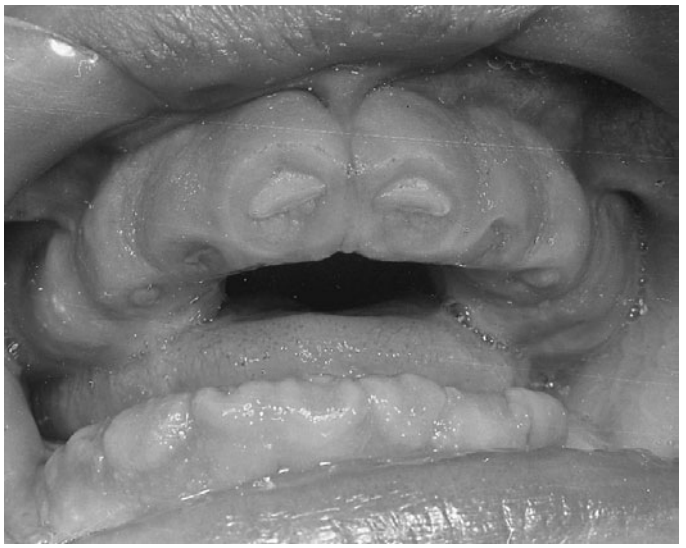

Fig. 26–6. *Gingival fibromatosis and sensorineural hearing loss*. Gingival fibromatosis has buried many teeth.

5. Jorgenson R, Crocker ME: Variations in the inheritance and expression of gingival fibromatosis. J Periodontol 45:472–477, 1974.

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Gingival fibromatosis, hearing loss, and supernumerary teeth

Wynne et al (1), in 1995, described three generations of a family in which affected members had gingival overgrowth (onset at the time of deciduous tooth eruption). Hearing loss, supernumerary teeth, and hypertelorism were present in some affected family members. There are some similarities to *Jones syndrome* (gingival enlargement with hearing loss), but Wynne et al believe this is distinct.

Reference (Gingival fibromatosis, hearing loss, and supernumerary teeth)

1. Wynne SE et al: Hereditary gingival fibromatosis associated with hearing loss and supernumerary teeth—a new syndrome. J Periodontol 66:75–79, 1995.

Gingival fibromatosis, hypertrichosis, cherubism, mental and somatic retardation, and epilepsy (Ramon syndrome)

Ramon et al (4), in 1967, and de Pina-Neto et al (1), in 1986, reported sibs in two different families with gingival fibromatosis, hypertrichosis, cherubism, mental retardation, and seizures. In the first kindred, two sibs were involved; in the latter, four sibs and their second cousin. Sibs were described by Pridmore et al (3).

Progressively cherubic facies associated with bony changes characteristic of cherubism (bilateral multilocular radiolucent lesions of the mandible and maxilla) became evident after the fourth year.

The gingival enlargement has been a constant feature. It becomes manifest at 2 years of age, is slowly progressive, and ultimately prevents normal jaw closure (Fig. 26–7). Tooth eruption is considerably delayed and incomplete. In most cases, the incisors and canines erupt. The palate tends to be narrow. Gingival biopsy showed a peculiar perivascular pattern of collagen fibers that compress the blood vessels (3).

Pigmentary retinopathy was noted on follow-up (2).

Mild to moderate mental retardation became evident during the first few years of life. By the fourth year, all patients experienced major seizures. Stunted growth was evident in nearly all the affected. Hearing loss was found in two sibs (3).

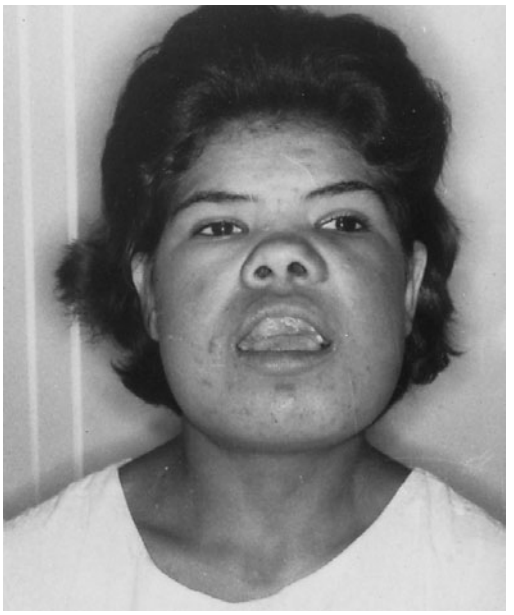

Fig. 26–7. *Gingival fibromatosis, hypertrichosis, cherubism, mental and somatic retardation, and epilepsy (Ramon syndrome)*. Combination of cherubism and gingival fibromatosis. (From JM de Pina Neto et al, Am J Med Genet 25:433, 1986.)

Hypertrichosis was present in about 50%. de Pina-Neto et al (1) suggested that juvenile rheumatoid arthritis might also be a component of the disorder. It is entirely possible that this actually represents polyarticular pigmented villonodular synovitis (vide infra). Telangiectasia and angiokeratoma of the soles were documented (3). Giant hypertrophy of the labia minora has also been noted (2).

Affected sibs with normal but consanguineous parents certainly suggest autosomal recessive inheritance (1,4).

It should be pointed out that cherubism has also been found in association with *neurofibromatosis, Noonan syndrome*, and *Noonan-like syndrome with polyarticular pigmented villonodular synovitis*. Perhaps we are really dealing with a contiguous gene deletion syndrome.

References [Gingival fibromatosis, hypertrichosis, cherubism, mental and somatic retardation, and epilepsy (Ramon syndrome)]

1. de Pina-Neto JM et al: Cherubism, gingival fibromatosis, epilepsy, and mental deficiency (Ramon syndrome) plus juvenile rheumatoid arthritis. Am J Med Genet 25:433–442, 1986.

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Gingival fibromatosis and unusual facies

Goldblatt and Singer (1) reported male and female sibs with gingival fibromatosis and unusual facies characterized by macrocephaly, bushy eyebrows, hypertelorism, downslanting palpebral fissures, hypoplastic nasal alae, and cupid bow mouth. An isolated example was reported to one of us (RJG) in March 1998 by A. Lin.

Reference (Gingival fibromatosis and unusual facies)

1. Goldblatt J, Singer SL: Autosomal recessive gingival fibromatosis with distinctive facies. Clin Genet 42:306–308, 1992.

Gingival fibromatosis, unusual facies, café-au-lait pigmentation, and congenital skin telangiectases

Giansanti et al (1) reported a male with gingival fibromatosis, brachycephaly, hypertelorism, multiple congenital skin telangiectases, and café-au-lait pigmentation. The mother had only multiple telangiectases.

Reference (Gingival fibromatosis, unusual facies, café-au-lait pigmentation, and congenital skin telangiectases)

1. Giansanti JS et al: Gingival fibromatosis, hypertelorism, anti-mongoloid obliquity, multiple telangiectases and café-au-lait pigmentation; a unique combination of developmental anomalies. J Periodontol 44:299–302, 1973.

Gingival fibromatosis and growth hormone deficiency

Oikarinen et al (1) described five of eight children with gingival fibromatosis in association with growth hormone deficiency due to lack of growth hormone release factor.

Inheritance appears to be autosomal recessive.

Reference (Gingival fibromatosis and growth hormone deficiency)

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Hyperkeratosis palmoplantaris and periodontoclasia in childhood (Papillon-Lefèvre syndrome and Haim-Munk syndrome)

Papillon and Lefèvre (35), in 1924, described a syndrome consisting of hyperkeratosis of palms and soles and destruction of the supporting tissues of both primary and secondary dentitions. Over 250 cases have subsequently been described. Comprehensive surveys are those of Haneke (22), Hart and Shapira (23), and Hattab et al (28).

The syndrome has autosomal recessive inheritance. Parental consanguinity has been found in about 40% (8,14,21,32). The frequency of the disorder is approximately 1/4,000,000 (17). The disorder has high frequency in Saudi Arabia. The gene has been mapped to chromosome 11q14 (13,24,30) and represents mutations in the lysosomal protease, cathepsin C gene (22a,25,46). Cathepsin C is an enzyme which processes and activates several serine proteases critical to immune and inflammatory responses of myeloid and lymphoid cells. A founder effect has been noted (49).

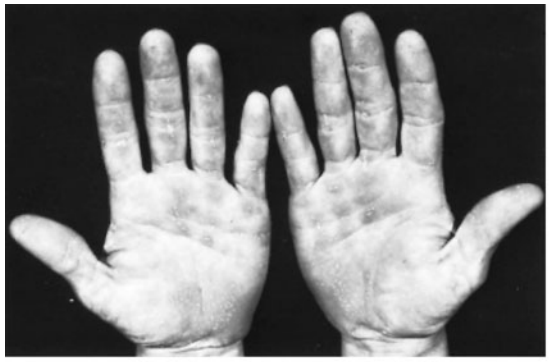
For a discussion of Haim–Munk syndrome, see *Differential diagnosis*.

Skin. Sometime between the second and fourth years of life, or on rare occasions even earlier, the palms and soles become diffusely red and scaly. The hyperkeratotic involvement of the palms is usually quite well demarcated, extending to the edges and over thenar eminences and to the volar wrists. The soles are usually more severely involved, the process frequently spilling over the edges, where it may be marked, extending to the Achilles tendon (Fig. 26–8). Occasionally, the knees, elbows, external malleoli, tibial tuberosities, and dorsal finger and toe joints may exhibit a psoriasiform scaly redness (3,32). Thickening of plantar skin with resultant cracking may make walking difficult. The degree of hyperkeratosis is not severe, but normal skin markings become accentuated and involved skin may assume a parchmentlike quality. The degree of involvement seems to fluctuate, possibly becoming worse during winter. The skin apparently improves somewhat with age but some degree of palmoplantar hyperkeratosis remains throughout life. Nails are rarely, if ever, involved. Relapsing pyoderma is seen in 20% (14).

Other findings. Calcium deposits in the attachment of the tentorium and choroid plexus (17,37,40) have been reported, but possibly this finding is aleatory.

Increased susceptibility to infection with *A. actinomycetemcomitans* has been suggested, but its specificity is dubious (2,7,21,22,29) because

Fig. 26–8. *Hyperkeratosis palmoplantaris and periodontoclasia in childhood (Papillon-Lefèvre syndrome)*. (A–C) Sharply demarcated hyperkeratosis of hands and feet. (C from RK Hall, Aust Dent J 9:185, 1963.)



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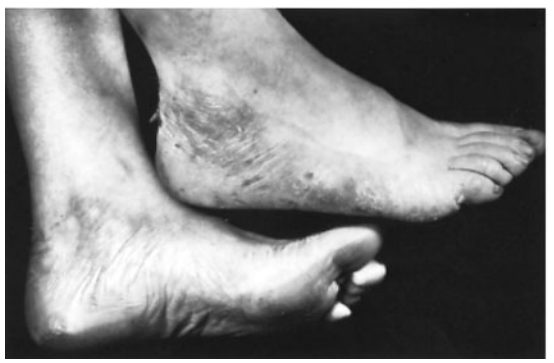

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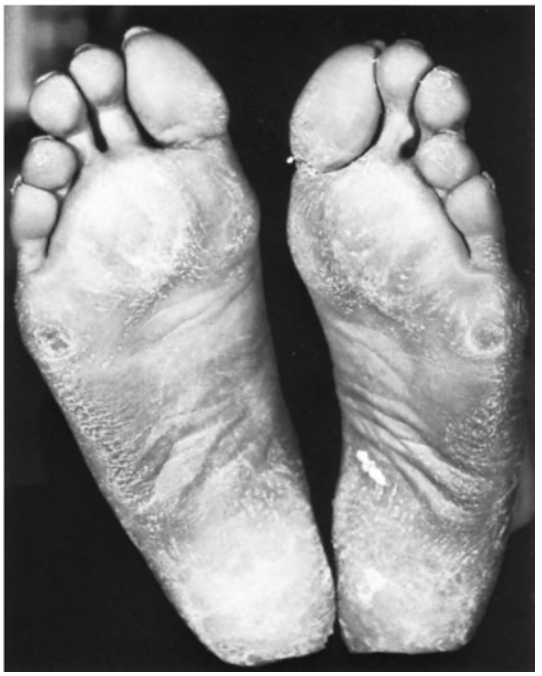

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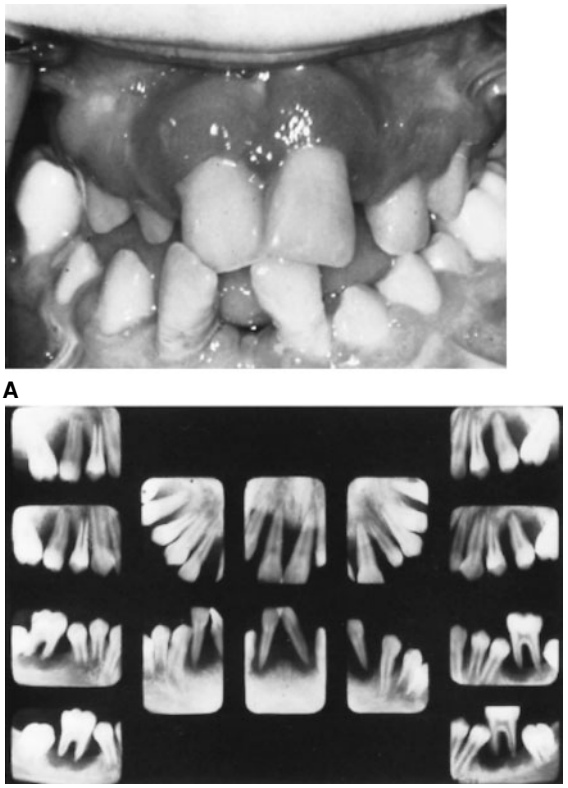

Fig. 26–9. *Hyperkeratosis palmoplantaris and periodontoclasia in childhood (Papillon-Lefèvre syndrome).* (A) Severe periodontal disease in 7-year-old child. (B) Radiograph showing extensive periodontal destruction. (From JS Giansanti et al, Oral Surg 35:30, l973.)

the same finding may occur in juvenile periodontitis (18) (see below). There is a 12% risk for liver abscess (34).

Oral manifestations. The development and eruption of the deciduous teeth proceed normally, but almost simultaneously with the appearance of palmar and plantar hyperkeratosis, the gingiva swell, bleed, and become boggy. Marked halitosis develops. Destruction of the periodontium follows almost immediately the eruption of the last primary molar tooth. The teeth are involved in roughly the same order in which they erupt. Deep periodontal pocket formation precedes the exfoliation of teeth. By the age of 4 years, nearly all primary teeth are lost. After exfoliation, the inflammation subsides and the gingiva resumes its normal appearance. The mouth then appears normal until the secondary (permanent) dentition erupts, when the process is repeated in essentially the same manner. Most teeth are lost by 14 years. In some cases, the third molars do not exfoliate. The alveolar process is often completely destroyed. Even during active periodontal breakdown, the rest of the oral tissues appears perfectly normal (Fig. 26–9).

Differential diagnosis. All disorders of diffuse palmoplantar hyperkeratosis must be excluded. However, none but Papillon–Lefèvre syndrome is associated with premature periodontal destruction with the exception of Haim–Munk syndrome (see below).

Haim and Munk (20) and others (1,19,39,40,43,47) reported an unusual syndrome in several members of three related, inbred Jewish families from Cochin, India. They exhibit congenital palmoplantar keratosis, progressive periodontal destruction, pes planus, recurrent pyogenic skin infections, arachnodactyly with tapered pointed phalangeal ends and a clawlike volar curve (Fig. 26–10). In contrast to Papillon–Lefèvre syndrome, the skin manifestations were more severe and extensive and had later onset. The periodontium also was less severely affected. It was shown in 2000 to be due to an allelic mutation (26) as was juvenile periodontitis (27).

Premature loss of deciduous and/or permanent teeth is seen in trauma, acrodynia, histiocytosis X, *hypophosphatasia*, leukemia, various neutropenias, acatalasia, Chediak–Higashi syndrome, and juvenile periodontitis (15,16,31) (see above). The defect in Chediak-Higashi syndrome appears to be due to mutations in cathepsin G (46).

Hypophosphatasia, a condition transmitted as an autosomal recessive trait because of a deficiency in alkaline phosphatase, may be associated with a ricketslike condition. In addition to genua valga, bowing of the femora and tibiae, enlarged wrists, and other signs, the teeth are prematurely shed, are often hypoplastic, and are deficient in cementum. There is no gingival inflammation. Increased amounts of phosphoethanolamine are present in the urine.

Acatalasia is transmitted as an autosomal recessive trait and rarely has been observed outside Japan or Korea. It is characterized by progressive gangrenous lesions involving the gingiva and alveolar bone, resulting in exfoliation of teeth (38).

Hyperkeratosis palmaris has been seen in binary association with a host of other disorders (15,17). It may also occur in the syndrome of *hyperkeratosis palmoplantaris and attached gingival hyperkeratosis*.

Autosomal dominantly inherited palmoplantar hyperkeratosis has been associated with short stature, unusual facies, hearing loss, seizures, clinodactyly, dysplastic nails, and oligodontia (42).

Brown et al (4) and Bullon et al (5) reported a late-onset (fourth decade) variant of Papillon-Lefèvre syndrome.

Laboratory aids. Various immunologic defects have been reported. These have included impaired in vitro reactivity to T and B cell mitogens

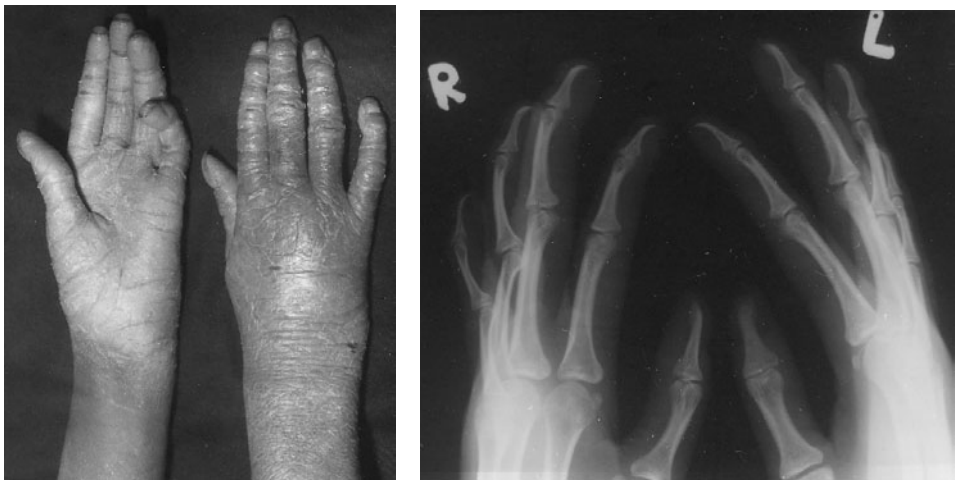

Fig. 26–10. *Hyperkeratosis palmoplantaris and periodontoclasia in childhood (Haim-Munk syndrome).* (A,B) Severe hyperkeratosis of hands with arachnodactyly. Note tapered pointed terminal phalanges exhibiting clawlike volar curve. (From S Haim and J Munk, Br J Dermatol 77:42, 1965.)

(30,48), a neutrophil chemotactic defect, altered phagocytosis, and reduced intracellular killing of *S. aureus* and *C. albicans* (7,10,11,13). Lymphocyte subset and monocyte function abnormalities have also been described (10,11,13,22,38). However, others have not found defective function (6,41,45).

References [Hyperkeratosis palmoplantaris and periodontoclasia in childhood (Papillon-Lefèvre syndrome and Haim-Munk syndrome)]

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Palmoplantar hyperkeratosis, atrichia, mental retardation, and premature loss of teeth

Steijlen et al (1) described four affected sibs (three female, one male) among seven children of unrelated parents.

The atrichia was congenital and generalized. Palmoplantar hyperkeratosis became apparent by 11/2–2 years. It extended to the dorsal surface of the hands. The achilles tendon area was similarly affected. All had keratosis pilaris. Teeth were lost early but were removed because of a dysplastic defect of unknown nature.

Retardation was moderate to severe.

Inheritance is probably autosomal recessive.

An extensive differential diagnosis was presented by the authors but none fit. Also see *atrichia, somatic and mental retardation, and skeletal anomalies.*

Reference (Palmoplantar hyperkeratosis, atrichia, mental retardation, and premature loss of teeth)

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Hyperkeratosis palmoplantaris and attached gingival hyperkeratosis

Fred et al (1), in 1964, reported a kindred with hyperkeratosis palmoplantaris and attached gingival hyperkeratosis. In 1974, while visiting

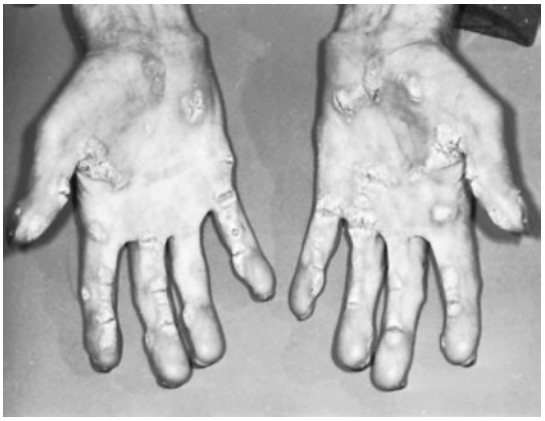

Fig. 26–11. *Hyperkeratosis palmoplantaris and attached gingival hyperkeratosis*. Focal hyperkeratoses of palms.

Athens, Greece, RJ Gorlin had the opportunity to see another family with the same disorder (5). Other families have been reported (3,4,6,11). Another possible kindred has been noted by Roth et al (8).

Autosomal dominant inheritance is indicated by transmission of the disorder through several generations (1,3–5,11). There was male-to-male transmission in all kindreds. Although no specific gene mapping of this form has been carried out, there is resemblance to the tylosis-esophageal cancer gene at 17q24 (9).

Skin and skin appendages. Hyperkeratosis of the palms seems trauma related (Fig. 26–11). Hyperhidrosis is noted in the hyperkeratotic areas. The hyperkeratotic areas appear around puberty in most patients and progress in severity with age. The finger- and toenails exhibit subungual and circumungual keratin deposits. First involved are the toes at 4–5 years of age followed by fingernail changes at 8–9 years. Follicular keratosis of the sebaceous areas of the face is common. Focal to widespread hyperkeratosis of the sole is more marked over the weight-bearing areas: heels, toe pads, and metatarsal heads (Fig. 26–12). These may be painful, inhibiting ambulation (11).

Oral manifestations. Sharply marginated hyperkeratosis involves the labial and lingual attached gingiva (Fig. 26–13). The hard palate, beneath denture-bearing areas, and the lateral areas or dorsum of the tongue may be also affected. The hyperkeratotic areas appear in early childhood and increase in severity with age.

Differential diagnosis. There are many disorders that may be associated with hyperkeratosis palmoplantaris (2). Generalized oral hyperkeratosis, especially that of the buccal mucosa, has been noted in patients with *autosomal dominant tylosis and carcinoma* as well as with congenital strictures and squamous cell carcinoma of the esophagus (7,8,10).

Laboratory aids. Paranuclear bodies are seen in the spinous and granular cell layers of the keratinocytes of the gingival epithelium. Ultrastructural changes show these to be condensed tonofilaments (11).

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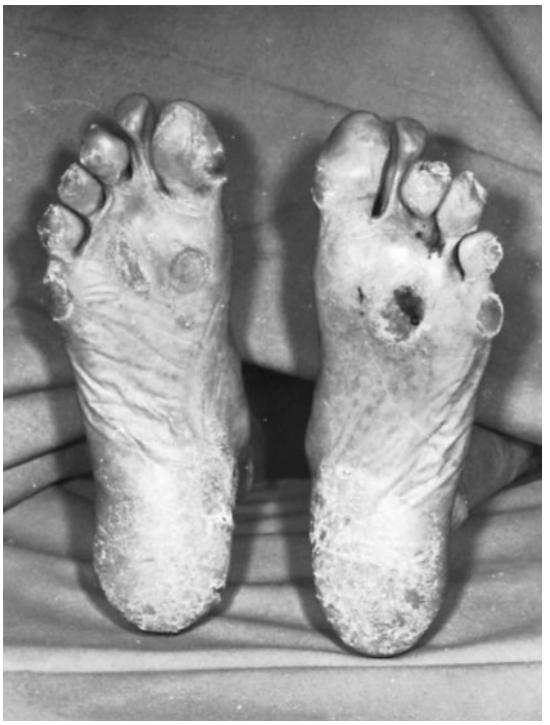

Fig. 26–12. *Hyperkeratosis palmoplantaris and attached gingival hyperkeratosis*. Numerous focal hyperkeratoses of soles, especially over pressure points.

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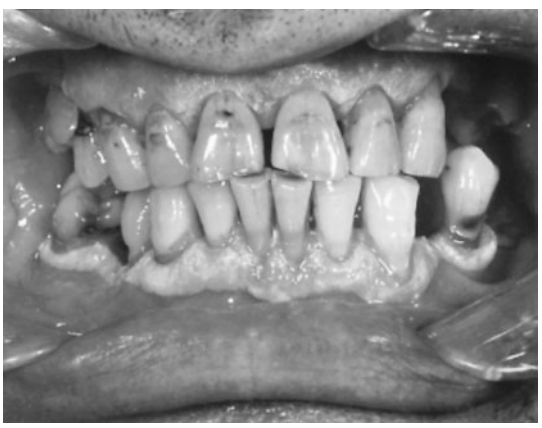
Fig. 26–13. *Hyperkeratosis palmoplantaris and attached gingival hyperkeratosis*. Hyperkeratosis limited to fixed gingiva.



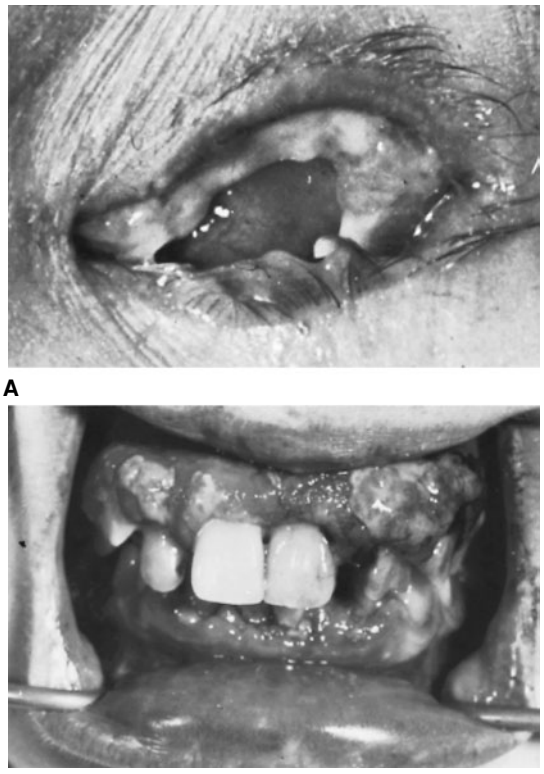


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Fig. 26–14. *Oral and conjunctival amyloidosis and mental retardation*. (A) Atrophy of bulb, amyloid deposits in conjunctiva. (B) Amyloid deposits in gingiva, imparting appearance of icing. (From J Hornová and O Dluhosová, Oral Surg 25:457, 1968.)

Oral and conjunctival amyloidosis and mental retardation (Hornová-Dluhosová syndrome)

Hornová and Dluhosová (6) reported a boy and his mentally retarded sister. Within the first year of life, the eyelids were noted to be swollen, with nodular deposits of amyloid in the conjunctiva. Congenital cataracts, atrophy of ocular bulb, and amaurosis were also present. Amyloid deposits found in the enlarged boggy gingiva imparted the appearance of icing (Fig. 26–14).

Autosomal recessive ligneous conjunctivitis, caused by mutation in the plasminogen gene at 6q26, may also exhibit gingival and other mucosal involvement (1,2,5,7), and the relationship to a condition characterized by an amyloidaceous ulcerated gingival and conjunctival disorder is not known (2–4).

References [Oral and conjunctival amyloidosis and mental retardation (Hornová-Dluhosová syndrome)]

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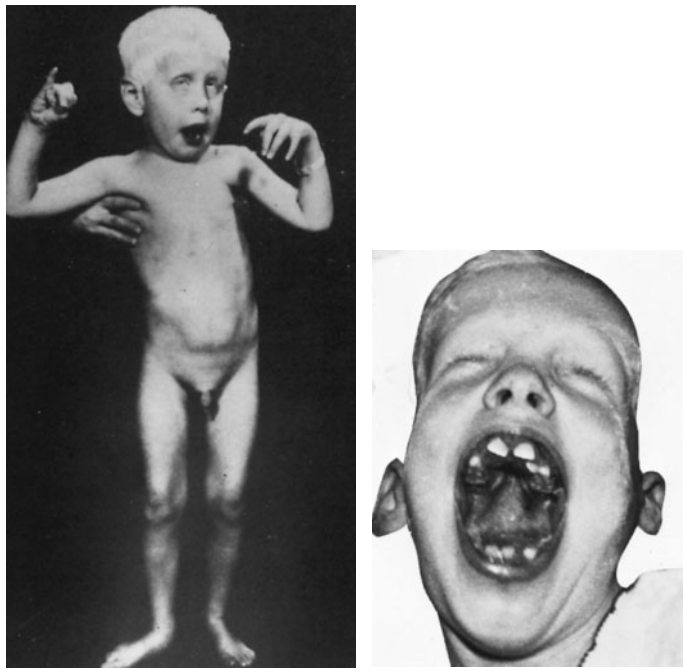

A B

Fig. 26–15. *Gingival fibromatosis, hypopigmentation, microphthalmia, mental retardation, and athetosis (Cross syndrome)*. (A) 4-year-old boy with silvery white hair and ptosis. (B) Note microphthalmia, hypopigmented skin, enlarged gingiva. (A from MA Patton et al, J Med Genet 24:118, 1987. B from HE Cross et al, J Pediatr 70:398, 1967.)

Gingival fibromatosis, hypopigmentation, microphthalmia, mental retardation, and athetosis (Cross syndrome)

Cross et al (2), in 1967, described Amish sibs with microphthalmia, cloudy cornea, and hypopigmented skin (Fig. 26–15). Since then several examples have been reported in other groups (1–4,6,8–12).

There is severe postnatal growth retardation (4).

Ocular anomalies include microphthalmia, enophthalmia, microcornea, corneal opacities, cataracts, nystagmus, and blindness (1).

By the third month of life, there are signs of spastic tetraplegia with athetoid movement. All patients have been severely mentally retarded and exhibit axial hypotonia.

The hypopigmented skin and silver-gray metallic-appearing hair, evident at birth, are deficient in tyrosinase-positive melanosomes (1,12).

Gingival fibromatosis, less severe than in *gingival fibromatosis, hypertrichosis, epilepsy, and mental retardation*, is a rare feature. We suspect that it is secondary to an antiseizure medication and not primary. Witkop et al (12) were the first to note the association. Courtens et al (1) and Passarge and Fuchs-Mecke (7) found enamel and dentin hypoplasia.

Autosomal recessive inheritance has been established (2,4,9).

The syndrome of oculocutaneous hypopigmentation with osteoporosis and a Morquio-like body phenotype , described by Hernández et al (5), appears not to be Cross syndrome, although osteoporosis has occasionally been reported in Cross syndrome (2,9). The syndrome has been described in association with Bartter syndrome, but we suspect that this is aleatory (11).

References [Gingival fibromatosis, hypopigmentation, microphthalmia, mental retardation, and athetosis (Cross syndrome)]

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Chapter 27
Syndromes with Unusual Dental Findings

Oculo-facio-cardio-dental syndrome

Marashi and Gorlin (5,6), in 1990 and 1992, described three examples of binary combination of congenital cataracts and canine radiculomegaly. They cited an earlier example of Hayward (3) in which canine radiculomegaly, delayed dentition, persistent primary teeth, oligodontia, and congenital cataracts were found in an 18-year-old female. Wilkie et al (11) reported a mother and daughter with congenital cataract, microphthalmia, and septal heart defect, suggesting that this combination represented a new syndrome. Gorlin et al (2) employed the name *oculo-facio-cardio-dental syndrome*. About a dozen examples have been described to date (1–11).

The occurrence of this syndrome in two generations (4,11, van der Smagt and Hilhorst-Hofstee, personal communication, 1998) and in 12 females but in no males suggests that the syndrome is X-linked dominant, lethal in the male.

Facies. The patient has long and narrow facies. The eyebrows are laterally curved and thick. The nose is sharp with a clearly defined bifid tip. High nasal bridge was noted in at least seven patients. The philtrum tends to be long. Cleft palate or submucous cleft palate has been noted in 50% (1,5,7,10) (Fig. 27–1).

Fig. 27–1. *Oculo-facio-cardio-dental syndrome*. Patient has long sharp nose with indented tip. Congenital cataracts were removed with secondary glaucoma. VSD has been reported. Hammer toes had been corrected.

Eyes. Eye changes, noted in 80% and evident at birth, consist of congenital cataract with or without luxated lenses (1,3,5,7,10,11) and microphthalmia or microcornea (1,5,10,11) with resultant or secondary glaucoma (1,5,10,11). There may be persistent hyperplasia of the primary vitreous. Ptosis and/or blepharophimosis has also been noted (1,3,10,17). Exotropia is very common.

Teeth. Surely the most unmistakable and constant finding is canine radiculomegaly (Fig. 27–2). This is not manifest orally, but its unique nature is seen on a panoramic radiograph of the jaws and may be discovered accidentally. The root ends of the canine teeth do not close until adulthood, the roots continuing to grow until the orbit and lower border of the mandible are reached by the maxillary and mandibular canines, respectively (Fig. 27–3). Other teeth may exhibit root elongation. Other dental anomalies include oligodontia, significantly delayed eruption, persistence of primary teeth, and malocclusion. Fused teeth and supernumerary teeth were noted by Schulze et al (10). One of us (RJG) has noted an elongated canine in a male who otherwise has no stigmata of the syndrome. A single elongated canine has been reported in a short female. The case was not otherwise elaborated (12).

Heart. Cardiac anomalies of various types (ASD, VSD, mitral valve prolapse) have been documented in at least 7 of the 12 patients (1,3,9–11).

Extremities. Cutaneous soft tissue syndactyly of toes 2–3 was found in six patients and hammertoes 2–4 have been described (3,7,9–11). Radioulnar synostosis has been noted (9). The small joints of the hand may be hyperextensible, and the feet may be flat.

Miscellaneous. Findings included septate vagina (11), sensorineural hearing loss (1), nasolacrimal duct obstruction (1,11), small corpus callosum (9), and Dandy-Walker malformation (van der Smagt and Hilhorst-Hofstee, personal communication, 1998) or small vermis (9). Depressive disorder has been reported in a few cases (4,7). Mild scoliosis has been noted.

Diagnosis. Because of the congenital cataracts and congenital heart anomalies, many patients have been misdiagnosed as having *rubella embryopathy*.

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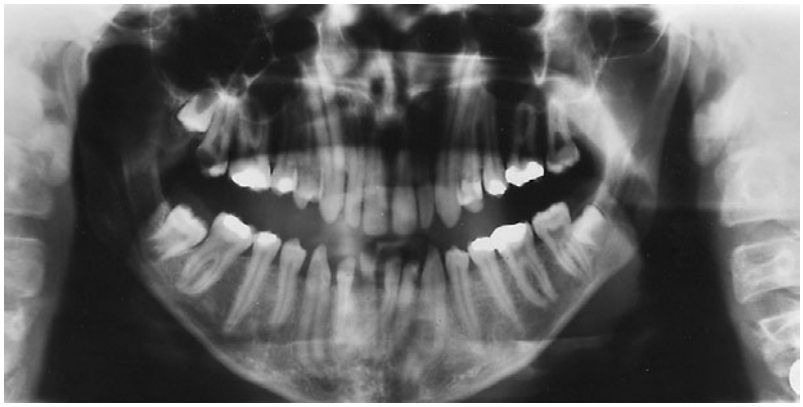

Fig. 27–2. *Oculo-facio-cardio-dental syndrome*. Note remarkable length (>45 mm) of all four canine teeth. Normal length of canines is about 26 mm.

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Fig. 27–3. *Oculo-facio-cardio-dental syndrome*. Extracted canine tooth with open root end. These teeth will grow until they penetrate cortex and cut off their own blood supply.

Cataracts and dental abnormalities (Nance-Horan syndrome)

The syndrome of screwdriver-shaped incisors and congenital posterior cataracts was first described in detail by Nance et al (9) and Horan and Billson (5) in 1974. However, Walsh and Wegman (16) may have described the disorder as early as 1937, although they did not evaluate the dentition. The disorder has X-linked inheritance. Several other families have been published (2,4,6,10,14,15). The gene has been mapped to Xp22.13–p22.31 (1,7,8,11,12,17). The gene appears to be proximate to the amelogenin gene (3).

Eye. Congenital cataracts or microcornea are constant features in affected males, resulting in impaired vision and nystagmus. Posterior Y-sutural cataracts are constant in female carriers. Their corneal diameters are reduced (Fig. 27–4). However, females usually have normal vision. Rarely, cataracts in females are progressive and, with age, may become complete (14). Glaucoma develops in approximately one-half the males.

Intelligence. Mild or moderate mental retardation has been reported in 30% in several kindreds (2,5,7,13–15). In general, it is not associated with motor delay but may be associated with autism (13). It is not expressed in female carriers.

Other findings. Shortened fifth metacarpals are seen in at least 90% of affected males and females. The face is long. The pinnae tend to be simplified and outstanding in over 90% of males and 40% of females. The nose is prominent with a prominent bridge. The vermilion of the upper lip is thin and flat.

Oral manifestations. Affected males have characteristic dental anomalies that include tapered, screwdriver-shaped notched incisors, resulting in diastemas between the teeth (9) (Fig. 27–5A,B). Molars and premolar cusps may also be tapered, the cervical width being greater than the occlusal width (LS Levin, unpublished). The molars may have a mulberrylike form (5). Deciduous and permanent teeth are affected. Maxillary supernumerary incisors (mesiodens) are also noted in at least 65%.

LS Levin has evaluated an affected male in the kindred reported by Goldberg and Hardy (4) who had a supernumerary tooth in the anterior mandible. Carrier females have similarly, although less severely affected, dentitions (Fig. 27–5C). Bixler et al (2) found bilateral absence of the mandibular canines.

There is some overlap with *Lenz microphthalmia syndrome*. There are many syndromes with gene localization overlapping that of Nance–Horan syndrome (13).

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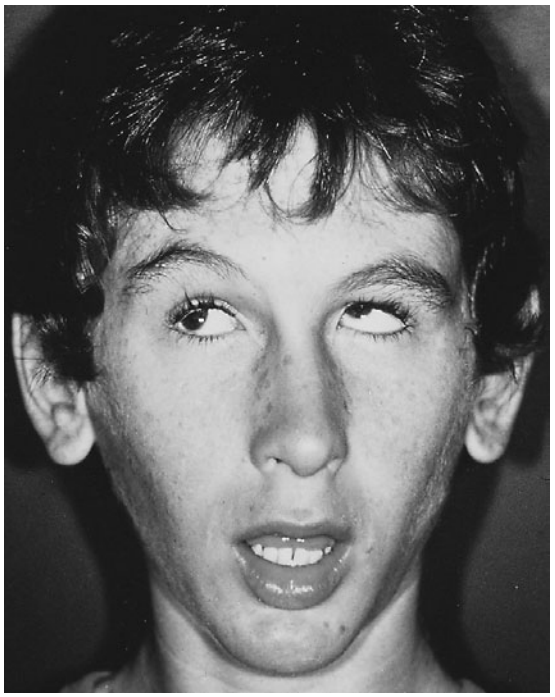

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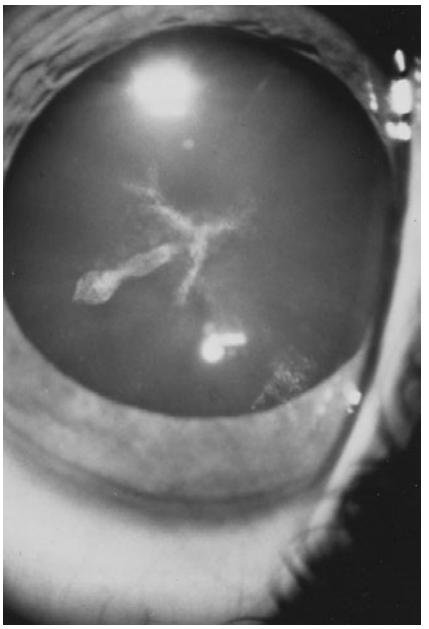

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Fig. 27–4. *Cataracts and dental abnormalities (Nance-Horan syndrome).* (A) Facies showing microphthalmia, strabismus, large anteverted pinnae. (B) Y-sutural cataract in a carrier female. The cataracts in affected males are total at birth. (A from WK Seow et al, Pediatr Dent 7:307, 1985.)

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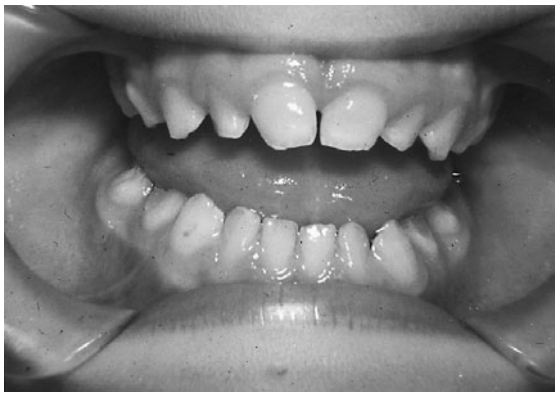
Fig. 27–5. *Cataracts and dental abnormalities (Nance-Horan syndrome).* (A) Deciduous dentition of an affected male. The maxillary deciduous incisors are tapered. (B) Permanent dentition of an affected male. The permanent incisors are tapered. Notches in incisal edges are mamelons. (C) Heterozygote dentition showing diastemas and screwdriver-shaped incisors. (C courtesy of D Bixler, Indianapolis, Indiana.)



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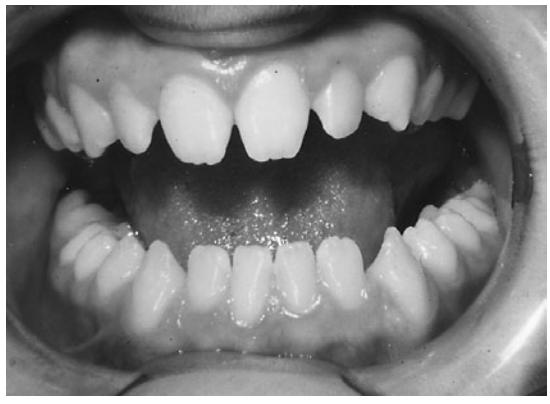

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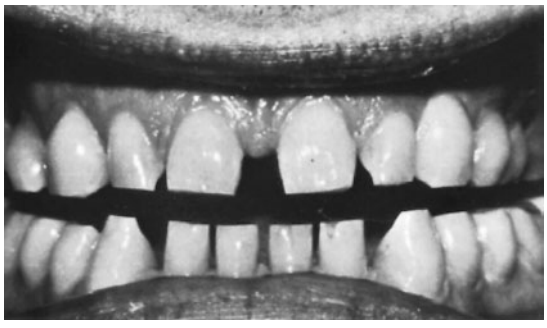

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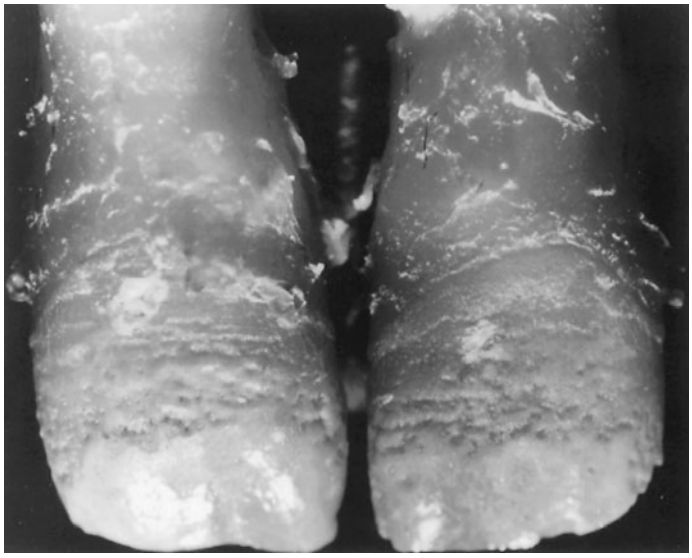


Fig. 27–7. *Tricho-dento-osseous syndrome*. Deciduous incisors showing generalized enamel pitting, most pronounced near the junction of the crown and the root. (From J Lichtenstein et al, Am J Hum Genet 24:569, 1972.)

Tricho-dento-osseous syndrome and tricho-onycho-dental syndrome

Robinson et al (28), in 1966, and Lichtenstein, Jorgenson, Melnick, and co-workers (14,20,22) described a syndrome of amelogenesis imperfecta, taurodontism, curly hair, and, at times, sclerotic bones. Inheritance is autosomal dominant. Other reports have described binary combination of amelogenesis imperfecta of the hypomaturation-hypoplasia type and taurodontism (3,4,7,9,23,25,37,39). Tricho-dento-osseous syndrome stands on its own as a distinct entity on clinical (5,38) and molecular grounds (25). Tricho-dento-osseous syndrome has autosomal dominant inheritance (7,32), the gene having been mapped to 17q21 (11) due to a deletion mutation on a transcription factor, *DLX3*. Mutations in the *DLX3* gene have been identified (25). Gage (9) suggested X-linked inheritance in a family he described, indicating heterogeneity.

There may be two types of tricho-dento-osseous (TDO) syndrome. In the classic form (TDO-I), the scalp hair is kinky or curly in 85% (43), and the lashes are long (32) (Fig. 27–6). The nails may exhibit splitting of the superficial layers in 40% (21,28). The hair tends to straighten in approximately 50% by the second or third decade (22,43). The teeth have pitted thin hypoplastic yellowish-brown enamel and are prone to abscess formation in over 75% (2,7,11,14,21,24,43) (Fig. 27–7). Pulp chambers are enlarged. The roots tend to be short and open. The deciduous and permanent molars are all severely taurodont (43) (Fig. 27–8). The teeth may be delayed in eruption and, not uncommonly, several permanent teeth are impacted. Electron microscopic study has shown a thin enamel layer with randomly distributed depressions and pits. The mineral content of the enamel is close to that of the underlying dentition (22).

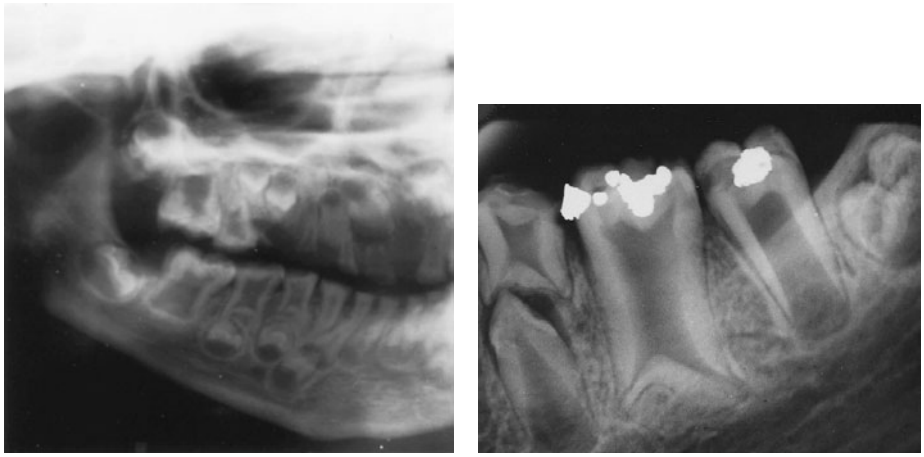
Fig. 27–6. *Tricho-dento-osseous syndrome*. Uncombable hair.

Only Lichtenstein et al (21) suggested sagittal synostosis, but this has never been confirmed. The long bones, calvaria, skull base, frontal bone, and mastoids have increased density with decreased pneumatization of sinuses in 65% of families (Fig. 27–9). Skeletal maturation is delayed and some patients exhibit short ramus, long mandibular body length, longer cranial base, and wider mandibular angle (18,21).

TDO-II, described by Shapiro et al (33) and Quattromani et al (26), is also manifest by curly hair and the same dental changes seen in TDO-I although there is no tendency toward discoloration of the enamel. The long bones do not appear to have increased density. The clavicles are undertubulated. The calvaria manifests not only increased density but increased thickness and obliterated diploë. Frontal sinuses and mastoids tend to be obliterated. The base of the skull shows both increased density and thickness. In contrast to TDO-I, patients with TDO-II have macrocephaly. Whether these two forms represent true heterogeneity is not known. Rivas et al (27) found evidence for linkage between TDO-I locus and ABO, Kell, and Gc loci in the family reported by Lichtenstein et al (21). One would anticipate linkage studies in TDO-II families.

Tricho-onycho-dental syndrome, described by Leisti and Sjöblom (19) and others (17,34,36), is characterized by curly hair that is relatively sparse and easily detachable. There is decreased facial, axillary, and pubic hair. The enamel is hard and thin and has indistinct enamel rods. The dentin is dysplastic and fills the pulp, being similar to that seen in dentin dysplasia, type I. There is some tendency toward precocious eruption of teeth, taurodontism, and short open roots, but no tendency for the permanent teeth to be impacted. The teeth are lost early. The long bones and calvaria have increased density, and the calvaria is increased in thickness. There is narrowing of ear canals among affected males and a tendency toward mandibular prognathism.

Taurodontism may occur as an isolated finding in 0.5%–4% of the population (16) and in many syndromal associations (13): *taurodontism, oligodontia, and sparse hair*; microcephalic dwarfism, microdontia, and diminished anterior root formation (10,29); *trisomy 21 syndrome* (12); *X-chromosome aneuploidy* (1,6,13,35); osteoporosis (8); *Ackerman syndrome, taurodontism, microdontia, and dens invaginatus*, and apparent *monosomy 21* (44). There are many forms of amelogenesis imperfecta



A B

Fig. 27–8. *Tricho-dento-osseous syndrome*. (A) Radiograph of deciduous dentition and developing permanent dentition. Deciduous molars and first permanent molars are taurodont, and the enamel is thin. (B) Extreme taurodontism. (A from RJ Jorgenson and RW Warson, Oral Surg 36:693, 1973. B courtesy of EJ Burkes, Chapel Hill, North Carolina.)

(40,41). Seow (30) distinguished amelogenesis imperfecta from TDO syndrome by the finding of taurodontism in the lower first permanent molar. The trichodental syndrome (16) consists of autosomal dominant inheritance of short hair and oligodontia. A superb discussion of taurodontism is that of Witkop et al (42). Approximately 33% of patients with hypodontia have at least one permanent molar with taurodontism (31).

Short stature with pitted enamel hypoplasia has been noted (16a).

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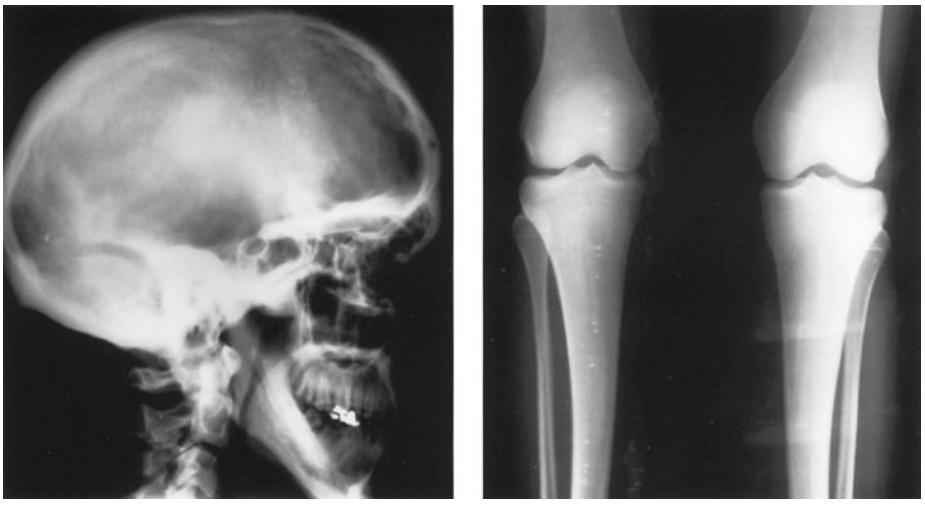

A B

Fig. 27–9. *Tricho-dento-osseous syndrome*. (A) Skull radiograph showing increased bone density and thickening of chondrocranium. The mandibular angles are more oblique than normal. (B) Increased density of long bones. (A from J Lichtenstein et al, Am J Hum Genet 24:569, 1972. B courtesy of R Jorgenson, San Antonio, Texas.)

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39. Winter GB et al: Hereditary amelogenesis imperfecta: A rare autosomal dominant type. Br Dent J 127:157–164, 1969.
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44. Wyandt HE et al: Study of a patient with apparent monosomy 21 owing to translocation: 45,XX,21−,t(18q+). Cytogenetics 10:413–426, 1971.

Odontoonychodermal dysplasia

Fadhil et al, in 1983, described three inbred Lebanese kindred and seven individuals with hyperhidrosis, palmoplantar hyperkeratosis, dry sparse hair, dystrophic nails, teeth with reduced crown form, and oligodontia. Arnold et al (1) reported a similarly affected Dutch case.

Inheritance is autosomal recessive.

References (Odontoonychodermal dysplasia)

1. Arnold WP et al: Variant of odontoonychodermal dysplasia? Am J Med Genet 59:242–244, 1995.
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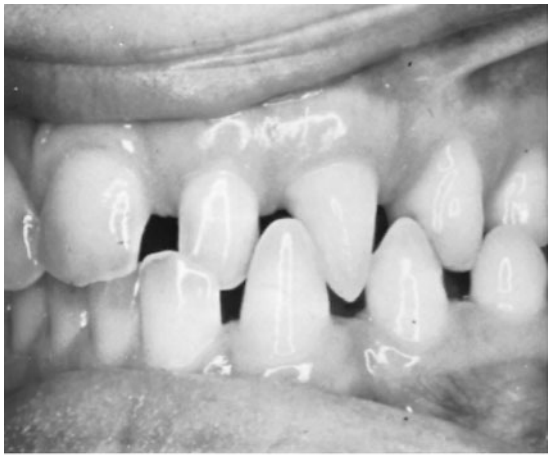
Witkop tooth-nail syndrome (hypodontia and nail dysgenesis) and Fried syndrome

Hypodontia and nail dysgenesis ("tooth and nail" syndrome) was first delineated by Witkop (23), although an earlier case was described by Weech in 1929 (22). It is characterized chiefly by missing teeth and nail dysplasia. Evidence suggests that the syndrome has autosomal dominant inheritance (2,6,8,14). We cannot be certain regarding classification of the disorder documented by Langsteger and Hartwagner (15). Several authors (1–5,8,12,19) reported isolated patients with hypodontia and nail anomalies but without family history. Heterogeneity cannot be excluded (11,14). Nonsense mutations in *MSX1* at 4p16.1 cause the disorder (14a).

Oral findings. Many permanent teeth are congenitally missing or have coniform crowns (4,8,14) (Fig. 27–10A). In some patients, deciduous teeth are also coniform or absent (11,14). The teeth most often missing are mandibular incisors, second molars, and maxillary canines. Taurodontia is apparently not a common finding in this syndrome, although one patient depicted by Hudson and Witkop (14) had taurodont first permanent molars. Deciduous teeth had normal pulp chambers and root canals.

Fig. 27–10. *Witkop tooth-nail syndrome*. (A) Oligodontia and conical tooth crown form. (B,C) Hypoplasia of fingernails and toenails. (A from JS Giansanti et al, Oral Surg 37:576, 1974.)



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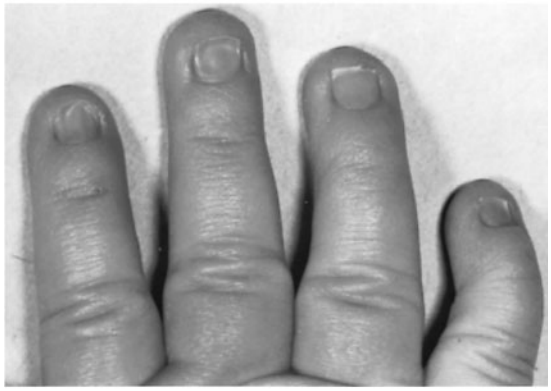

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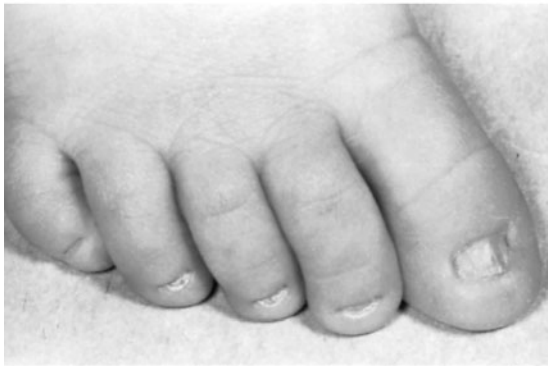

C

Nails. Fingernails and/or toenails are hypoplastic, spoon shaped, and slow growing (8,14) (Fig. 27–10B,C).

Other findings. Although some patients have fine, thin, slow-growing hair (8,14), this abnormality has not been documented in all patients with the disorder. Microscopic examination of the hair has not revealed any obvious abnormality (9,17). Sweating was reported as normal (8,14).

Differential diagnosis. Differential diagnosis includes X-linked and autosomal recessive *hypohidrotic ectodermal dysplasia*. However, patients with this disorder have a typical facies, thin, sparse, slow-growing hair, decreased sweating, and lack of many teeth. Nails are usually not dysplastic. Patients with hypodontia and taurodontia have been reported (21); however, nails and hair were not described. Hypodontia and hypoplastic nails may occur with hearing loss (16).

LS Levin has seen two sibs with hypodontia, taurodontia, and sparse, slow-growing, blond hair. Fingernails and toenails were spoon shaped, thin, and slow growing. The sibs lacked primary maxillary incisors and molars, and the anterior primary teeth were pegged. The deciduous molars were taurodont and nearly all permanent teeth were missing. The parents were normal. Inheritance may be autosomal recessive. Four sibs with a similar constellation of abnormalities were reported by Stenvik et al (20), but the parents were not examined. Fried (7) reported first cousins, each born to consanguineous couples who had congenitally absent and conically shaped deciduous teeth, fine, slow-growing scalp hair, scanty eyebrows, thin fingernails, small thin concave toenails, and normal sweating. The status of the permanent teeth was unknown (Fig. 27–11). This has been called *Fried syndrome*.

We cannot accept the cases of Murdoch-Kinch et al (18) or Hodges and Harley (13) as examples of Witkop tooth and nail syndrome.

References [Witkop tooth-nail syndrome (hypodontia and nail dysgenesis) and Fried syndrome]

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2. Capper A, Bekir NM: Congenital ectodermal defect. Arch Pediatr 54: 160–165, 1937. (Case 2.)
3. Carabok JI, Pigott KLM: A case of partial anodontia, with associated ectodermal dysplasia. Br Dent J 100:311–312, 1956.
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11. Gorlin RJ et al: A selected miscellany: Tooth-nail syndrome. Birth Defects 11(2):45–46, 1975. (Same as Family B in Ref. 14.)
12. Hinrichsen CFL: Ectodermal dysplasia. Aust Dent J 8:101–102, 1963.
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14a. Jumlongras D et al: A nonsense mutation in MSX1 causes Witkop syndrome, Am J Med Genet 69, 2001.
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Autosomal dominant choanal atresia with maxillary hypoplasia, prognathism, and hypodontia

Ramos-Arroyo et al (1) reported two sibs and a cousin with bilateral choanal atresia, tall forehead, maxillary hypoplasia, relative mandibular prognathism, and hypodontia.

Inheritance appears to be autosomal dominant with variable expressivity.

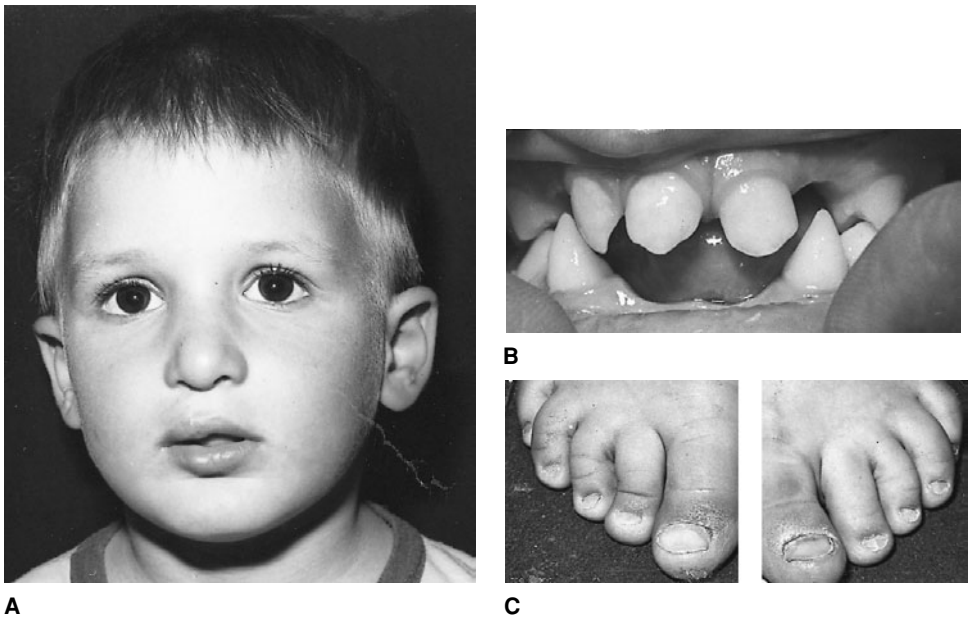


Fig. 27–11. *Fried syndrome*. (A) One of two sibs with fine slow-growing scalp hair and scanty eyebrows. (B) Conical crown forms and oligodontia. (C) Thin concave toenails. (From K Fried, J Med Genet 14:137, 1977.)

Reference (Autosomal dominant choanal atresia with maxillary hypoplasia, prognathism, and hypodontia)

1. Ramos-Arroyo MA et al: Familial choanal atresia with maxillary hypoplasia, prognathism, and hypodontia. Am J Med Genet 95:237–240, 2000.

Anodontia and strabismus

Beierle and Jorgenson (1), in 1978, described a male child with complete failure of formation of deciduous or permanent teeth. Superior oblique muscles of the eye were overactive, and strabismus and rotary nystagmus were evident bilaterally on lateral gaze. Brows, lashes, and lacrimation were normal. Scalp hair was normal in distribution and amount.

Seaver (L Seaver, personal communication, 1998), on follow-up, discovered the same phenotype in the patient's son.

Autosomal dominant inheritance is apparent.

Reference (Anodontia and strabismus)

1. Beierle LE, Jorgenson RJ: Anodontia in a child: Report of a case. J Dent Child 45:483–487, 1978.

Acrodental dysostosis (Weyers syndrome, Curry-Hall syndrome)

Weyers (7–9) reported several unrelated children with postaxial hexadactyly, bony cleft of the mandibular symphysis, and anomalies of the incisors and oral vestibule. Curry and Hall (1) reported several members of a large family with postaxial polydactyly, conical teeth, nail dysplasia, and short limbs. Additional affected kindreds have been described by Shapiro et al (5) and Roubicek and Spranger (3). There is autosomal dominant inheritance (1–7,9). It maps to chromosome 4p16 where it is allelic with *Ellis-van Creveld syndrome* (2,4).

Somatic growth is somewhat retarded. Shortening of limbs is very mild. Postaxial hexadactyly of the hands and feet is variable in expression. There may be fusion of the fifth and sixth metacarpals. Rarely, hexadactly is limited to a postminimus digit. In some cases there has been complete or partial fusion of the proximal phalanges of the fifth and sixth toes (Fig. 27–12).

Fingernails and toenails may be dysplastic and discolored with thick vertical striations and splitting. The thumb and hallucal nails and the fifth toenails are most severely affected.

The facies, apart from the short somewhat retroussé nose with anteverted nostrils, is not unusual. The alae are rounded, giving the end of the nose a somewhat bulbous appearance. Although failure of fusion of the mandibular symphysis was a constant finding in patients of Weyers, all were under 1 year of age. We suspect there was only delay in fusion. Incisors in both dentitions have been described as small with conical crown form but, in some cases, as absent (Fig. 27–13). Occasionally, there are mucosal bands that obliterate the oral vestibule anteriorly, similar to those seen in *Ellis-van Creveld syndrome*. Spranger and Tariverdian (6) reported a father with Weyers syndrome and a daughter with *Ellis-van Creveld syndrome*.

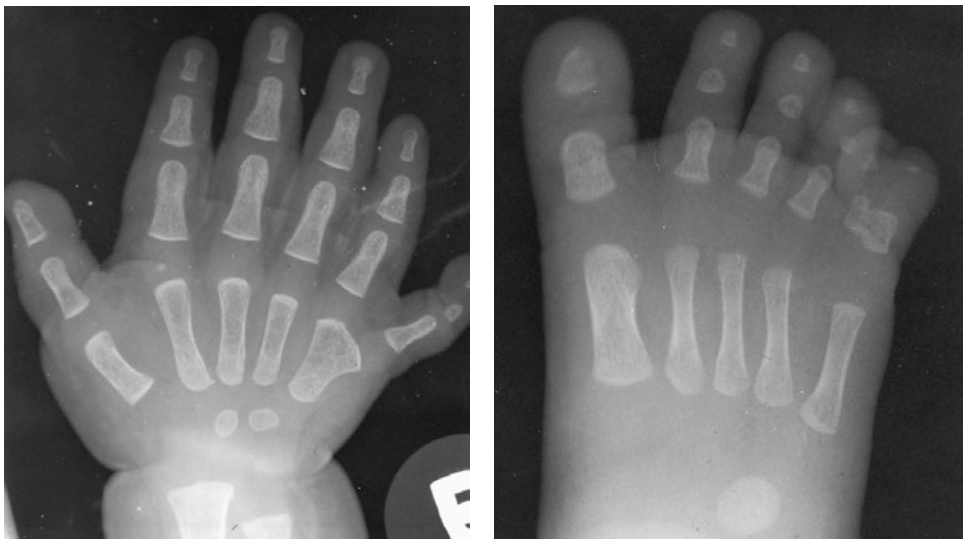
References [Acrodental dysostosis (Weyers syndrome, Curry-Hall syndrome)]

1. Curry CJR, Hall BD: Polydactyly, conical teeth, nail dysplasia, and short limbs: A new autosomal dominant malformation syndrome. Birth Defects 15(5B):253–263, 1979.
2. Howard TD et al: Autosomal dominant postaxial polydactyly, nail dystrophy, and dental abnormalities maps to chromosome 4p16, in the region containing the Ellis–van Creveld syndrome locus. Am J Hum Genet 61:1405–1412, 1997.
3. Roubicek M, Spranger J: Weyers acrodental dysostosis in a family. Clin Genet 26:587–590, 1984.
4. Ruiz-Perez VL et al: Mutations in a new gene in Ellis-van Creveld syndrome and Weyers acrodental dysostosis. Nat Genet 24:283–286, 2000.
5. Shapiro SD et al: Curry-Hall syndrome. Am J Med Genet 17:579–583, 1984.
6. Spranger S, Tariverdian G: Symptomatic heterozygosity in the Ellis–van Creveld syndrome? Clin Genet 47:217–220, 1995.
7. Weyers H: Über eine korrelierte Missbildung der Kiefer and Extremitätenakren (dysostosis acro-facialis). Fortschr Roentgenstr 77:562–567, 1952.
8. Weyers H: Hexadactylie, Unterkieferspalt und Oligodontie—ein neuer Symptomen-komplex: Dysostosis acrofacialis. Ann Paediatr (Basel) 181:45–60, 1953.
9. Weyers H: Zur Kenntnis der Chondroektodermaldysplasie (Ellis–van Creveld). Z Kinderheilkd 78:111–129, 1956.

Hyperhidrosis, premature graying of the hair, and premolar hypodontia (PHC syndrome, Böök syndrome)

Böök (1), in 1950, reported the PHC syndrome: *P*remolar aplasia, *H*yperhidrosis, and *C*anities prematura in a large kindred. The syndrome has autosomal dominant inheritance with complete penetrance. Salinas et al (2) reported a single patient with absence of premolar teeth and hyperhidrosis.

Canities prematura (early, diffuse whitening of the hair) was the most common sign. It appeared usually between the sixth and twenty-third years of life and progressed slowly. About one-third of the patients presented whitening of the hair in other parts of the body. About 65% had marked functional hyperhidrosis. Although often palmoplantar, it involved the axillas and forehead less severely. One or more premolars were absent, with corresponding retention of the deciduous precursors.



A B

Fig. 27–12. *Acrodental dysostosis (Weyers syndrome, Curry-Hall syndrome)*. (A) Postaxial hexadactyly with fusion of metacarpals V and VI. (B) Postaxial hexadactyly of feet. (From M Roubicek and J Spranger, Clin Genet 26:585, 1984.)

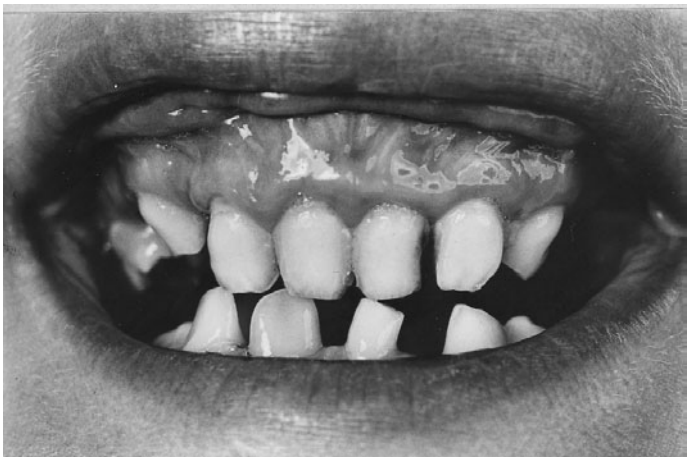


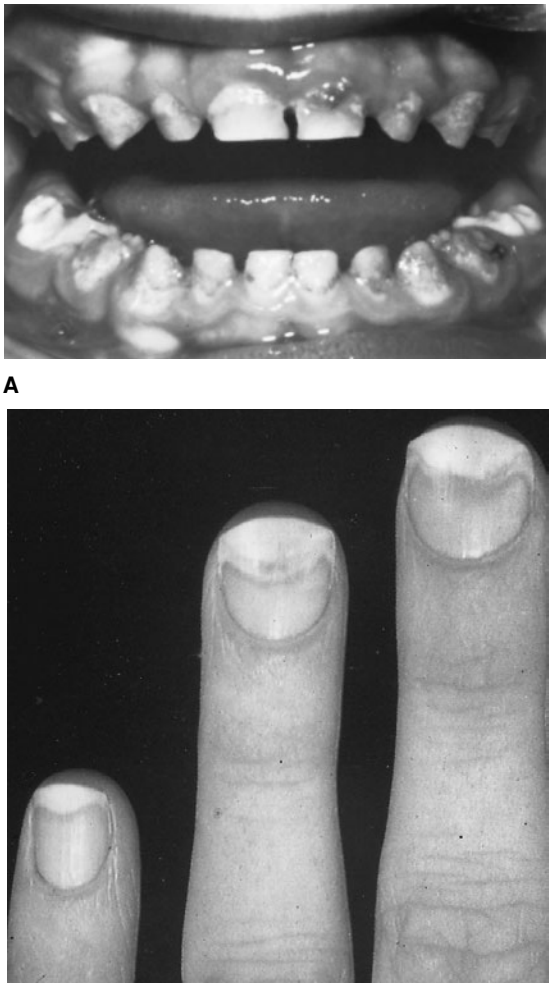
Fig. 27–13. *Acrodental dysostosis (Weyers syndrome, Curry-Hall syndrome)*. Reduced crown form and absent incisor in lower jaw. (From M Roubicek and J Spranger, Clin Genet 26:585, 1984.)

References [Hyperhidrosis, premature graying of the hair, and premolar hypodontia (PHC syndrome, Böök syndrome)]

1. Böök JA: Clinical and genetical studies of hypodontia: I. Premolar aplasia, hyperhidrosis, and canities prematura: A new hereditary syndrome in man. Am J Hum Genet 2:240–263, 1950.
2. Salinas CF et al: Congenitally missing teeth and severe hyperhidrosis: Böök syndrome or a new ectodermal dysplasia syndrome? Dysmorphol Clin Genet 6:59–63, 1992.

Amelogenesis imperfecta and terminal onycholysis (ameloonychohypohidrotic dysplasia)

Witkop and colleagues (1–3) described a kindred exhibiting hypoplastic hypocalcified enamel, multiple unerupted permanent teeth that underwent resorption, terminal onycholysis, seborrheic dermatitis of scalp, xerosis with keratosis pilaris of buttocks, and functional hypohidrosis (Fig. 27–14). Inheritance is autosomal dominant.



A

B

Fig. 27–14. *Amelogenesis imperfecta and terminal onycholysis*. (A) Enamel, largely missing on some teeth, is hypomineralized. (B) Terminal onycholysis. (A from CJ Witkop Jr, Schweiz Monatsschr Zahnheilkd 82:917, 1972.)

References [Amelogenesis imperfecta and terminal onycholysis (ameloonychohypohidrotic dysplasia)]

1. Witkop CJ Jr: Genetics. Schweiz Monatsschr Zahn 82:917–951, 1972.
2. Witkop CJ Jr, Sauk JJ Jr: Heritable disorders of enamel. In: Oral Facial Genetics. Stewart RW, Prescott GH (eds), C.V. Mosby, St. Louis, 1976.
3. Witkop CJ Jr et al: Hypoplastic enamel, onycholysis and hypohidrosis inherited as an autosomal dominant trait. Oral Surg 39:71–86, 1973.

Amelogenesis imperfecta, epilepsy, and mental deterioration (Kohlschütter syndrome)

Kohlschütter et al (3), in 1974, reported five male sibs with a sudden generalized seizure disorder that had its onset between 1 and 4 years of age. Infants had normal development until the appearance of epilepsy; progressive mental and motor deterioration followed, the degree being correlated with the frequency and severity of the seizures. MRI showed cerebral atrophy. Death occurred between 4 and 9 years. All had markedly hypocalcified amelogenesis imperfecta (Fig. 27–15). Associated findings included hypohidrosis, mildly elevated sodium and chloride, but markedly increased potassium in the sweat, and myopia. Other kindreds were reported by Christodolou et al (1), Petermöller et al (4), Zlotogora et al (6), Guazzi et al (2), and Wygold et al (5). Approximately 20 cases have been reported.

Inheritance is autosomal recessive. However, we suspect that it is heterogeneous.

References [Amelogenesis imperfecta, epilepsy, and mental deterioration (Kohlschütter syndrome)]

1. Christodolou J et al: A syndrome of epilepsy, dementia, and amelogenesis imperfecta: Genetic and clinical features. J Med Genet 25:827–830, 1988.
2. Guazzi G et al: Ataxia, mental deterioration, and epilepsy in a family with dominant enamel hypoplasia: A variant of Kohlschütter-Tönz syndrome? Am J Med Genet 50:79–83, 1994.
3. Kohlschütter A et al: Familial epilepsy and yellow teeth—a disease of the central nervous system associated with enamel hypoplasia. Helv Paediatr Acta 29:283–294, 1974.
4. Petermöller M et al: Kohlschütter syndrome: Syndrome of epilepsy-dementia-amelogenesis imperfecta. Neuropediatrics 24:337–338, 1993.
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Amelogenesis imperfecta and platyspondyly

In 1996, Verloes et al (2) described male and female sibs, the offspring of consanguineous Moroccan parents. In addition to mild growth retardation, both manifested generalized platyspondyly with short pedicles, narrow intervertebral and interpediculate distances, rectangular-shaped vertebral bodies with posterior scalloping with herniation of nuclei, and broad femoral necks (brachyolmia). The boy had pectus carinatum and

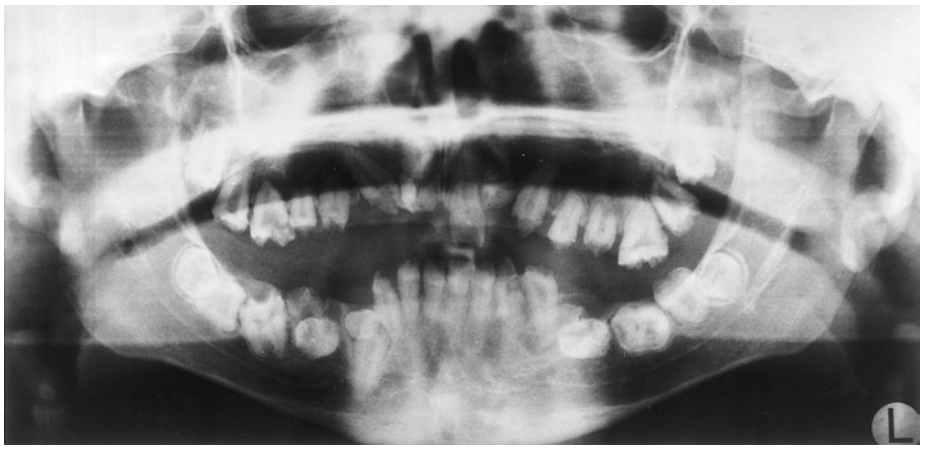


Fig. 27–15. *Kohlschütter syndrome*. Note extensive loss of enamel even on unerupted teeth. (Courtesy of R Kuba and M Ahmad, Minneapolis, Minnesota.)

limited extension at the elbows. In addition, both sibs had hypoplastic amelogenesis imperfecta and oligodontia.

Houlston et al (1) noted a Pakistani boy, the offspring of consanguineous parents, with amelogenesis imperfecta, taurodontism, platyspondyly, and short stature.

Four other forms of brachyolmia are discussed by Verloes et al (2). One must exclude *tricho-dento-osseous (TDO) syndrome*.

Inheritance of this syndrome is probably autosomal recessive.

References (Amelogenesis imperfecta and platyspondyly)

1. Houlston RS et al: Taurodontism and disproportionate short stature. Clin Dysmorphol 3:251–254, 1994.

2. Verloes A et al: A new form of skeletal dysplasia with amelogenesis imperfecta and platyspondyly. Clin Genet 49:2–5, 1996.

Amelogenesis imperfecta and nephrocalcinosis

MacGibbon (4), Lubinsky et al (3), and Hall et al (1) reported sibs with amelogenesis imperfecta, nephrocalcinosis, aneuresis, and polyuria. The aneuresis and polyuria began at approximately 2 years of age. The nephrocalcinosis became apparent radiographically at 5 years. Urinary tract infections and pyelonephritis developed in late childhood and early adulthood with malignant hypertension and uremia eventuating during the third decade.

Both primary and secondary dentitions completely lacked enamel. The primary teeth erupted on time, but several permanent teeth remained unerupted with resorption of crowns within the alveolus. Large follicles were noted around the crowns of developing teeth, and multiple pulp calcifications, frequently dagger shaped, were present in the pulp chambers.

Lubinsky et al (3) found abnormalities of calcium-binding proteins with increased levels of osteocalcin, reduced urinary carboxyglutamic acid, and reduced urinary excretion of calcium and phosphate.

Nephrocalcinosis is rare in children but has been associated with renal tubular acidosis, hyperparathyroidism, medullary sponge kidney, Bartter syndrome, hyperoxaluria, and various conditions in which blood calcium is increased or there is increased excretion of calcium in the urine from whatever etiology. It has even been associated with *McCune–Albright syndrome* and *Janssen metaphyseal chondrodysplasia*.

Amelogenesis imperfecta has been seen in a number of conditions, inter alia *Morquio syndrome, tricho-dento-osseous syndrome, amelogenesis imperfecta with taurodontism* (see *TDO syndrome* for discussion)*, oculo-dento-osseous dysplasia,* and the various *epidermolyses bullosa*.

Inheritance is autosomal recessive.

References (Amelogenesis imperfecta and nephrocalcinosis)

1. Hall RK et al: Amelogenesis imperfecta and nephrocalcinosis syndrome. Case study of clinical features and ultrastructure of tooth enamel in two siblings. Oral Surg Oral Med Oral Pathol 79:583–592, 1995.

2. Kessel D et al: Two unusual cases of nephrocalcinosis in infancy. Pediatr Radiol 22:470–471, 1992.

3. Lubinsky M et al: Syndrome of amelogenesis imperfecta, nephrocalcinosis, impaired renal function, and possible abnormality of calcium metabolism. Am J Med Genet 20:233–243, 1985.

4. MacGibbon D: Generalized enamel hypoplasia and renal dysfunction. Aust Dent J 17:61–63, 1962.

Amelogenesis imperfecta and cone-rod dystrophy

Jalili and Smith (1), in 1988, described 29 affected with progressive cone-rod dystrophy and amelogenesis imperfecta in an extended Arab family from the Gaza Strip. Inheritance was clearly autosomal recessive.

Photophobia and pendular nystagmus starting in the first 2 years of life and total achromatopsia characterized the ophthalmologic findings. Visual acuities ranged from 6/36 to no light perception.

All those affected with the eye problems had rough brown teeth. The enamel was rapidly lost due to hypocalcified amelogenesis imperfecta.

Reference (Amelogenesis imperfecta and cone-rod dystrophy)

1. Jalili IK, Smith NJD: A progressive cone-rod dystrophy and amelogenesis imperfecta: A new syndrome. J Med Genet 25:738–740, 1988.

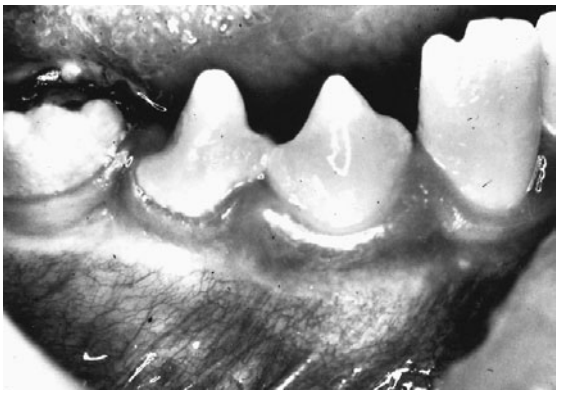
Unusual facies and lobodontia

The canines and premolars have pointed cusps, causing Robbins and Keene (3) to label the condition lobodontia. The molars are multituberculate with single conical roots (Fig. 27–16).

There is general reduction in crown size and there may be hypodontia. The incisors tend to be invaginated or shovel shaped. The cingulum of incisors and premolars is accentuated (1–5).

Inheritance is autosomal dominant (3).

Fig. 27–16. *Unusual facies and lobodontia*. Teeth resemble those of a wolf.



References (Unusual facies and lobodontia)

1. Brook AH, Winder M: Lobodontia—a rare inherited dental anomaly. Report of an affected family. Br Dent J 147:213–215, 1979.
2. Gorlin RJ: Otodental syndrome, oculo-facio-cardio-dental (OFCD) syndrome, and lobodontia: Dental disorders of interest to the pediatric radiologist. Pediatr Radiol 28:802–803, 1998.
3. Robbins I, Keene HF: Multiple morphologic dental anomalies. Oral Surg 16:683–690, 1964.
4. Schulze C: Erbbedingte Formanomalien sämtlicher Zähne-ein neues Syndrom? Zahnartliche Welt Rundschau 85:80–94, 178–182, 1976.
5. Shuff RY: A patient with multiple conical teeth. Dent Prosth 22:414–417, 1972.

Unusual facies, digital anomalies, and supernumerary teeth

Ravine et al (personal communication, 1995) corresponded regarding a syndrome of supernumerary teeth and tracheal subglottic hypoplasia predisposing to recurrent croup in childhood.

The hands appeared unusual with prominent distal and proximal interphalangeal joints, clinodactyly of the fifth fingers, brachydactyly of fingers and toes, club feet, and external rotation of hips.

The facies is unusual due to prominent forehead and prominent widow's peak. Progressive conductive hearing loss and supernumerary teeth were noted.

Four generations were involved with male-to-male transmission. Autosomal dominant inheritance is evident.

Unusual facies and autosomal dominant hypohidrotic ectodermal dysplasia (Bocian-Rimoin syndrome)

Bocian and Rimoin (1), in 1979, reported an autosomal dominant form of ectodermal dysplasia characterized by hypohidrosis; sparse body hair, scalp hair, eyebrows, and eyelashes; thin, slow-growing nails; hypoplastic nasal bridge; hypoplastic nasal alae; anteverted nostrils; long philtrum; and thin inverted upper lip. Tooth eruption was somewhat delayed. Oligodontia resulted in a number of deciduous teeth being maintained. The enamel was hypoplastic.

Somewhat similar findings are seen in the autosomal dominantly inherited disorder(s) described by Harrod et al (2), Saihan and Warin (4), and Jorgenson et al (3). However, unusual facies was not noted.

We wonder if this is not *Hay-Wells syndrome*.

References [Unusual facies and autosomal dominant hypohidrotic ectodermal dysplasia (Bocian-Rimoin syndrome)]

1. Bocian M, Rimoin DL: A new autosomal dominant syndrome of hypohidrotic ectodermal dysplasia and unusual facies. Birth Defects 15(5B):239–251, 1979.
2. Harrod MJ et al: Dominantly inherited hypohidrotic ectodermal dysplasia with dental anomalies. Birth Defects 13(3C):236, 1976.
3. Jorgenson RJ et al: Autosomal dominant ectodermal dysplasia. J Craniofac Genet Dev Biol 7:403–412, 1987.
4. Saihan E, Warin RP: Ectodermal dysplasia. Br J Dermatol 97(Suppl 34): 1977.

Unusual facies and autosomal recessive hypohidrotic ectodermal dysplasia (Kopyść syndrome)

Kopyść et al (1) described two sibs, male and female, with hypodontia, teeth with conical crown form, sparse, thin, brittle scalp hair, pili annulati, follicular hyperkeratosis of trunk and limb, and hyperopia. Sweating was normal (Fig. 27–17).

Inheritance is probably autosomal recessive.

Reference [Unusual facies and autosomal recessive hypohidrotic ectodermal dysplasia (Kopyść syndrome)]

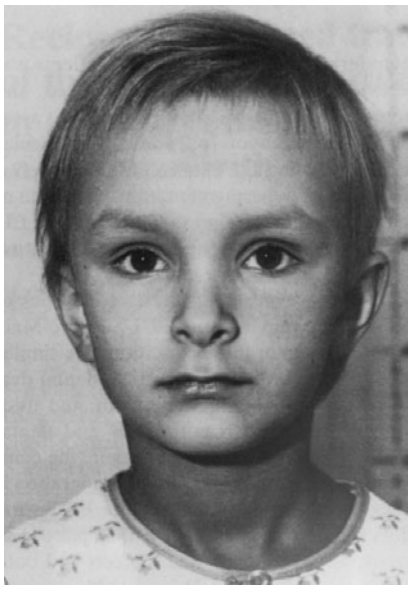
1. Kopyść Z et al: A new syndrome in the group of euhidrotic ectodermal dysplasia. Hum Genet 70:376–378, 1985.

Lacrimo-auriculo-dento-digital (LADD) syndrome (cup-shaped ears, anomalies of the teeth and lacrimal ducts, and mixed hearing loss) (Levy-Hollister syndrome)

The lacrimo-auriculo-dento-digital (LADD) syndrome was first delineated in 1973 by Hollister et al (7). Features included nasolacrimal duct obstruction with chronic dacryocystitis, absent lacrimal puncta, cup-shaped ears, peg-shaped teeth with enamel hypoplasia, various preaxial digital anomalies, clinodactyly, and hearing loss. A single patient described by Levy (11) probably had the same syndrome, leading to an alternate eponym, Levy-Hollister syndrome. A possible earlier example is that of Faber (4). Over 35 cases have been described in the literature (1–16).

Inheritance is clearly autosomal dominant.

Almost all affected persons had nasolacrimal duct anomalies, including duct aplasia or hypoplasia, nasolacrimal duct obstruction, absent



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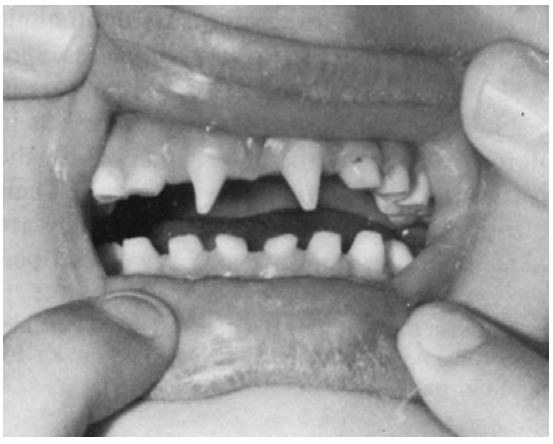

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Fig. 27–17. *Unusual facies and autosomal recessive hypohidrotic ectodermal dysplasia (Kopyść syndrome).* (A) Sparse, thin and brittle scalp hair. Note broad dorsum of nose. (B) Note conical crown form of upper incisors. (B from Z Kopyść et al, Hum Genet 70:376, 1985.)

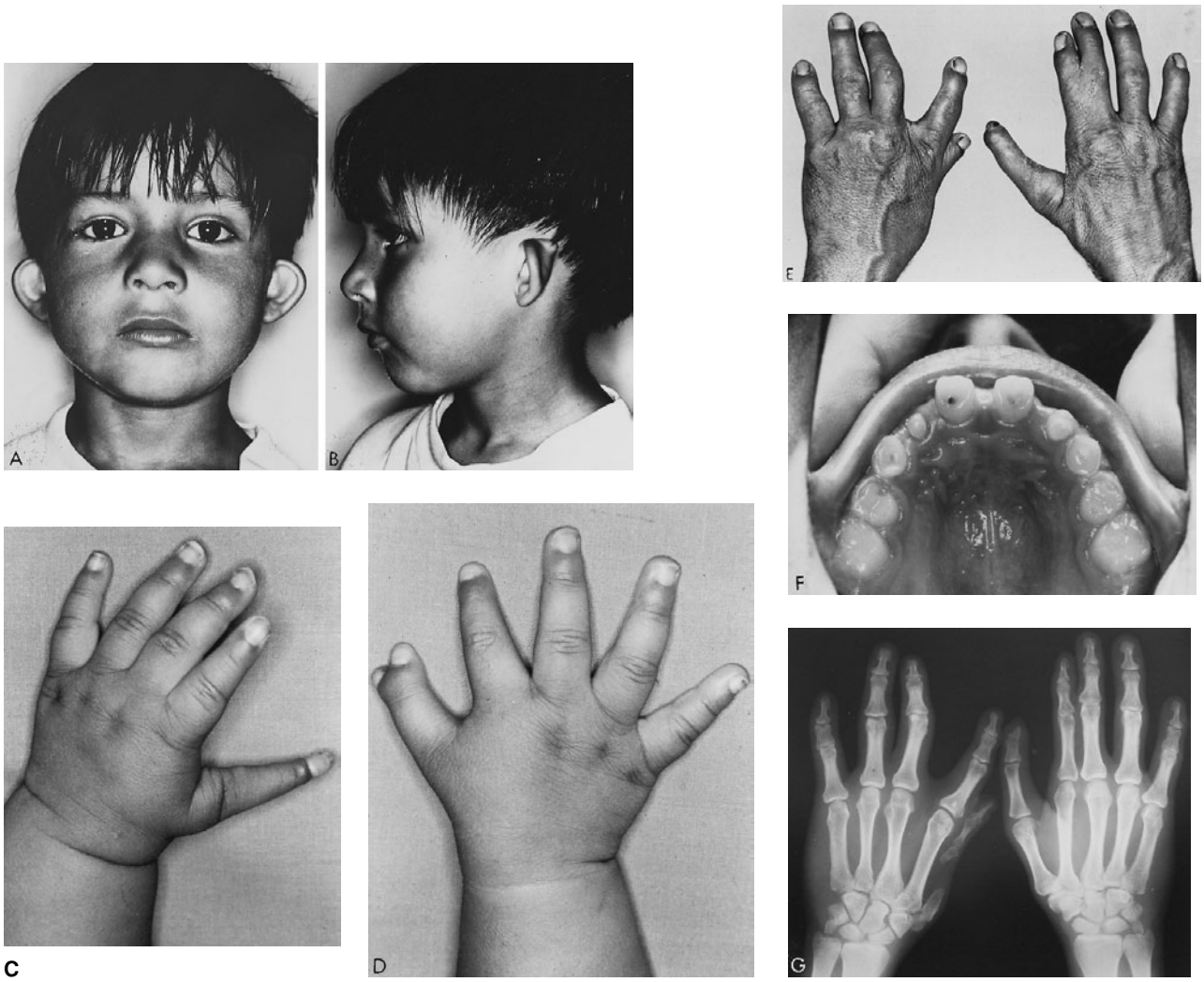

Fig. 27–18. *Lacrimo-auriculo-dento-digital syndrome*. (A,B) Prominent cup-shaped ears extend at right angles from the side of the head. The eyes have a watery, glistening appearance, and on the right there is an overflow of tears from the outer canthus. (C,D) Long, tapering thumbs with large nail, bifid thumb tip with extra ectopic nail and tapering of second and third digits bilaterally. (E) Right hand has long, tapering thumb with ectopic nail and syndactyly. Left hand has rudimentary thumb fused to index finger, prominent interdigital cleft between second and third fingers, and ulnar deviation of third digit. (F) Maxillary lateral incisors have conical crown form. Premolar cusp patterns are abnormal and show excessive wear. (G) Radiograph of hands seen in E. Tip of right thumb has extra tuftlike ossification center. Left hand shows hypoplasia of greater multangular and phalanges of thumb. Metacarpal is represented by two widely separated ossification centers. (From D Hollister et al, J Pediatr 84:438, 1972.)

lacrimal puncta usually associated with chronic epiphora, dacryocystitis, and recurrent kerato-conjunctivitis. Nasolacrimal duct fistulas (9) and completely absent tearing (15,16) were also described. Absence of the parotid glands and Stensen's ducts has been noted (4,13) as well as salivary gland anomalies (10,15,16).

Digital anomalies are variable and include duplicated terminal phalanx of the thumb, digitalized thumb, triphalangeal thumb, thenar muscle hypoplasia, preaxial polydactyly, exaggerated interdigital cleft between the second and third fingers, syndactyly of the second and third digits, and fifth finger clinodactyly (Fig. 27–18). Metacarpophalangeal profiles show shortness of distal phalanges. Other limb anomalies include shortening of the radius and ulna, radioulnar synostosis, and, occasionally, absent radius (5,9). The multiplicity of radial anomalies led Temtamy and McKusick (14) to suggest that LARD (lacrimo-auriculo-radio-dental) syndrome might be a better acronym. Lower limb anomalies are unusual, but Roodhooft et al (12) described one patient with a supernumerary "metatarsoid" bone and possible phalangeal duplication of the fifth toe. Bamforth and Kaurah (1a) noted broad halluces and anomalies of the first two toenails, and Francannet et al (5) reported 1–2 syndactyly of toes.

Dental anomalies have included hypodontia and peg-shaped incisors, as well as enamel dysplasia of both deciduous and permanent teeth. Tooth discoloration, enamel thinning, excessive wear, and premature decay have often led to full mouth edentulation by adolescence or early adulthood. Hollister et al (7) suggested that the dysplasia might be due to a mild amelogenesis imperfecta-like defect, probably of the hypocalcification type, but this has not been confirmed by pathologic studies.

Hollister et al (7) reported one family member with unilateral renal agenesis. Shiang and Holmes (13) noted a patient with unilateral small scarred kidney and first degree hypospadias. Roodhooft et al (12) described one patient with blunted and dilated renal calyces. Bamforth and Kaurah (1a) reported two deaths due to renal agenesis.

Characteristically, simple cup-shaped ears with a short helix and underdeveloped anthelix have been present in 17 of 20 reported cases. The cup-shaped ears may be unilateral, bilateral, or asymmetrical (7,15) (Fig. 27–18).

Mixed conductive and sensorineural hearing loss, either unilateral or bilateral, has frequently been reported. It has ranged in severity from mild to severe (3,7).

Epiglottic hypoplasia has been noted (1).

While each individual feature of the LADD syndrome may occur as an isolated autosomal dominant trait, their combination is unique. The autosomal dominant *branchio-oto-renal (BOR) syndrome* is similar, with

hearing loss, malformed pinnae, lacrimal duct stenosis, and renal anomalies. It is distinguished from LADD syndrome by auricular pits, branchial fistulas or cysts, and the absence of dental and digital anomalies. *Townes-Brocks syndrome*, in which there is ear deformity, sensorineural hearing loss, preaxial polydactyly, and imperforate anus, can be distinguished from LADD syndrome by the presence of anomalies of the anus and feet, and the absence of abnormalities of the lacrimal ducts and teeth. Absence of the parotid glands has been associated with lacrimal apparatus malformations in the *ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome*. Occasionally individuals with LADD syndrome have split-hand malformation (6,10). However, the EEC syndrome can usually be distinguished by the presence of ectodermal defects, renal anomalies, and oral clefting. In point, Hennekam (6) and Lacombe et al (10) raised the question whether LADD syndrome and EEC syndrome represent a single causal entity.

References [Lacrimo-auriculo-dento-digital (LADD) syndrome (cup-shaped ears, anomalies of the teeth and lacrimal ducts, and mixed hearing loss) (Levy-Hollister syndrome)]

1. Azar T et al: Epiglottic hypoplasia associated with lacrimo-auriculo-dental-digital syndrome. Ann Otol Rhinol Laryngol 109:779–781, 2000.

1a. Bamforth JS, Kaurah P: Lacrimo-auriculo-dento-digital syndrome: Evidence for lower limb involvement and severe congenital renal abnormalities. Am J Med Genet 43:932–937, 1992.

2. Calabro A et al: Lacrimo-auriculo-dento-digital (LADD) syndrome. Eur J Pediatr 146:536–537, 1987.

3. Ensink RJH et al: Congenital conductive hearing loss in the lacrimoauriculodentodigital syndrome. Arch Otolaryngol Head Neck Surg 123:97–99, 1997.

4. Faber M: A case of congenital xerostomia. Acta Paediatr Scand 30:148–151, 1942.

5. Francannet C et al: LADD syndrome in five members of a three-generation family and prenatal diagnosis. Genet Couns 5:85–91, 1994.

6. Hennekam RCM: LADD syndrome: A distinct entity? Eur J Pediatr 146: 94–95, 1987.

7. Hollister DW et al: Lacrimo-auriculo-dento-digital syndrome. J Pediatr 83:438–444, 1973.

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10. Lacombe D et al: Split hand/split foot deformity and LADD syndrome in a family: Overlap between EEC and LADD syndromes. J Med Genet 30:700–703, 1993.

11. Levy WJ: Mesoectodermal dysplasia. Am J Ophthalmol 63:978–982, 1967.

11a. Murdoch-Kinch CA, Miles DA: Clinical and radiographic features of the lacrimo-auriculo-dento-digital syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 81:727–735, 1996.

12. Roodhooft AM et al: Lacrimo-auriculo-dento-digital (LADD) syndrome with renal and foot anomalies. Clin Genet 38:228–232, 1990.

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15. Thompson E et al: Phenotypic variations in LADD syndrome. J Med Genet 22:382–385, 1985.

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Multiple anterior dens invaginatus and sensorineural hearing loss

A female child seen by Kantaputra and Gorlin (1) had double dens invaginatus of maxillary central incisors combined with premolarization of maxillary lateral incisors and first deciduous molars. She was missing two lower right permanent incisors. There was dens invaginatus of the lower left central and lateral incisors (Fig. 27–19).

Facial appearance was normal except for some fullness at the bridge of the nose and somewhat dilated nostrils). She had bilateral, moderately severe sensorineural hearing loss. Although estimate of IQ was approximately 75, this may well have been in error due to a combination of hearing loss and shyness.

Reference (Multiple anterior dens invaginatus and sensorineural hearing loss)

1. Kantaputra PN, Gorlin RJ: Double dens invaginatus of molarized maxillary central incisors, premolarization of maxillary lateral incisors, multituberculism of mandibular incisors, canines and first molar, and sensorineural hearing loss. Clin Dysmorphol 1:128–136, 1992.

Supernumerary teeth and steroid dehydrogenase deficiency

Lyngstadaas et al (1) described a highly inbred Saudi-Arabian family in which three sibs and a cousin exhibited progressive liver degeneration. Two of the sibs developed giant cell hepatitis early in infancy and died before the fourth year of life. A deficiency of 3β-hydro-Δ5-C27 steroid dehydrogenase was demonstrated, an enzyme that synthesizes bile acids from cholesterol. The propositus exhibited 11 supernumerary teeth.

Inheritance is autosomal recessive.

Reference (Supernumerary teeth and steroid dehydrogenase deficiency)

1. Lyngstadaas SP et al: Severe dental aberrations in familial steroid dehydrogenase deficiency: A new association. Clin Genet 49:249–254, 1996.

Natal teeth and Turnpenny ectodermal dysplasia

Turnpenny et al (1,2), in 1994–5, suggested a new form of ectodermal dysplasia involving skin, hair, and teeth. Inheritance was autosomal dominant.

Scalp hair was thin and body hair was sparse. Sweating appeared to be normal. Two of four had natal teeth.

Acanthosis nigricans was manifested in late childhood.

One must exclude *Clouston syndrome*. Natal teeth occur with a plethora of syndromes such as *Wiedemann-Rautenstrauch syndrome, pachyonychia congenita, Ellis-van Creveld syndrome, Hallermann-Streiff syndrome*, and others.

References (Natal teeth and Turnpenny ectodermal dysplasia)

1. Turnpenny PD et al: A new dominantly inherited ectodermal dysplasia presenting with natal teeth. J Med Genet 31:171, 1994.

2. Turnpenny PD et al: A four generation hidrotic ectodermal dysplasia family: An allelic variant of Clouston syndrome? Clin Dysmorphol 4:324–333, 1995.

Natal teeth and steatocystoma multiplex

There have been two reports of the binary combination of natal teeth and steatocystoma multiplex. This was first noted by McDonald and Reed (2) in 1976. A five-generation kindred with large numbers of affected has been reported by King and Lee (1) in 1987.

This obviously overlaps with *pachyonychia congenita*, but in no case were the nails involved. The reader is also referred to *natal teeth, oligodontia, and syringomas* (see below).

References (Natal teeth and steatocystoma multiplex)

1. King NM, Lee AMP: Natal teeth in steatocystoma multiplex—a new syndrome. J Craniofac Genet Dev Biol 7:311–317, 1987.

2. McDonald RM, Reed WB: Natal teeth in steatocystoma multiplex complicated by hidradenitis suppurativa. Arch Dermatol 112:1132–1134, 1976.

Natal teeth, oligodontia, and syringomas

Morrison and Young (2) reported a father and daughter with variable expression of multiple syringomas, natal teeth, and oligodontia.

A single maxillary incisor was found in the daughter at birth. The secondary dentition consisted of only four molars. Multiple natal teeth

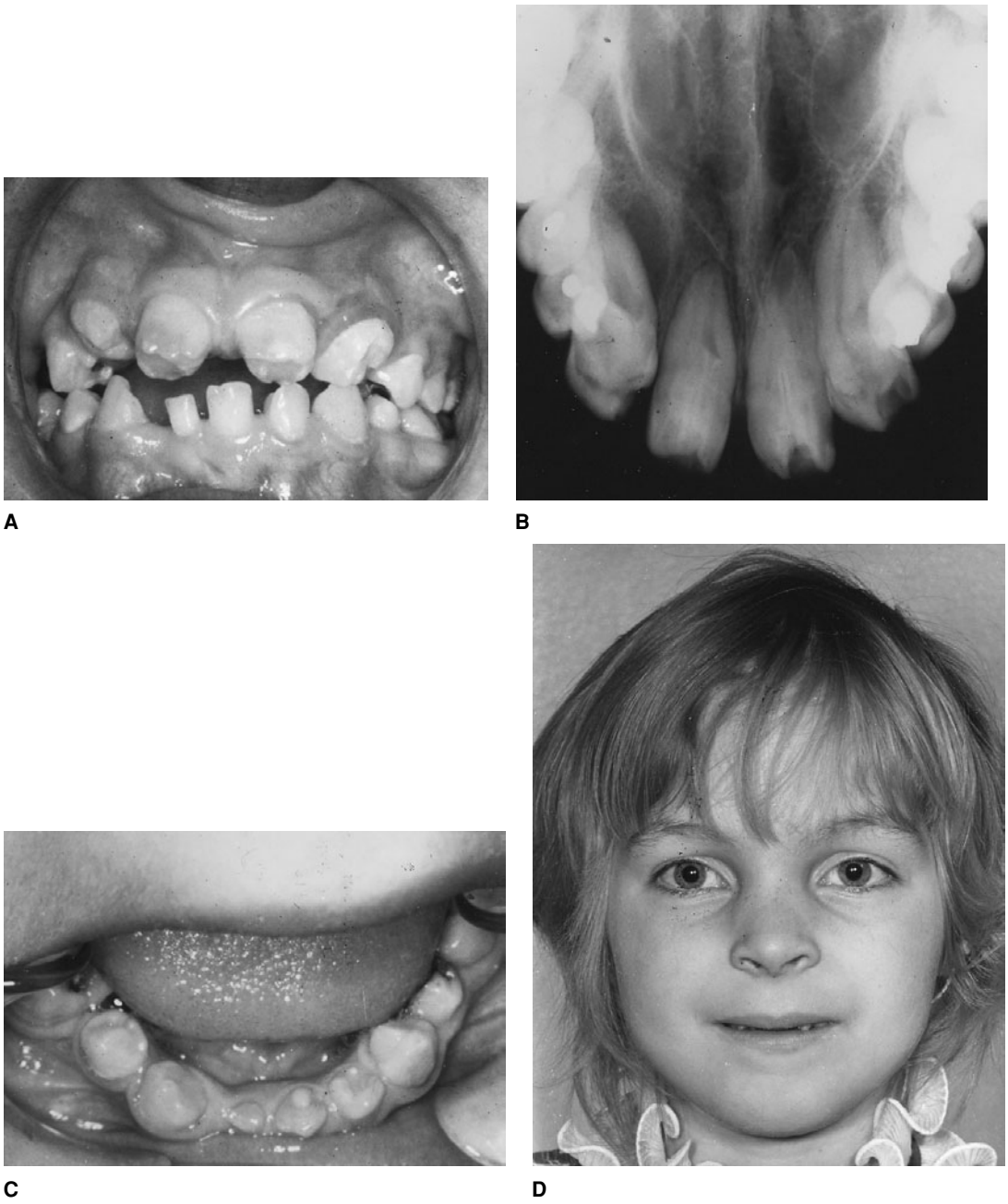


Fig. 27–19. *Multiple anterior dens invaginatus and sensorineural hearing loss*. (A) Molarized maxillary central incisors having three cusps labially, two cusps lingually, and one cusp mesially. Premolarized maxillary lateral incisor with one cusp labially and lingually. (B) Radiograph reveals both maxillary central and lateral incisors with two root canals. Double dens invaginatus is observed in the maxillary central incisors. (C) Multituberculism of the mandibular left incisors, canines, and first premolars. (D) Seven-year-old female with broad nasal bridge, dilated nostrils, and sensorineural hearing loss. (From PN Kantaputra and RJ Gorlin, Clin Dysmorphol 1:128, 1992.)

were also found in the father. As in the case of his daughter, his primary dentition was very incomplete and his secondary teeth consisted of only two large molars.

At puberty, numerous syringomas appeared over the forehead and malar areas of the daughter.

Syringomas may occasionally occur in two or more generations (1) with greater expression in females.

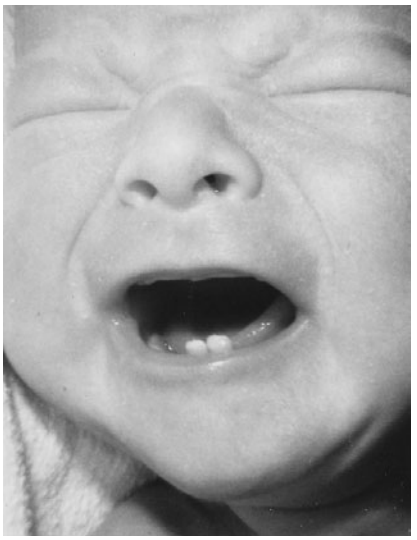
References (Natal teeth, oligodontia, and syringomas)

1. Headington JT et al: Clear cell glycogenosis in multiple syringomas. Arch Dermatol 106:353–356, 1972.

2. Morrison PJ, Young ID: Syringomas, natal teeth, and oligodontia: A new ectodermal dysplasia? Clin Dysmorphol 5:363–366, 1996.

Natal teeth, patent ductus arteriosus, and intestinal pseudo-obstruction

Harris et al (1) reported brothers with dilatation and hypomobility of the small bowel and short or microcolon without anatomic obstruction. Incomplete rotation of the midgut was also noted. Both had congenital mandibular central incisors and patent ductus arteriosus, and both died within the first few months of life (Fig. 27–20). X-linked or autosomal recessive inheritance is possible.



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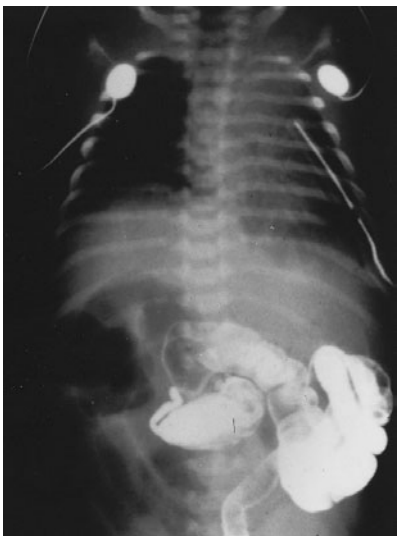

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Fig. 27–20. *Natal teeth, patent ductus arteriosus, and intestinal pseudo-obstruction*. (A) Natal teeth. (B) Barium contrast showing microcolon and malrotation. (A from DJ Harris et al, Clin Genet 9:479, 1976. B courtesy of DJ Harris, Kansas City, Missouri.)

Reference (Natal teeth, patent ductus arteriosus, and intestinal pseudo-obstruction)

1. Harris DJ et al: Natal teeth, patent ductus arteriosus and intestinal pseudo-obstruction: A lethal syndrome in the newborn. Clin Genet 9:479–482, 1976.

Natal teeth, bifid tongue, and profound sensorineural hearing loss

An apparently unique association of natal teeth, bifid tongue, and profound sensorineural hearing loss was reported in a Saudi Arabian male child by Darwish et al (1).

The natal teeth were lower central incisors. The tongue tip was bifid. The lingual frenum was in normal position without undue traction on the tongue. Hearing loss was profound without additional description.

While the association of the three anomalies may be one of chance, odds against this would appear to be great.

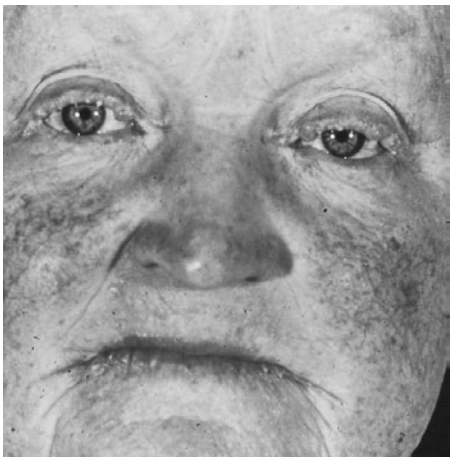
Reference (Natal teeth, bifid tongue, and profound sensorineural hearing loss)

1. Darwish S et al: Natal teeth, bifid tongue, and deaf mutism. J Oral Med 42:49–56, 1987.

Oligodontia, hypotrichosis, palmoplantar hyperkeratosis, and apocrine hidrocystomas of eyelid margins (Schöpf-Schulz-Passarge syndrome)

Schöpf et al (11) described two sisters with oligodontia, palmoplantar hyperkeratosis, and hyperhidrosis that began at puberty with hair loss occurring at 25 years, rosacea at 50 years, and 1–3 mm beaded cysts of both upper and lower eyelid margins at 60 years (Figs. 27–21 and 27–22). The deciduous teeth were lost late and only a few if any rudimentary permanent teeth developed. This was also documented by Monk et al (7). The nails were brittle, narrow, and exhibited longitudinal furrowing. About 15 patients have been described (1–5,7–9,11–14).

Fig. 27–21. *Oligodontia, hypotrichosis, palmoplantar hyperkeratosis, and apocrine hidrocystomas of eyelid margins*. (A–C) Proposita had oligodontia, sparse scalp hair, eyelid margin cysts, hyperkeratosis of soles. (Courtesy of E Schöpf, Heidelberg, Germany.)



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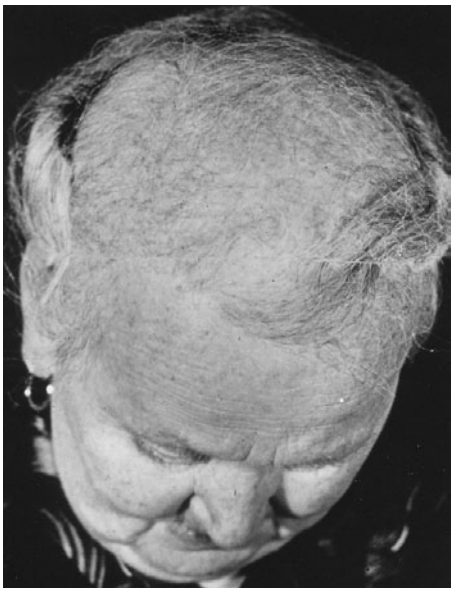

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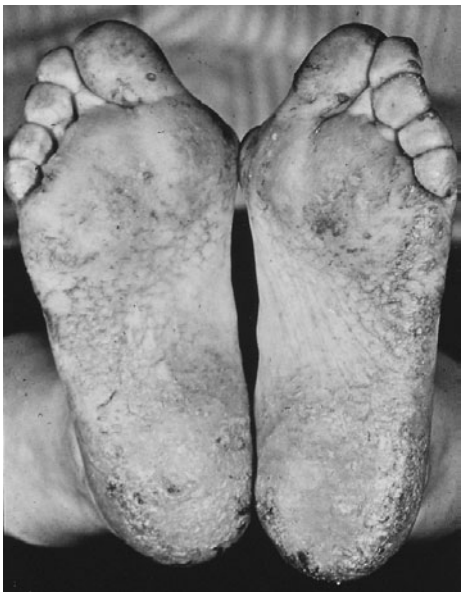

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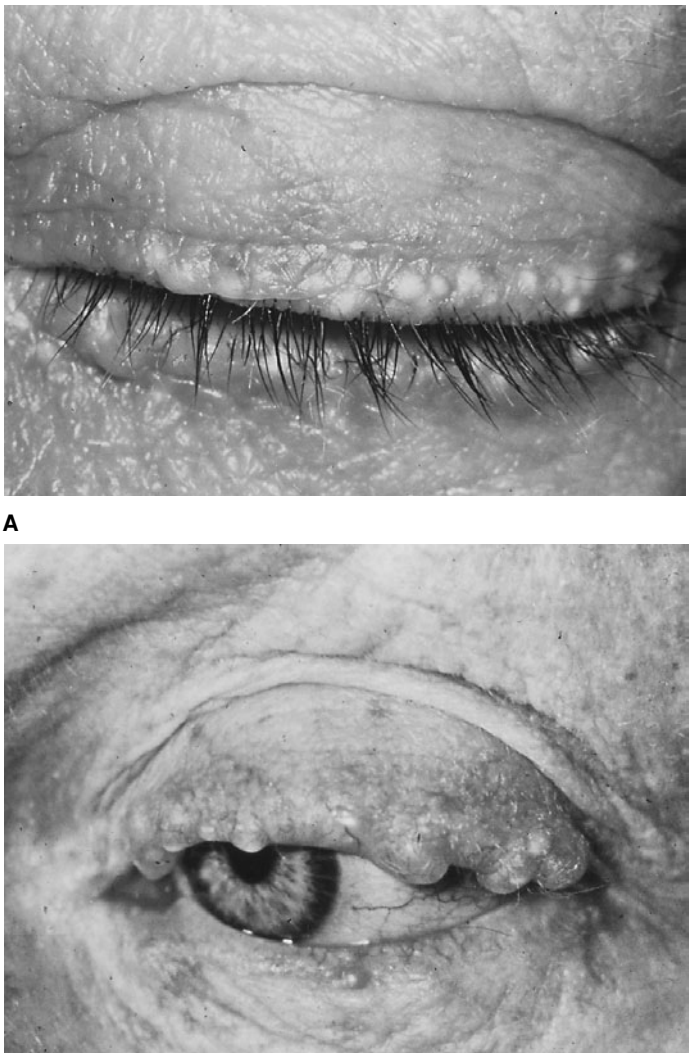

Fig. 27–22. *Oligodontia, hypotrichosis, palmoplantar hyperkeratosis, and apocrine hidrocystomas of eyelid margins*. (A,B) Beaded eyelid margins. (A from RL Font et al, Arch Ophthalmol 104:1811, 1986. B courtesy of E Schöpf, Heidelberg, Germany.)

The eyelid cysts are lined by two layers of cells: an outer myoepithelial layer and an inner layer of cuboidal cells with acidophilic cytoplasm. There were papillary infoldings. The cysts were interpreted as apocrine hidrocystomas arising from the glands of Moll. Photophobia, basal cell carcinoma, squamous cell carcinoma, eccrine poroma, and hypernephroma have been found in some patients (7–9).

Affected sibs (3,7,8,11) and consanguinity (7,11) indicate autosomal recessive inheritance. Küster and Hammerstein (5) showed autosomal dominant inheritance. Craigen et al (2) reported four males, three from one sibship, the other a half brother through the father. Uniparental isodisomy is possible, but it is probably a heterogeneity. Although classified as a keratoderma, there is as yet no evidence that the gene maps to 17q24 (13).

Multiple bilateral apocrine hidrocystomas of the eyelids may be an isolated finding (6,10).

References [Oligodontia, hypotrichosis, palmoplantar hyperkeratosis, and apocrine hidrocystomas of eyelid margins (Schöpf-Schulz-Passarge syndrome)]

1. Burket JM et al: Eyelid cysts, hypodontia and hypotrichosis. J Am Acad Dermatol 10:922–925, 1984.

2. Craigen WJ et al: Schöpf-Schulz-Passarge syndrome with an unusual pattern of inheritance. Am J Med Genet 71:186–188, 1997.

3. Font RL et al: Apocrine hidrocystomas of the lids, hypodontia, palmoplantar hyperkeratosis, and onychodystrophy. Arch Ophthalmol 104:1811–1813, 1986.

4. Hamm H et al: Schöpf-Syndrom—eine Blickdiagnose unter den ektodermalen Dysplasien. Zbl Haut Geschl Krankh 157:940, 1990.

5. Küster W, Hammerstein W: Das Schöpf-Syndrom. Hautarzt 43:763–766, 1992.

6. Langer K et al: Multiple apocrine hidrocystomas on the eyelids. Am J Dermatopathol 11:570–573, 1989.

7. Monk BE et al: Schöpf-Schulz-Passarge syndrome. Br J Dermatol 127: 33–35, 1992.

8. Nordin H et al: Familial occurrence of eccrine tumours in a family with ectodermal dysplasia. Acta Derm Venereol (Stockh) 68:523–530, 1988.

9. Perret C: Schöpf syndrome. Br J Dermatol 120:131–132, 1989.

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11. Schöpf E et al: Syndrome of cystic eyelids, palmo-plantar keratosis, hypodontia and hypotrichosis as a possible autosomal recessive trait. Birth Defects 7(8):219–221, 1971.

12. Starink TM, Keijser MH: Multiple eyelid hidrocystoma, eccrine poromatosis, hypodontia, hypotrichosis syndrome (Schöpf syndrome). Br J Dermatol 123:543–544, 1990.

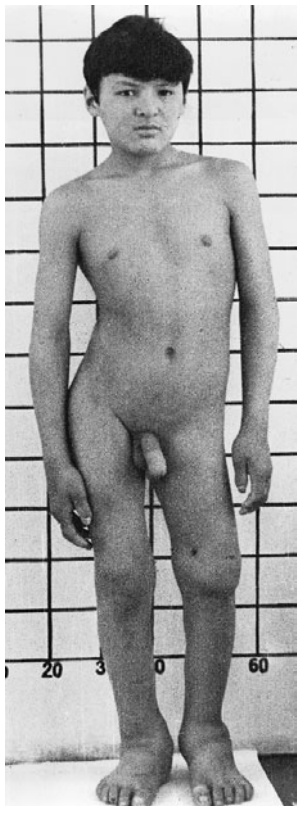
13. Stevens HP et al: Linkage of an American pedigree with palmoplantar keratoderma and malignancy (palmoplantar ectodermal dysplasia type III) to 17q24: Literature survey and proposed updated classification of the keratodermas. Arch Dermatol 132:640–651, 1996.

14. Verplancke P et al: The Schöpf-Schulz-Passarge syndrome. Dermatology 196:443–446, 1998.

Oligodontia, keratitis, skin ulceration, and arthroosteolysis

Kozlova et al (1) described five sibs with a syndrome of recurrent skin ulceration, arthralgias, fever, fistulous osteolysis around joints, nail dystrophy, and keratitis that eventuated in blindness. The fingers became clawed. Involvement of the growth plates of the tibia and femur led to asymmetric shortness with secondary scoliosis (Fig. 27–23).

Fig. 27–23. *Oligodontia, keratitis, skin ulceration, and arthroosteolysis*. Note severe scoliosis, shortening of left leg, enlargement and deformity of knees and ankles, and cicatrized fistulous scars about knees. (From SI Kozlova et al, Am J Med Genet 15:205, 1983.)



Several teeth were missing; others had reduced crown form.
Inheritance is autosomal recessive.

Reference (Oligodontia, keratitis, skin ulceration, and arthroosteolysis)

1. Kozlova SI et al: Self-limited autosomal recessive syndrome of skin ulceration, arthroosteolysis with pseudoacromegaly, keratitis and oligodontia in a Kirghizian family. Am J Med Genet 15:205–210, 1983.

Oligodontia and congenital sensorineural hearing loss

Two pairs of sibs with sensorineural hearing loss and oligodontia have been reported by Lee et al (2), in 1978, and Glass and Gorlin (1), in 1979.

In one family (2), both children were missing permanent maxillary lateral incisors; one was missing the permanent canines as well. In the second family (1), at least 10 permanent teeth were missing, with several diastemas present (Fig. 27–24).

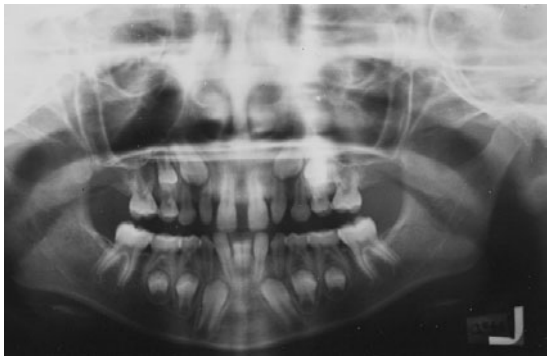
Both children in the first family (2) experienced episodes of dizziness beginning at age 2. Projectile vomiting accompanied the dizzy spells beginning at age 6 1/2 in one child. This finding was not present in the other family (1).

In all four children, profound bilateral sensorineural hearing loss was diagnosed by 11 months of age. Tympanograms and vestibular responses were normal in all the children.

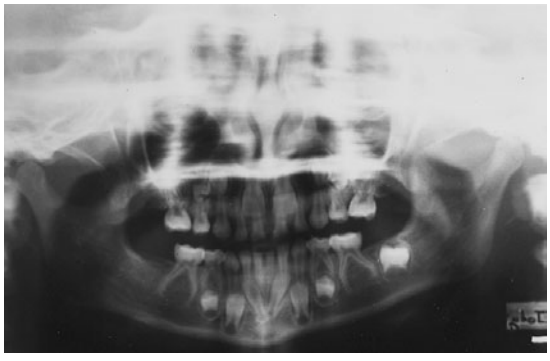
References (Oligodontia and congenital sensorineural hearing loss)

1. Glass L, Gorlin RJ: Congenital profound sensorineural hearing loss and oligodontia: A new syndrome. Arch Otolaryngol 105:621–622, 1979.
2. Lee M et al: Autosomal recessive sensorineural hearing loss, dizziness, and hypodontia. Arch Otolaryngol 104:292–293, 1978.

Fig. 27–24. *Oligodontia and congenital sensorineural hearing loss*. (A,B) Absence of numerous permanent teeth in siblings. (From L Glass and RJ Gorlin, Arch Otolaryngol 105:621, 1979.)



A



B

Oligodontia and polycystic ovarian syndrome

Hattah and Angmar-Månsson (1) described two sisters with marked oligodontia with pubertal hirsutism, menstrual disturbances, and enlarged polycystic ovaries.

Parental consanguinity was reported. Possibly the syndrome has autosomal recessive inheritance. No other cases of this combination have been described (2).

References (Oligodontia and polycystic ovarian syndrome)

1. Hattah FN, Angmar-Månsson B: Oligodontia of the permanent dentition in two sisters with polycystic ovarian syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 84:368–371, 1997.
2. Schalk-van der Weide Y et al: Symptomatology of patients with oligodontia. J Oral Rehabil 21:247–261, 1994.

Oligodontia, microcephaly, short stature, and characteristic facies

Bankier et al (1) reported autosomal dominant inheritance of a syndrome of microcephaly, low normal intelligence, short stature, and dental anomalies.

The face was characterized by a broad forehead, long narrow nose, and flat recessed midface. Scalp hair tended to be fine and wispy. There was marked deficiency of teeth, and those that were present often had conical crown form and/or diminished crown size.

Other examples are those of Stoll et al (3) and Melamed et al (2).

References (Oligodontia, microcephaly, short stature, and characteristic facies)

1. Bankier A et al: Dental dysplasia, microcephaly, and diminutive build—new autosomal dominant syndrome. Am J Med Genet (in press).
2. Melamed Y et al: Oligodontia, short stature, and small head circumference and normal intelligence. Clin Genet 46:316–318, 1994.
3. Stoll C et al: Oligodontia, microcephaly and facial dysmorphia syndrome. Genet Couns 9:29–32, 1998.

Hypodontia and Dupuytren contracture

Three three-generation Finnish families were investigated for hypodontia with Dupuytren contracture.

Among 32 members, 5 had contractures and 4 had hypodontia (1).

Reference (Hypodontia and Dupuytren contracture)

1. Ranta H et al: Familial hypodontia associated with Dupuytren's disease. Scand J Dent Res 98:457–460, 1990.

Medullary sponge kidney and anodontia of permanent dentition

Khowry et al (2), in 1988, described two male and two female sibs with absence of permanent teeth and familial medullary sponge kidney.

Absence of the permanent dentition in individuals who have deciduous precursors has been shown to be an autosomal recessive trait by Gorlin et al (1). Medullary sponge kidney is not considered to be a genetic disorder but has been seen in association with congenital *hemihyperplasia*; yet among these four sibs, each affected had both diseases. Therefore, it is very unlikely that two different disorders are running in the same family.

References (Medullary sponge kidney and anodontia of permanent dentition)

1. Gorlin RJ et al: Complete absence of the permanent dentition: An autosomal recessive disorder. Am J Med Genet 5:207–209, 1980.
2. Khowry Z et al: Familial medullary sponge kidney in association with congenital absence of teeth (anodontia). Nephron 48:231–233, 1988.

Microdontia, hypodontia, short bulbous roots and root canals with strabismus, short stature, and borderline mentality

A 15-year-old female was reported by Bazopoulou-Kyrkanidou et al (1) with absence of permanent teeth. The deciduous dentition was marked by microdontia, hypodontia, and short bulbous roots. Short stature and borderline mentality were also noted (1). Absence of permanent teeth was described by Gorlin et al (3) as an autosomal recessive trait. Witkop and Jaspers (6) noted short roots and short stature as a dominant trait. Sauk and Delaney (5) and Gardner and Girgis (2) reported short roots, taurodontism, and microcephaly, and Ireland et al (4) noted short roots, taurodontism, and multiple dens invaginatus.

References (Microdontia, hypodontia, short bulbous roots and root canals with strabismus, short stature, and borderline mentality)

1. Bazopoulou-Kyrkanidou E et al: Microdontia, hypodontia, short bulbous roots and root canals with strabismus, short stature, and borderline mentality. Oral Surg Oral Med Oral Pathol 74:93–95, 1992.
2. Gardner DG, Girgis SS: Taurodontism, short roots and external resorption associated with short stature and a small head. Oral Surg Oral Med Oral Pathol 44:271–273, 1977.
3. Gorlin RJ et al: Complete absence of the permanent dentition: An autosomal recessive disorder. Am J Med Genet 5:207–209, 1980.
4. Ireland EJ et al: Short roots, taurodontia, and multiple dens invaginatus. J Pedodontics 11:164–175, 1987.
5. Sauk JJ Jr, Delaney JR: Taurodontism, diminished root formation and microcephalic dwarfism. Oral Surg Oral Med Oral Pathol 36:231–235, 1973.
6. Witkop CJ Jr, Jaspers MT: Teeth with short thin dilacerated roots in patient with short stature: A dominantly inherited trait. Oral Surg Oral Med Oral Pathol 54:553–559, 1982.

Otodental syndrome

In 1972, Levin and Jorgenson (7) described a syndrome of dental anomalies and sensorineural hearing loss. To date, several unrelated families have been described (1–3,5–10,12–14); one case report is doubtful (11). Inheritance is clearly autosomal dominant with variable expressivity.

The incisors of both dentitions are spared. The crowns of the canines and posterior teeth are enlarged, bulbous, and malformed with multiple prominent lobules. The deciduous dentition is more severely involved. The relation between cusps and major grooves is eliminated, hence the use of the term, *globodontia*. An enamel defect is frequently noted on the facial surface of the canine teeth. Premolar teeth are frequently missing or small in size. There is often delayed eruption of the deciduous malformed teeth or even of the permanent posterior teeth (1,2,13). One can observe duplicated pulp chambers with denticle formation and a longitudinal dental septum and early pulpal obliteration. The molar teeth have a tendency toward conical or taurodont root form. Complex and/or compound odontomas have also been described in the posterior maxilla and mandible (1,9,13) (Figs. 27–25 to 27–27).

Sensorineural hearing loss to about 65 dB is found at all frequencies but is more pronounced at about 1000 Hz. It usually plateaus by the fourth decade (3). The age of onset of the hearing loss ranges from early childhood to middle age (3,6,8), which may complicate making the diagnosis of the disorder.

References (Otodental syndrome)

1. Beck-Mannagetta J et al: Odontome und pantonale Hörstörung bei otodentalem Syndrom. Dtsch Zahnartzl Z 39:232–241, 1984.
2. Chen RJ et al: "Otodental" dysplasia. Oral Surg Oral Med Oral Pathol 66:353–358, 1988.
3. Cook RA et al: Otodental dysplasia: A five year study. Ear Hear 2:90–94, 1981.

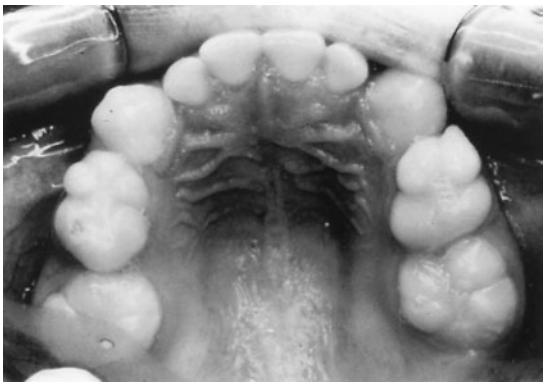


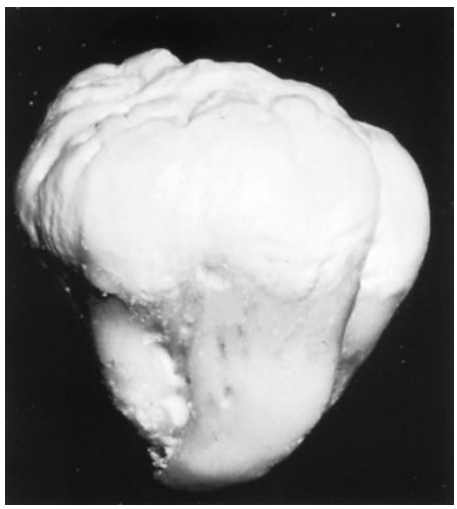
Fig. 27–25. *Otodental syndrome*. Occlusal view of teeth showing globodontia. Normal sized maxillary incisors contrast sharply with bulbous canine and molar teeth. (Courtesy of CJ Witkop Jr, Minneapolis, Minnesota.)

4. Denes J, Csiba A: An unusual case of hereditary developmental anomalies of the cuspids and molars. Fogorv Sz 62:208–212, 1969.
5. Gundlach KKH, Witkop CJ Jr: Globodontie-eine neue erbliche Zahnformanomalie. Dtsch Zahnarztl Z 32:194–196, 1977.
6. Jorgenson RJ et al: Otodental dysplasia. Birth Defects 11(5):115–119, 1975.
7. Levin LS, Jorgenson RJ: Familial otodental dysplasia: A "new" syndrome. Am J Hum Genet 24:61a, 1972.
8. Levin LS et al: Otodental syndrome. A new ectodermal dysplasia. Clin Genet 8:136–144, 1975.
9. Salmerón JI et al: Odontogenic tumours and dental anomalies in children. Craniomaxillofac Surg Suppl 1:151, 1996.
10. Santos-Pinto L et al: Otodental syndrome: Three familial case reports. Pediatr Dent 20:208–211, 1998.
11. Stewart DJ, Kinirons MJ: Globodontia. Br Dent J 152:287–288, 1982.
12. Van Doorne L et al: Otodental syndrome. Int J Oral Maxillofac Surg 27: 121–124, 1998.
13. Winter GB: The association of ocular defects with the otodental syndrome. J Int Assoc Dent Child 14:83–87, 1983.
14. Witkop CJ Jr: Globodontia in the otodental syndrome. Oral Surg 41: 472–483, 1976.

Postaxial polydactyly-dental-vertebral syndrome

Rogers et al (1) and Temtamy and McKusick (2) reported a syndrome of bilateral broad halluces, postaxial polydactyly of hands and feet, short middle phalanges of hands, short pointed distal phalanges,

Fig. 27–26. *Otodental syndrome*. Globodontia of 6-year-molar. (From J Beck-Mannagetta et al, Dtsch Zahnarztl Z 39:232, 1984.)



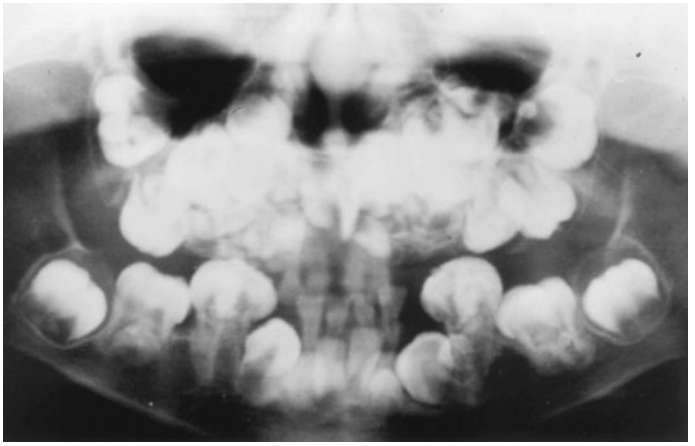


Fig. 27–27. *Otodental syndrome*. Panoramic radiograph showing 5-year-old with normal anterior teeth, globodontia of canines and molars. (From J Beck-Mannagetta et al, Dtsch Zahnarztl Z 39:232, 1984.)

abnormal vertebral bodies (variable fusion, hemivertebrae, butterfly form, small size), congenital torticollis, narrow spinal canal, kyphoscoliosis, and pectus (Figs. 27–28 and 27–29A,B). The pinnae were malformed, the neck was webbed with low posterior hairline, and the mandible was prognathic. Dental anomalies included dens invaginatus, fusion, macrodontia, hypodontia, enamel dysplasia, and short roots (Fig. 27–29C).

Inconstant features included high forehead, hydrocele, phimosis, agenesis of lower ribs, and congenital heart defects.

Inheritance appears to be autosomal recessive (1).

References (Postaxial polydactyly-dental-vertebral syndrome)

1. Rogers JG et al: A postaxial polydactyly-dental-vertebral syndrome. J Pediatr 90:230–235, 1977.
2. Temtamy S, McKusick V: The genetics of hand malformations. Birth Defects 14(3):411–413, 1978.

Short stature and delayed dental eruption

Arvystas (1) described autosomal dominant inheritance of short stature, prolonged retention of deciduous dentition, and delayed eruption of secondary teeth. There was frontal bossing, midface hypoplasia, Wormian bones in the lambdoidal sutures, widely open anterior fontanel in infancy, and delayed skeletal maturation.

Reference (Short stature and delayed dental eruption)

1. Arvystas MG: Familial generalized delayed eruption of the dentition with short stature. Oral Surg 41:235–243, 1976.

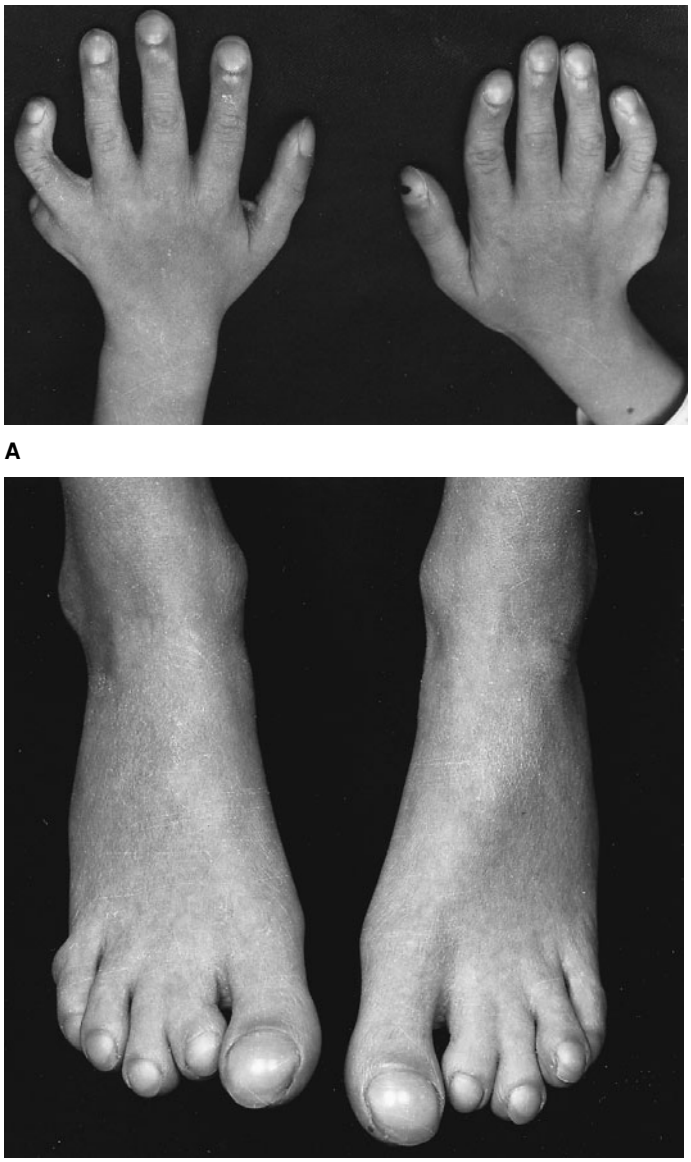
Short stature and short, thin, dilacerated dental roots

Witkop and Jaspers (3) reported a family with short stature and teeth with short, thin, dilacerated roots in four generations. Inheritance was compatible with either autosomal or X-linked dominant inheritance.

The tooth crowns were somewhat bulbous with cervical constriction and drastically abbreviated short, thin, dilacerated (bent) roots. The enamel was normal (Fig. 27–30).

Height did not exceed 155 cm. Wormian bones were observed in lambdoidal and coronal sutures.

Perhaps the condition reported by Shaw (2) is a different one. No taurodontism was noted, nor was dilaceration. Bazopoulou-Kyrkanidou et al (1) reported a female with short bulbous roots and short stature, but that is still a different condition.



A

B

Fig. 27–28. *Postaxial polydactyly-dental-vertebral syndrome*. (A) Postaxial polydactyly. (B) Broad halluces. (From JG Rogers et al, J Pediatr 90:230, 1977.)

References (Short stature and short, thin, dilacerated dental roots)

1. Bazopoulou-Kyrkanidou E et al: Microdontia, hypodontia, short bulbous roots and root canals with strabismus. Oral Surg Oral Med Oral Pathol 74:94–95, 1992.
2. Shaw L: Short root anomaly in a patient with severe short-limbed dwarfism. Int J Paediatr Dent 5:249–252, 1995.
3. Witkop CJ Jr, Jaspers MT: Teeth with short, thin, dilacerated roots in patients with short stature: A dominantly inherited trait. Oral Surg 54:553–559, 1982.

Solitary maxillary central incisor, short stature, and choanal atresia (monosuperocentroincisivodontic dwarfism)

Rappaport et al (22,23), in 1976–1977, described the association between single maxillary central incisor and isolated growth hormone deficiency (Fig. 27–31). Vanelli et al (28) and Bierman-Franke et al (6) discussed

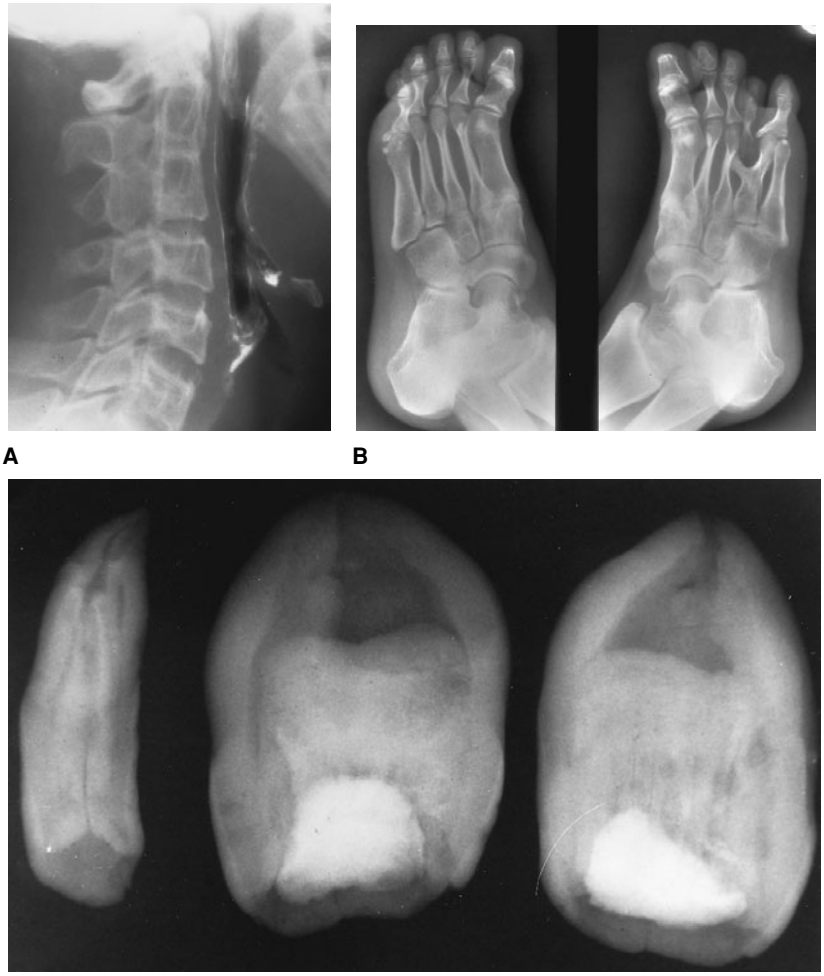


Fig. 27–29. *Postaxial polydactyly-dental-vertebral syndrome.* (A) Hypoplasia and fusion of cervical vertebrae. (B) Talus, calcaneus, and first and second cuneiforms are fused. Distal end of right fourth metatarsal is bifurcated. (C) Radiograph of extracted teeth showing grossly widened incisors with dens invaginatus, obliterated pulp chambers and canals, short roots. (From JG Rogers et al, J Pediatr 90:230, 1977.)

the association. Superb analyses are those of Hall et al (12) and Lo et al (17). RJ Gorlin has seen this combination with congenital cataracts.

About 70% of patients are short (17). Growth hormone levels are reduced in approximately 50% (11,17). Choanal atresia and/or nasal pyriform aperture stenosis is a constant feature of the syndrome (1,12,17,29) as is prominent midpalatal ridge (12). About 35% exhibit hypotelorism.

It is not rare to have a single maxillary central incisor, normal growth, and normal growth hormone levels (18,21,24,30). Combinations with VACTERL association (12,30) and CHARGE association (12,13) have been noted. Single central incisor has been reported in approximately 20% of those with *del(18p)* or *r*(18) (3,10,17,24). It may also occur with short stature and ocular coloboma (16), with del(7q36.1) (19), *XXX syndrome* (20), and with autosomal dominant *holoprosencephaly* (6,8,14,25) due to mutation of the *Sonic Hedgehog* gene. More mothers than fathers have this mutation (27). Süss et al (26) described a single maxillary central incisor in one sib and holoprosencephaly in another sib. Single maxillary central incisor occurs much more frequently in alobar *holoprosencephaly* with severe facial dysmorphism than it does as a "microform" in autosomal dominant holoprosencephaly (9). These patients lack a superior

Fig. 27–30. *Short stature and short thin dilacerated dental roots*. Bulbous crowns and short dilacerated roots. (From CJ Witkop Jr and MT Jaspers, Oral Surg 54:553, 1982.)

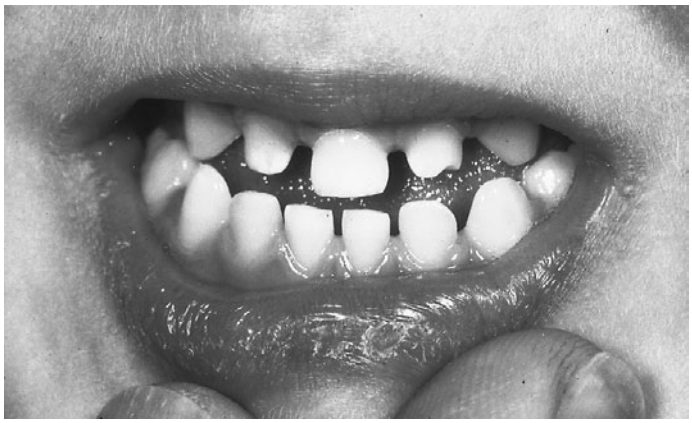


Fig. 27–31. *Solitary maxillary central incisor and short stature*. Note single central incisor.

labial frenum. Winter et al (32) described solitary maxillary central incisor with precocious puberty and hypothalamic hamartoma. Microphthalmia has been reported with single central incisor and hypopituitarism (2). *Hypophyseal short stature and cleft lip* is discussed in Chapter 23. Single maxillary central incisor has been found in association with iris coloboma and hypomelanosis of Ito (5) (a nonspecific chromosomal mosaicism) and with unusual forms of ectodermal dysplasia (7,31). Fleming et al (11) reported that they had seen single central incisor in *Klippel–Feil anomaly*.

References [Solitary maxillary central incisor, short stature, and choanal atresia (monosuperocentroincisivodontic dwarfism)]

1. Arliss H, Ward RF: Congenital nasal pyriform aperture stenosis: Isolated anomaly vs. developmental fold defect. Arch Otolaryngol Head Neck Surg 118:989–991, 1992.
2. Artman HG, Boyden E: Microphthalmia with single central incisor and hypopituitarism. J Med Genet 27:192–193, 1990.
3. Aughton DJ et al: Single maxillary central incisor in a girl with del(18p) syndrome. J Med Genet 28:530–532, 1991.
4. Bartholomew DW et al: Single maxillary central incisor and coloboma in hypomelanosis of Ito. Clin Genet 32:370–373, 1987.
5. Berry SA et al: Single central incisor in familial holoprosencephaly. J Pediatr 104:877–880, 1984.
6. Biermann-Franke H et al: Das "Syndrom des einzelnen Schneiderzahnes und Wachstumhormonmangel." Monatsschr Kinderheilkd 139:421–424, 1991.
7. Buntinx I, Baraitser M: A single maxillary incisor as a manifestation of an ectodermal dysplasia. J Med Genet 26:648–650, 1989.
8. Camera G et al: Single maxillary central incisor and holoprosencephaly. Pathologica 84:425–428, 1992.
9. Cohen MM Jr: Perspectives on holoprosencephaly. Part III. Spectra, distinctions, continuities, and discontinuities. Am J Med Genet 34:271–288, 1989.
10. Dolan LM et al: 18p-syndrome with a single central maxillary incisor. J Med Genet 18:396–398, 1981.
11. Fleming P et al: Single maxillary central incisor in association with midline anomalies. Br Dent J 168:476–479, 1990.
12. Hall RK et al: Solitary median maxillary central incisor, short stature, choanal atresia/midnasal stenosis (SMMCI) syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 84:651–662, 1997.
13. Harrison M et al: Solitary maxillary central incisor as a new finding in CHARGE association: A report of two cases. Int J Paediatr Dent 7:185–190, 1997.
14. Hattori H et al: Single central maxillary incisor and holoprosencephaly. Am J Med Genet 28:483–487, 1987.
15. Johnston VP: Holoprosencephaly: A developmental field defect. Am J Med Genet 34:258–264, 1989.
16. Liberfarb RM et al: Ocular coloboma associated with a solitary maxillary central incisor and growth failure: Manifestations of holoprosencephaly. Ann Ophthalmol 19:226–227, 1987.
17. Lo FS et al: Solitary maxillary central incisor and nasal pyriform aperture stenosis. Eur J Pediatr 157:39–44, 1998.
18. Mass E, Sarnat H: Single maxillary incisors in the midline. J Dent Child 58:413–416, 1991.
19. Masuno M et al: Two unrelated cases of single maxillary incisor with 7q terminal deletion. Jpn J Hum Genet 35:311–317, 1990.
20. Miura M et al: Triple X syndrome accompanied by a single maxillary central incisor. Pediatr Dent 15:214–217, 1993.
21. Parker RP, Vann WF Jr: Solitary maxillary incisor. Pediatr Dent 7:134–136, 1985.
22. Rappaport EB et al: Monosuperocentroincisivodontic dwarfism. Birth Defects 12(5):243–245, 1976.
23. Rappaport EB et al: Solitary central incisor and short stature. J Pediatr 91:924–928, 1977.
24. Santoro FP, Wesley RK: Clinical evaluation of two patients with a single maxillary central incisor. J Dent Child 50:379–381, 1983.
25. Simon AR, Roberts MW: Solitary incisor syndrome and holoprosencephaly. J Clin Pediatr Dent 17:175–177, 1993.
26. Süss J et al: Ein solitären Miltlerer oberer Schneiderzahn und Holoprosencephalie bei Geschwistern. Zeut Zahnarzt Z 45:785–788, 1990.
27. Suthers G et al: Skewed sex ratios in familial holoprosencephaly and in people with isolated single maxillary central incisor. J Med Genet 36:924–926, 1999.
28. Vanelli M et al: Incisive supèrieure unique et déficit en STH. Arch Fr Pediatr 37:321–322, 1980.
29. Walker PJ et al: Congenital nasal pyriform aperture stenosis with a single central maxillary incisor. Aust J Otolaryngol 2:283–286, 1996.
30. Wesley RK et al: Solitary maxillary central incisor and normal stature. Oral Surg 46:837–842, 1978.
31. Winter RM et al: Sparse hair, short stature, hypoplastic thumbs, single upper central incisor, and abnormal skin pigmentation: A possible new form of ectodermal dysplasia. Am J Med Genet 29:209–216, 1988.
32. Winter WE et al: Solitary central maxillary incisor associated with precocious puberty and hypothalamic hamartoma. J Pediatr 101:965–967, 1982.

Taurodontism, microdontia, and dens invaginatus

Casamassimo et al (1) described a family in which there was simultaneous occurrence of generalized microdontia, taurodontism of the first permanent molars, and teeth with multiple dens invaginatus (Figs. 27–32 and 27–33). The pedigree contained five affected males in five generations. There is good reason to suspect X-linked recessive inheritance.

Ireland et al (2) described taurodontism, multiple dens invaginatus, and short tooth roots in male and female sibs. Additional children of the father had similar anomalies. They suggested autosomal dominant inheritance.

References (Taurodontism, microdontia, and dens invaginatus)

1. Casamassimo PS et al: An unusual triad: Microdontia, taurodontism and dens invaginatus. Oral Surg 45:107–112, 1978.
2. Ireland EJ et al: Short roots, taurodontia and multiple dens invaginatus. J Pedodont 11:164–175, 1987.

Taurodontism, oligodontia, and sparse hair

Stoy (6) appears to be the first author to describe a syndrome of taurodontism, oligodontia, and sparse hair growth (Fig. 27–34). Several authors subsequently reported cases (1–5). Affected sibs were noted by Stenvik et al (5). All other examples were isolated cases. Care must be taken to exclude females heterozygous for *hypohidrotic ectodermal dysplasia*. Some examples may represent *Witkop tooth-nail syndrome*.

References (Taurodontism, oligodontia, and sparse hair)

1. Davidson LE, Woolass KF: Severe hypodontia in an eight-year-old child. Br Dent J 158:215–217, 1985.
2. Gorlin RJ: A selected miscellany: Oligodontia, taurodontia, and sparse hair growth. Birth Defects 11(2):39–50, 1975. (Same as Ref. 4.)
3. Haunfelder D: Ein Beitrag zu den Molaren mit prismatischen Wurzeln (sog. Taurodontismus). Dtsch Zahnarztbl 21:419–423, 1967.

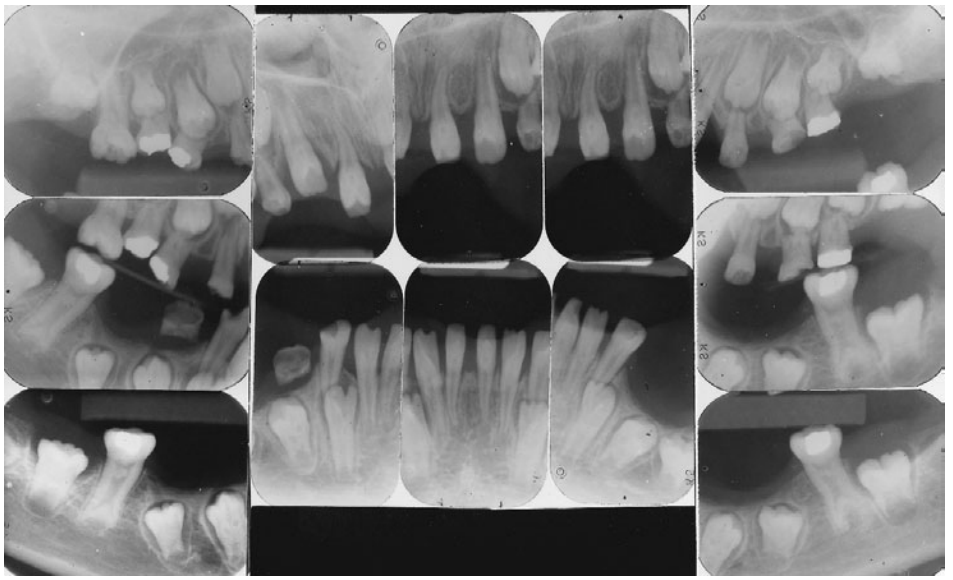


Fig. 27–32. *Taurodontism, microdontia, and dens invaginatus*. Periapical radiographs showing generalized microdontia, taurodontism of permanent molars, and several teeth with multiple dens invaginatus. (From PS Casamassimo et al, Oral Surg 45:107, 1978.)

4. Moller KT et al: Oligodontia, taurodontia and sparse hair: A syndrome. J Speech Hear Dis 38:268–271, 1973. (Same as Ref. 2.)
5. Stenvik A et al: Taurodontism and concomitant hypodontia in siblings. Oral Surg 33:841–845, 1972.
6. Stoy PJ: Taurodontism associated with other dental abnormalities. Dent Pract Dent Rec 10:202–205, 1960.

Taurodontism, pyramidal and fused molar roots, juvenile glaucoma, and unusual morphology of upper lip (Ackerman syndrome)

Ackerman et al (1) described a family in which several members in two generations exhibited pyramidal, taurodont, or fused molar roots with a single root canal, a finding noted on both sides of the kindred. Three of six sibs had only pyramidal molar roots.

Juvenile glaucoma was present in two of three sibs, and all had sparse body hair. The upper lip was full without cupid's bow, and there were thickening and widening of the philtrum. One of the sibs also had eruption of both lower eyelids, 3–4 soft tissue syndactyly of one hand, indurated hyperpigmented skin over the interphalangeal joints of the fingers, and clinodactyly of the fifth fingers (Fig. 27–35).

Reference [Taurodontism, pyramidal and fused molar roots, juvenile glaucoma, and unusual morphology of upper lip (Ackerman syndrome)]

1. Ackerman JL et al: Taurodont, pyramidal, and fused molar roots associated with other anomalies in a kindred. Am J Phys Anthropol 38:681–694, 1973.

Taurodontism and disproportionate short stature

Houlston et al (2), in 1944, reported a male with disproportionate short stature and taurodontism. Intelligence was normal. Seizures were noted at 12 years of age. His parents were consanguineous.

Thoracolumbar platyspondyly, lumbar lordosis, and dorsal concavity of lumbar vertebrae were found. The ilia were square with widening and flattening of the acetabular roof. Radiographs of the teeth showed amelogenesis imperfecta and marked taurodontism.

While there is overlap with the autosomal dominant *tricho-dento-osseous syndrome* and *Kohlschütter syndrome* (amelogenesis imperfecta, epilepsy, and mental retardation), this syndrome most clearly resembles that described by Congleton and Burkes (1).

References (Taurodontism and disproportionate short stature)

1. Congleton J, Burkes EJ Jr: Amelogenesis imperfecta and taurodontism. Oral Surg 48:540–544, 1979.
2. Houlston RS et al: Taurodontism and disproportionate short stature. Clin Dysmorphol 3:251–254, 1994.

Trichodental dysplasia

Eteson and Clark (1) reported a three-generation family with generalized shell teeth, sparse, short, slow-growing, brittle scalp hair, and curly eyelashes and eyebrows (Fig. 27–36).

An unrelated trichodental syndrome was described by Kersey (3). He reported the binary combination of sparse hair and oligodontia as an autosomal dominant disorder. Giannotti et al (2) found an isolated female with microcephaly and mental retardation. It is likely that these examples are heterogeneous.

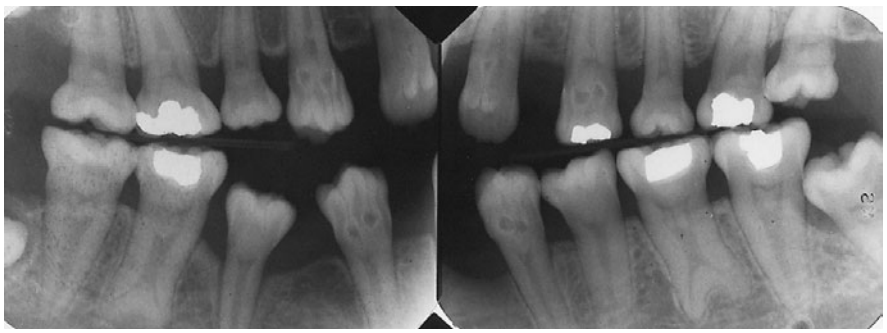
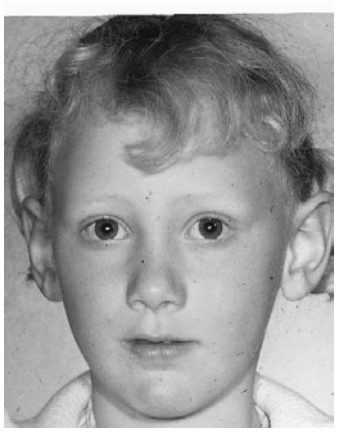


Fig. 27–33. *Taurodontism, microdontia, and dens invaginatus*. Periapical views showing taurodontism and multiple invaginations. (From PS Casamassimo et al, Oral Surg 45:107, 1978.)



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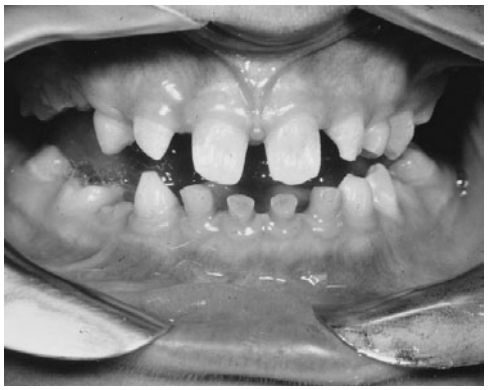


B

Fig. 27–34. *Taurodontism, oligodontia, and sparse hair*. (A,B) Sparse hair, oligodontia.

References (Trichodental dysplasia)

1. Eteson DJ, Clark RD: A new autosomal dominant tricho-dental dysplasia. March of Dimes Birth Defects Conference, Baltimore, 10–13 July 1988.
2. Giannotti A et al: Sporadic trichodental dysplasia with microcephaly and mental retardation. Clin Dysmorphol 4:334–337, 1995.
3. Kersey PJW: Tricho-dental syndrome: A disorder with a short hair cycle. Br J Dermatol 116:259–263, 1987.

ADULT syndrome

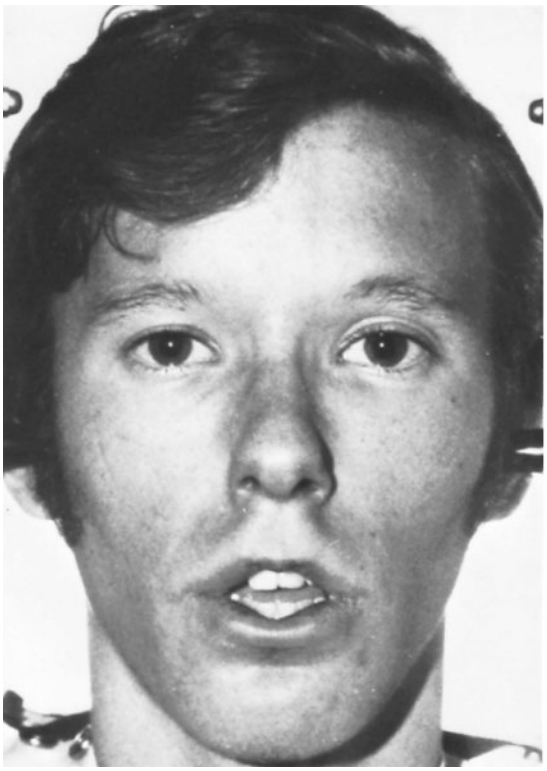
Propping and Zerres (2) reported autosomal dominant inheritance of what they call ADULT syndrome , an acronym for *A*cro-*D*ermato-*U*ngual-*L*acrimal-*T*ooth syndrome. There was considerable overlap with EEC syndrome (ectrodactyly, lacrimal duct obstruction, sparse hair, nail dysplasia, hypodontia, and loss of permanent teeth), but there were excessive freckling and hypoplastic breasts. There is good evidence that the syndrome results from mutation of the p63 gene with R298Q in the DNA-binding domain (2).

Boudghene-Stambouli and Merad-Boudia (1) noted recessive inheritance of a syndrome characterized by hypotrichosis, hyperkeratosis, nail dysplasia, small pointed teeth, and syndactyly of fingers and toes to various degrees.

References (ADULT syndrome)

1. Boudghene-Stambouli O, Merad-Boudia A: Association dysplasie ectodermique et syndactylie. Ann Dermatol Venereol 118:107–110, 1991.
2. Celli J et al: Heterozygous germline mutations in the p53 homolog p63 are the cause of EEC syndrome. Cell 99:143–153, 1999.
3. Propping P, Zerres K: ADULT-syndrome: An autosomal dominant disorder with pigment anomalies, ectrodactyly, nail dysplasia, and hypodontia. Am J Med Genet 45:642–648, 1993.

Fig. 27–35. *Taurodontism, pyramidal and fused molar roots, juvenile glaucoma, and unusual morphology of upper lip*. (A) Widened philtrum. (B) Full upper lip, lack of cupid's bow. (C) Pyramidal molar roots. (From JL Ackerman et al, Am J Phys Anthropol 38:681, 1973.)



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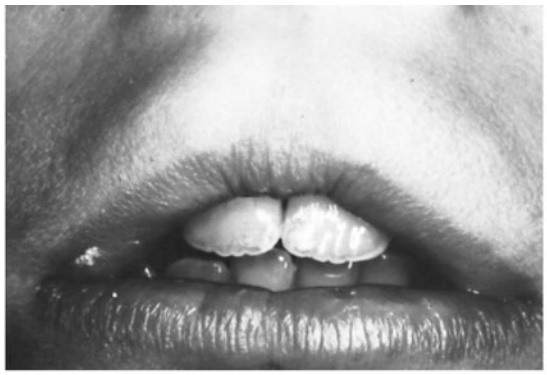

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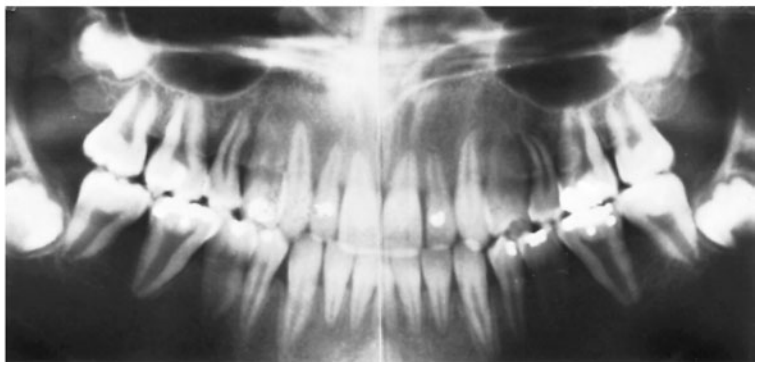

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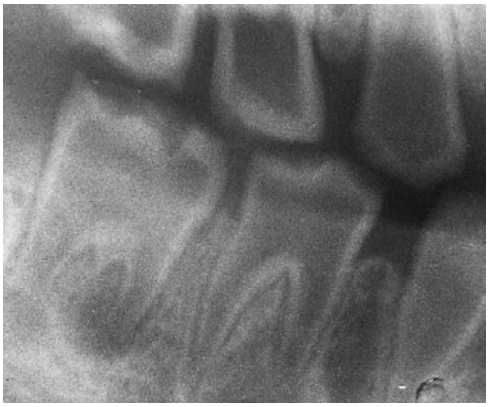


B

Fig. 27–36. *Trichodental dysplasia*. (A) Mother and child, both with short, brittle scalp hair, curly eyelashes and eyebrows. (B) Generalized shell teeth. (From DJ Eteson and RD Clark, March of Dimes Birth Defects Conference, Baltimore, 10–13 July 1988.)

Multiple odontoma-esophageal stenosis syndrome

Herrmann (3) reported a young male with huge tumors of the maxilla and mandible containing 1200 and 900 teeth, respectively, in various stages of development, including geminated and invaginated teeth. In 1973, Schmidseder and Hausamen (5) studied the same patient,noting that his two sons (one dying from pneumonia soon after birth) also manifested multiple odontomas of both jaws in infancy. The surviving infant was found to have a liver disorder and pulmonary stenosis. Subsequently, a daughter was born who again manifested odontomas. The boy experienced recurrences of odontomas that exhibited a higher degree of differentiation. He also suffered esophageal stenosis, as did his father (7).

Bader (1) reported multiple odontomas of both jaws in a female infant with calcified aortic stenosis, congenital cylindric bronchiectasis, leiomyomatosis of the esophagus with stenosis, hyperplasia of the myenteric plexus, and chronic interstitial cirrhosis of the liver. GL Barnes (personal communication, 1974) observed sibs with odontomas in four quadrants, malrotation and stenosis of the bowel, and iris colobomas.

Multiple odontomas were documented in male sibs by Schmitz and Witzel (6), but associated anomalies were not mentioned. Beisser (2) and Malik and Khalid (4) also reported multiple bilateral odontomas in both jaws.

In view of the occurrence of what appears to be a syndrome of multiple odontomas, chronic interstitial cirrhosis of the liver, and esophageal stenosis in two generations, it must be assumed that the disorder is inherited as an autosomal dominant trait. In the case of Schmitz and Witzel (6), the parents of the male sibs were normal.

References (Multiple odontoma-esophageal stenosis syndrome)

1. Bader G: Odontomatosis (multiple odontomas). Oral Surg 23:770–773, 1967.

2. Beisser V: Ein seltene Fall von selbständigem, multiplen Odontom beiderseits im Ober- und Unterkiefer und ein Literaturstiudium über diese Geschwülste des Zahn-, Mund- und Kieferbereiches. Thesis, Düsseldorf, 1964.

3. Herrmann M: Über von Zahnsystem ausgehende Tumoren bei Kindern. Fortschr Kiefer Gesichtschir 4:226–229, 1958.

4. Malik SA, Khalid M: Odontomatosis—a case report. Br J Oral Surg 11: 262–264, 1974.

5. Schmidseder R, Hausamen JR: Multiple odontogenic tumors and other anomalies. Oral Surg 39:249–258, 1975.

6. Schmitz__, Witzel A: Neubildung von Zähnen und zahnähnlichen Gebilden. Dtsch Mschr Zahnheilkd 19:126–130, 1901.

7. Schönberger W: Angeborene multiple Odontome und Dysphagie bei Vater und Sohn—eine syndromhafte Verknüpfung? Z Kinderheilkd 117:101–108, 1974.

Compound odontomas, maxillary hypoplasia, rectal stenosis, and sensorineural hearing loss

Seinsch (2), in 1982, described a boy with several anomalies including multiple compound odontomas, marked hypoplasia of the maxilla, submucous cleft palate, persistent buccopharyngeal membrane, high rectal stenosis, and sensorineural hearing loss. Although Gorlin et al (1) described several multiple odontomas-intestinal stenosis syndromes, none was associated with hearing loss.

References (Compound odontomas, maxillary hypoplasia, rectal stenosis, and sensorineural hearing loss)

1. Gorlin RJ et al: Syndromes of the Head and Neck, 3rd ed. Oxford University Press, New York, 1990.

2. Seinsch W: Missbildungssyndrome mit Schallenempfindungsschwerhörigkeit und Sprachenentwicklungsstörung. Laryngorhinootologie 61:314–315, 1982.

Enamel hypoplasia, leukonychia, and sensorineural hearing loss (Heimler syndrome)

A syndrome characterized by sensorineural hearing loss, amelogenesis imperfecta, and leukonychia was described in a pair of sibs by Heimler et al (1) in 1991 and by Tischkowitz et al (2) in 1999.

Primary teeth were normal, but the permanent teeth exhibited enamel hypoplasia. The teeth were discolored and, in addition, the molars and premolars were hypoplastic in both children (Fig. 27–37A).

The nails had transverse lines proximally (Beau's lines) and punctate leukonychia (Fig. 27–37B,C).

Profound bilateral sensorineural hearing loss was diagnosed at 18 months in one child and 2 1/2 years in the other. Hearing was normal for the first 2 years in the second child, so the loss was not congenital.

Urinalysis, serum calcium, phosphorus, and creatinine were all normal.

The presence of this condition in sibs of each sex and unaffected parents is strongly suggestive of autosomal recessive inheritance.

The differential diagnosis includes *Robinson syndrome*, which is inherited as an autosomal dominant trait and includes syndactyly and/or polydactyly in addition to nail and tooth anomalies.

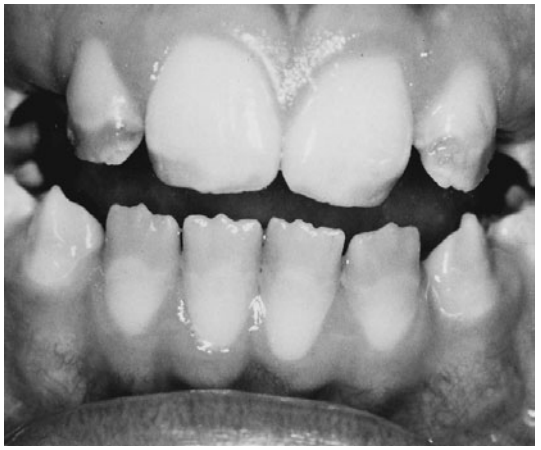
References [Enamel hypoplasia, leukonychia, and sensorineural hearing loss (Heimler syndrome)]

1. Heimler A et al: Sensorineural hearing loss, enamel hypoplasia and nail abnormalities in sibs. Am J Med Genet 39:192–195, 1991.

2. Tischkowitz M et al: Amelogenesis imperfecta, sensorineural hearing loss, and Beau's lines: A second case report of Heimler's syndrome. J Med Genet 36:941–943, 1999.

Multiple non-eruption of teeth, genua valga, and dysmorphic pinnae

Stoelinga et al (3) described autosomal recessive inheritance (parental consanguinity, four affected sibs) of multiple non-eruption of teeth with



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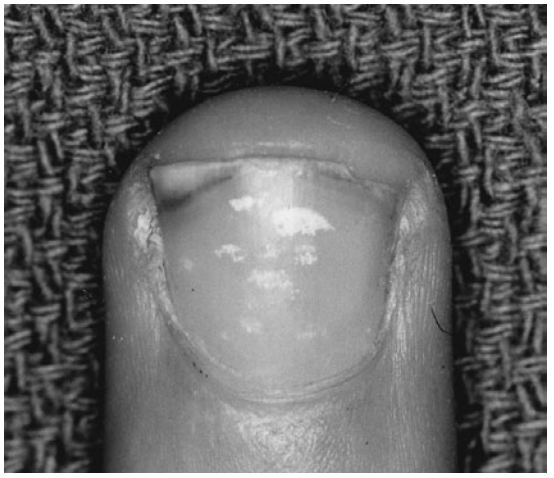

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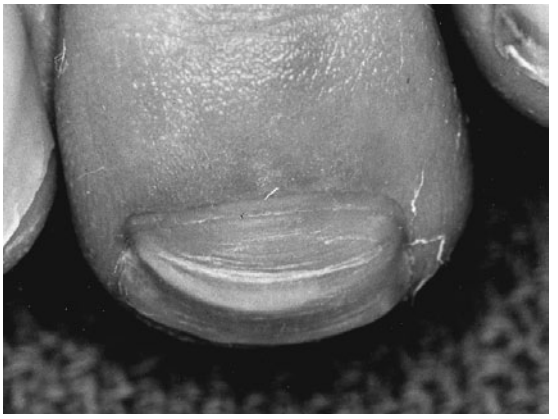


C

Fig. 27–37. *Enamel hypoplasia, leukonychia, and sensorineural hearing loss*. (A) Severe enamel dysplasia. (B) Leukonychia. (C) Beau's lines on toe nail. (From A Heimler et al, Am J Med Genet 39:192, 1991.)

resultant overclosure of bite. In addition to genua valga, the pinnae were low and posteriorly rotated.

Other cases of tooth retention which may be autosomal dominant are those of Pönitz (1) and Shokeir (2). Facially, the patients shown somewhat resembled those having *cleidocranial dysplasia*. We suspect that these represent cases of *pseudohypoparathyroidism*.

References (Multiple non-eruption of teeth, genua valga, and dysmorphic pinnae)

1. Pönitz W: Ein Beitrag zur multiplen Zahnretention. Dtsch Stomatol 23: 347–350, 1973.

2. Shokeir MHK: Complete failure of eruption of all permanent teeth: An autosomal dominant disorder. Clin Genet 5:322–326, 1974.

3. Stoelinga PJW et al: Multiple non-eruption of teeth, maxillo-zygomatical hypoplasia and other congenital defects: An autosomal recessive disorder. Clin Genet 10:222–225, 1976.

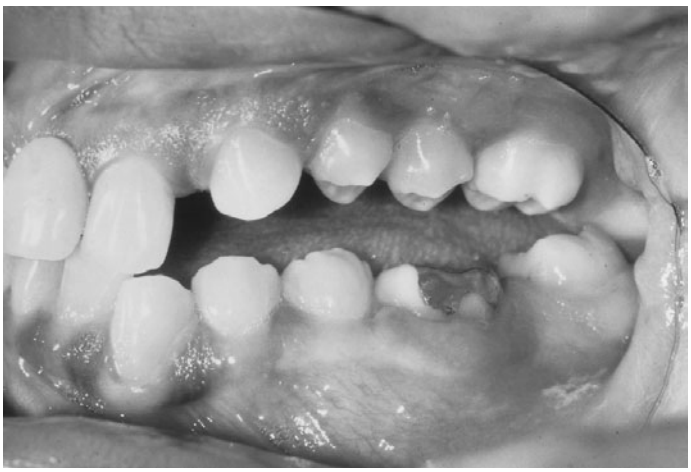
Ankylosed teeth, maxillary hypoplasia, and fifth finger clinodactyly

Pelias and Kinnebrew (1) reported a syndrome of ankylosed teeth, bilateral clinodactyly of the fifth fingers, and mild relative mandibular prognathism due to maxillary hypoplasia in four generations. Ankylosis of the teeth, usually an isolated finding, has also been reported in association with enamel defects (2) and with multiple missing teeth (3) (Fig. 27–38).

References (Ankylosed teeth, maxillary hypoplasia, and fifth finger clinodactyly)

1. Pelias MZ, Kinnebrew MC: Autosomal dominant transmission of ankylosed teeth, abnormalities of the jaws, and clinodactyly: A four-generation study. Clin Genet 27:496–500, 1985.

Fig. 27–38. *Ankylosed teeth, maxillary hypoplasia, and fifth finger clinodactyly*. Note failure of premolars and molars to meet at the occlusal plane. (From MZ Pelias and MC Kinnebrew, Clin Genet 27:496, 1985.)



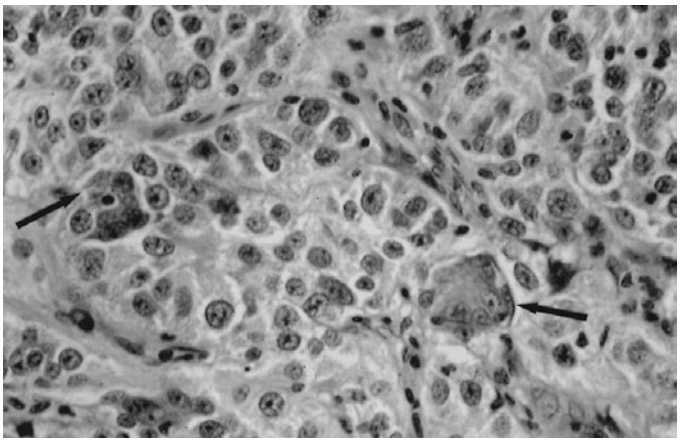


Fig. 27–39. *Neuroendocrine carcinoma of salivary glands, sensorineural hearing loss, and enamel hypoplasia*. Submandibular neoplasm showing loose, regular appearing cells manifesting neuroendocrine characteristics on immunohistochemistry, and ductlike structures with central epithelial cells and peripheral myoepithelial cells (arrows). (From L Michaels et al, Am J Med Genet 83:183, 1999.)

2. Rule JT et al: The relationship between ankylosed primary molars and multiple enamel defects. J Dent Child 39:29–35, 1972.

3. Stewart RE, Hansen RW: Ankylosis and partial anodontia in twins. J Calif Dent Assoc 2:50–52, 1974.

Neuroendocrine carcinoma of salivary glands, sensorineural hearing loss, and enamel hypoplasia

Michaels et al (1) described four sibs from the Isle of Man with low-grade neuroendocrine carcinoma of salivary glands, severe sensorineural hearing loss, and enamel hypoplasia.

The submandibular glands were involved in three cases, and the minor salivary glands of the nasal cavity and maxillary sinuses in one. The tumors manifested when the patients were in their thirties. The tumors consisted of well-differentiated neoplastic ducts surrounded by neoplastic myoepithelial cells, together with sheets of epithelial cells expressing neuroendocrine markers by immunohistochemistry (Fig. 27–39). Metastasis to the cervical neck nodes occurred in all four individuals.

In the two male patients, there was severe sensorineural hearing loss which developed in adult life, unilateral in one brother and bilateral in the other. In the brother with the bilateral sensorineural hearing loss, a vestibular schwannoma was noted on one side.

Amelogenesis imperfecta was seen in three of the four siblings and in four of their offspring. The teeth were described as having a brown-yellow surface with vertical bands suggestive of the X-linked hypoplastic type.

Reference (Neuroendocrine carcinoma of salivary glands, sensorineural hearing loss, and enamel hypoplasia)

1. Michaels L et al: Family with low-grade neuroendocrine carcinoma of salivary glands, severe sensorineural hearing loss, and enamel hypoplasia. Am J Med Genet 83:183–186, 1999.

Chapter 28
Well-Known Miscellaneous Syndromes

Alagille syndrome (arteriohepatic dysplasia)

In 1973, Watson and Miller (47) reported the association between intrahepatic cholestasis and pulmonary arterial stenosis. Alagille and coworkers (2), in 1975, added characteristic facies, mental, somatic, and sexual retardation, and vertebral and cardiac malformations. An earlier reference to the same condition is that of Vermassen and Boddaert (46). Low birthweight and growth retardation occur in about 50% , being more common in those with vertebral anomalies. Mueller et al (26) noted that about 25% die prior to the age of 5 years due to cardiovascular or hepatic complications. The chances of survival to 20 years without liver transplantation is about 50% (13). At least 150 cases have been reported (18).

Autosomal dominant inheritance with 95% penetrance and highly variable expressivity has been amply demonstrated (11,15a,18,21, 26,38,39,42,47). There is a high occurrence of new mutations (11). In at least 70%, various mutations in human *JAGGED 1 (JAG1)* gene have been found (45a,48). The gene encodes for a ligand for *NOTCH 1*, a transmembrane receptor (5,23,28). NOTCH intercellular signaling pathway mediates cell fate decisions during embryogenesis (23). Patients with isolated tetralogy of Fallot may have *JAG1* mutations (44). About 15% of the cases are sporadic (10). A deletion has been found at 20p12 in less than 7% (4,14,34,49). FISH is used. The frequency has been estimated at 1/70,000 live births (9).

Facies. Earlier than 1 year of age, the facies is not especially distinctive. Later prominent forehead, deep-set eyes, and long straight nose with flattened tip are seen in 95%. The frontonasal angle is straight, and there are flat midface, mild hypertelorism, and prominent chin. The pinnae are often outstanding (2,3,37,38). The postpubertal male has sparse facial hair (Fig. 28–1). Sokol et al (45) pointed out that the facies is not specific for Alagille syndrome but is a general feature of congenital intrahepatic cholestatic liver disease. In a recent study, about 80% were identifiable by the facies (19). Oligodontia and oral xanthomas have been noted in a patient (12a).

Eyes. Bilateral posterior embryotoxon (white line showing 2 mm over the limbus), pigmentary retinopathy, and strabismus are seen in about 85% (Fig. 28–2). Less frequent are ectopic pupil, band keratopathy, iris stromal hypoplasia (45%), choroidal folds, diffuse fundus hypopigmentation (57%), anomalous elevated optic disc and optic disc drusen (75%), and infantile myopia (7,12,15,27,31,32,35–37,39). Similar findings were found in one parent in 36% (12).

Cardiovascular. Peripheral pulmonary artery stenosis is found in 85%–95% (3). This may be an isolated finding (55%), but it may be found in combination with ASD, VSD, coarctation of the aorta, and tetralogy of Fallot (7%–10%) (26,38). In about 15%, there are isolated examples of congenital heart anomalies without peripheral pulmonary artery stenosis. The stenosis may occur at a single site or at multiple sites. Intracranial vascular anomalies may be found (6a,48a). Mutations in the *JAG1* gene can cause familial tetralogy of Fallot (10a).

Liver. Chronic cholestasis due to intrahepatic bile duct paucity with associated pruritus becomes evident during the first few months of life and persists (22). However, perhaps 25% do not manifest jaundice until later in infancy. Acholic stools and xanthomas may appear. There is hepatosplenomegaly, but no hepatic failure or portal hypertension. Cirrhosis eventuates in 10%–15% (17). Hepatic failure may eventuate (41). Hepatocarcinoma has been reported (1,6,16,17,20,30,33,41), perhaps being related to the loss of the gene on chromosome 20.

Skin. Palmar erythema and small telangiectases are frequent on the face and trunk. The skin of the proximal phalanges may be somewhat redundant (Fig. 28–3A), and supernumerary flexion creases of the digits are seen in about 30% (ID Krantz, personal communication, 2000).

Musculoskeletal. Vertebral anomalies of shape and/or segmentation (butterfly vertebrae, hemivertebrae, vertebral arch defects, reduced interpediculate distances, and plate irregularities) are present in about 85% (3,8,25,29) (Fig. 28–3B). A pointed anterior process on C-1 has been noted (38,40). Shortened distal phalanges and ulnae are common (8,22,37,38,40). Eleven pairs of ribs and fused ribs have also been observed. Osteopenia and retarded bone age are common (38,47). Radioulnar synostosis and narrow lumbar spine have also been reported (8). Short ulnae and short distal phalanges have been described (38). Those with short stature exhibit resistance to growth hormone (9).

A B C

Fig. 28–1. *Alagille syndrome*. (A–C) Note prominent forehead, deep-set eyes with upslanting palpebral fissures, straight nose with straight nasofrontal angle, flat midface. (Courtesy of I Krantz, N Spinner, D Piccoli, Philadelphia, Pennsylvania.)

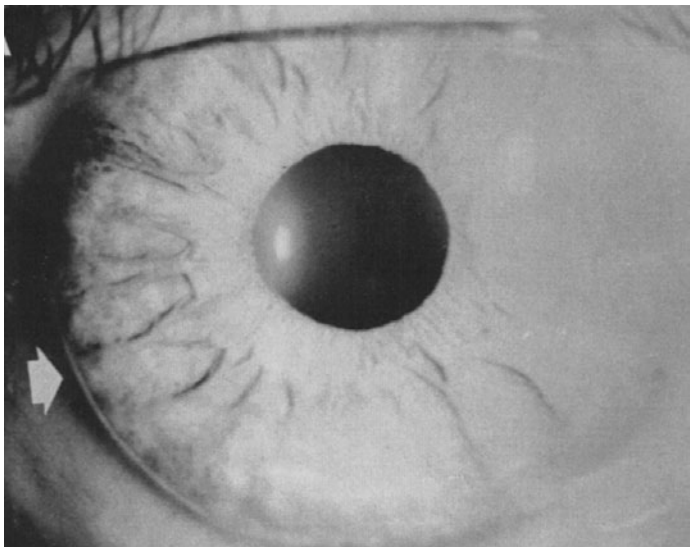


Fig. 28–2. *Alagille syndrome*. Posterior embryotoxin. Arrow points to white line that extends about 2 mm over the limbus. (From RF Mueller, J Med Genet 24:621, 1987.)

Genitourinary. Facial and body hair is sparse, but normal sexual function in males is common. Small kidneys, agenesis of a kidney, bifid kidney and its pelvis, mesangiolipidosis, and medullary cystic disease have been noted in 75% (3,38,47). Cystic dysplastic kidneys have also been reported (24).

Central nervous system. Minimal cerebral dysfunction has been described in about 60%. Poor school performance and misdemeanors are common. Reflexes may be absent or diminished. Moderate mental retardation has been reported in about 15% (2,3,47). The voice is often high pitched.

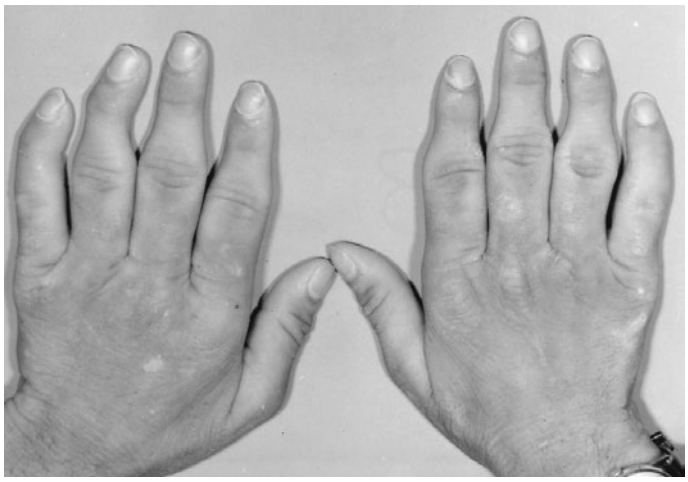
Pathology. Liver biopsy shows cholestasis and continued loss to the point of absence of interlobular bile ducts without fibrosis or cirrhosis in 95% (25,26). The common bile duct is hypoplastic but patent. Thyroid carcinoma has also been described (16).

Differential diagnosis. Prolonged neonatal cholestasis must be differentiated from extrahepatic biliary atresia, giant cell hepatitis, and various infections (rubella embryopathy). Arteriohepatic dysplasia must be differentiated from other forms of familial intrahepatic cholestasis such as Byler syndrome (a syndrome of abnormal bile acid synthesis), *Zellweger syndrome*, cholestasis-lymphedema syndrome, and α1-antitrypsin deficiency (46). Prominent Schwalbe lines (posterior embryotoxon) are seen in 8%–15% of normal individuals, in *Rieger syndrome* and other anterior chamber cleavage syndromes, and in *Bannayan–Riley–Ruvalcaba syndrome*. Pigmentary retinopathy is seen in a host of disorders. Riely et al (37,38) have exhaustively discussed differential diagnosis.

Peripheral pulmonary stenosis can be seen in myriad other conditions: rubella embryopathy, *Down syndrome, Williams syndrome, thalidomide embryopathy*, and various forms of nanism.

Laboratory aids. Atrophy of the interlobular bile ducts leads to defective secretion of bile. During the first 3 months of life there is moderate elevation of serum bilirubin and bile acids. The urine is dark and the stool is clay-colored. There is mild malabsorption of fat in children but not in adults. After 6 months of age, serum triglycerides and cholesterol become markedly elevated but this elevation also gradually disappears.

Hepatobiliary scintigraphy or operative cholangiography may be used to exclude obstructive causes of jaundice (e.g., biliary atresia). Ultrasound in older patients shows diffuse increases in echogenicity and loss of fine detail consistent with parenchymal liver disease (43). Kidney biopsy has shown mesangiolipidosis in about 70% (3).



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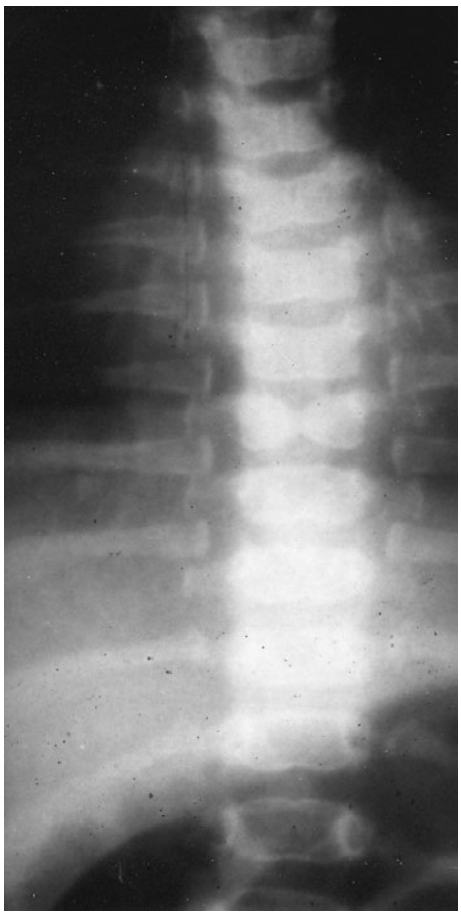

B

Fig. 28–3. *Alagille syndrome*. (A) Note enlarged proximal fingers. (B) Butterfly vertebra.

Pulmonary artery stenosis can be demonstrated by cardiac catheterization or inferred from Doppler echocardiography.

References [Alagille syndrome (arteriohepatic dysplasia)]

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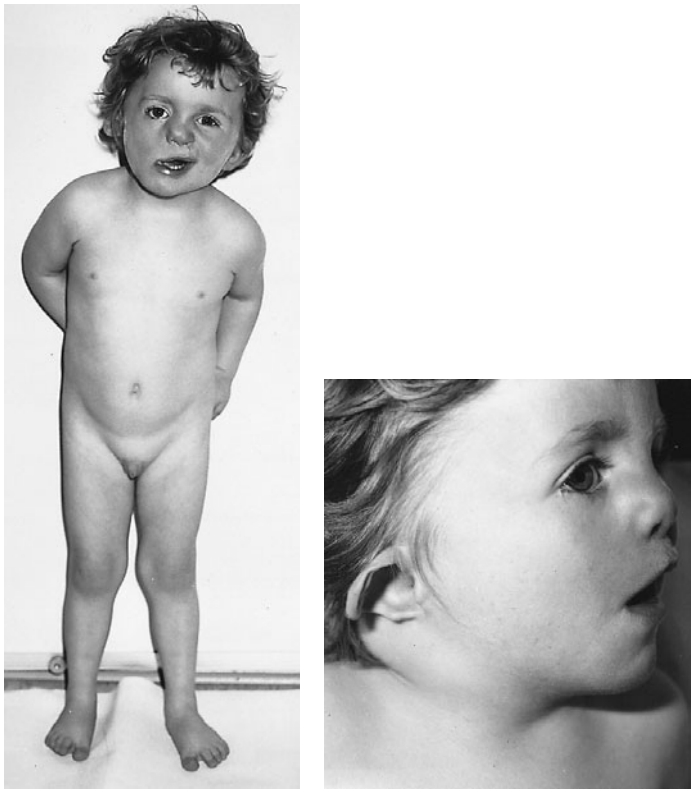
CHARGE association and Hall-Hittner syndrome

Although the association was described earlier by a number of authors (2,19,20,34), Pagon et al (27), in 1981, employed the mnemonic CHARGE (*C*oloboma, *H*eart defects, *A*tresia choanae, *R*etarded growth and development and/or CNS anomalies, *G*enital hypoplasia, and *E*ar anomalies and/or deafness). Several excellent reviews are available (11,20,24,26,27,30,35). At least 250 cases have been reported. Prevalence has been estimated to be 1 per 10,000 (5). The role of the neural crest has been discussed (33–35). Although most instances are sporadic, affected parent and child, affected sibs, and monozygous and dizygous twins have been reported (4,6,11,18,23,26,27). North et al (25) suggested that one or more responsible genes map to the 14q22 area. Other authors have noted a deletion in the 22q11 area (13,14). Martin et al (23) noted t(2;7)(p14;q21.11).

Hall-Hittner syndrome is a recognizable subgroup. Diagnostic characteristics include coloboma, choanal atresia, asymmetric facial palsy, neurogenic swallowing deficit, classic CHARGE ears, and absence/hypoplasia of semicircular canals (1,5,16).

Polyhydramnios has been noted in about 50% of the cases and in nearly all of those with bilateral choanal atresia. Approximately 35% die during the first 3 months of life. Males with bilateral choanal atresia, central nervous system anomalies, esophageal anomalies, and congenital heart disease have a higher mortality rate (35).

If ascertainment is done by using choanal atresia as a constant feature (100%), variable mental retardation, motor delay, and postnatal growth retardation (95%) are the most constant abnormalities. If this bias is not



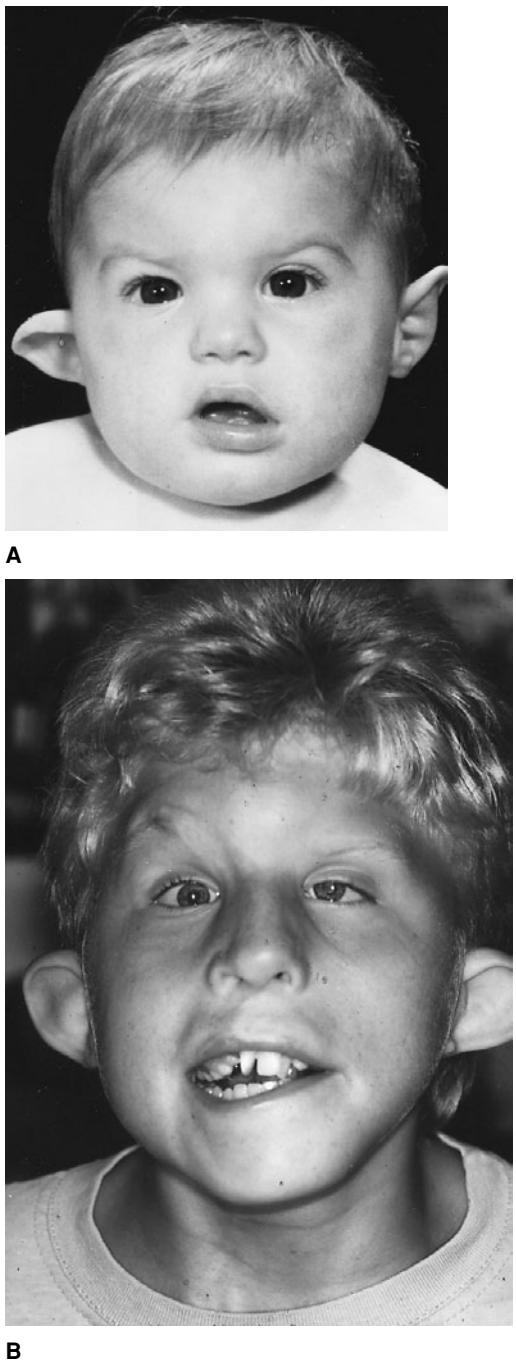
A B

Fig. 28–4. *CHARGE association*. (A,B) Mentally retarded child with choanal atresia, repaired cleft lip-palate, dysmorphic right ear with conduction hearing loss, right-sided facial palsy, coloboma of choroid and optic nerve, micropenis, cryptorchidism, pulmonary stenosis, and ASD. (Courtesy of HH Kramer, Düsseldorf, West Germany.)

introduced, about 55%–65% have choanal atresia (35). Birthweight and length are usually normal but postnatal growth is poor in 50%. Feeding problems are common in early infancy (17). Seen in about 90% are low-set, short, wide, asymmetric, outstanding, cup-shaped, simplified or lop ears, square face with malar flattening, pinched nostrils, long philtrum, prominent columella, cardiac defects (PDA, VSD, ASD, endocardial cushion defect, coarctation of aorta, vascular ring, hypoplastic left heart, tetralogy of Fallot) (10,21), unilateral or bilateral ocular coloboma of iris, retina, and/or disc, hypogenitalism in males (microphallus, poorly developed scrotum, cryptorchidism), and mental retardation (10,12,20,36,38). About 50% have central nervous system anomalies ranging from arhinencephaly to holoprosencephaly to other forebrain or hindbrain defects (22). Facial asymmetry, congenital microcephaly, high nasal bridge, malar hypoplasia, small mouth, cleft palate, swallowing difficulties, and congenital unilateral facial palsy have been noted in 40%–50% (Figs. 28–4 and 28–5 (8). Van Meter and Weaver (37) described two children with features linking CHARGE association and oculo-auriculo-vertebral spectrum. About 10%–15% exhibit postnatal microcephaly, micrognathia, and short neck. Mixed, progressive hearing loss, characterized by a wedge-shaped audiogram, is noted in 60% (35,36). Histologic examination of temporal bones has revealed the Mondini defect of the pars inferioris with complete absence of the pars superioris (28,32).

Less common anomalies (10%–30%) include tracheoesophageal fistula, esophageal atresia, minor renal malformations, and athelia (7,11, 15,26).

Choanal atresia is bilateral in 65% and it occurs more often on the left side (5,29). The ocular colobomas ranging from iris coloboma to clinical anophthalmia are seen in 80%–85% (31,35). Not uncommonly the coloboma is limited to the choroid and/or optic nerve. Nystagmus is noted in 25% (31). Occasionally, microphthalmos is noted. However, it



A B

Fig. 28–5. *CHARGE association*. (A,B) Rather typical face. Notice unusual pinnae. Mild degree of facial palsy. (A from CA Oley et al, J Med Genet 25:147, 1988.)

should be pointed out that if colobomatous microphthalmia is used as the constant feature, the overlap of the two associations is remarkable (18,19). Some patients exhibit the *DiGeorge sequence* (9). Hypopituitarism has been reported (3).

CHARGE association exhibits some overlap with *trisomy 13, del(4p), dup(4p), cat-eye syndrome, trisomy 22, del(9q), del(11q), del(13q)*, and VATER association (11,34). Choanal atresia is seen in combination with numerous syndromes (20). Undoubtedly many of the cases cited under our heading *cleft lip–palate, eye colobomas, vertebral anomalies, and mental retardation* are examples of CHARGE association. The X-linked *Abruzzo–Erickson syndrome* must be excluded. It combines cleft palate, short stature, hypospadias, and eye colobomas.

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FG syndrome (unusual facies, mental retardation, congenital hypotonia, and imperforate anus)

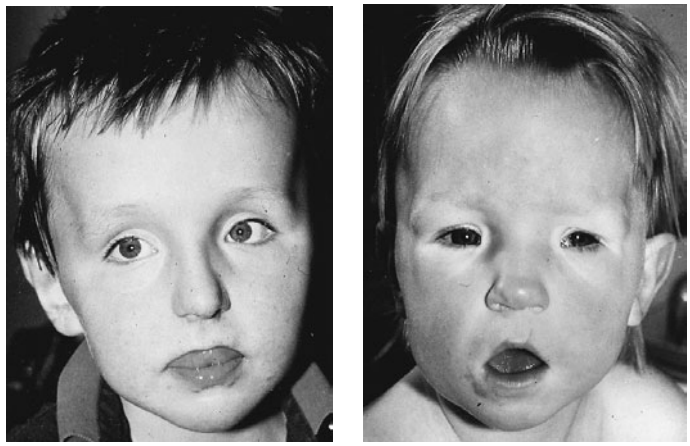
Opitz and Kaveggia (13), in 1974, reported a syndrome consisting of mental retardation, unusual facies, imperforate anus, and other anomalies. Opitz et al (14,15) subsequently expanded the syndrome to include characteristic personality, megalencephaly, joint contractures, and broad thumbs and/or halluces. About 55 patients have been reported 1,5,10,11,15,15a,17–19,21,25).

Inheritance is clearly X-linked with about 30% of heterozygotes manifesting stigmata (21,22). The *FGS1* gene has been mapped to Xq12–q21.31 (3,8,25). A second gene appears to be involved (4a,5a). There appears to be skewed inactivation of the X chromosome (8). A paracentric inversion has been noted (4).

Stature is variable. Initial size is short but there is catch-up growth. In others, birth size is normal but there is postnatal growth failure in 65%, possibly because of severe illness. About 30% of the patients die during the first few weeks of life from congenital heart disease or amniotic fluid aspiration. There also appears to be a second peak at about 2 years when death results from pneumonia.

Facies. The facies is quite variable and gradually disappears with age (19). The head, usually normal size at birth, becomes relatively macrocephalic and plagiocephalic in about 70%. Craniosynostosis has been documented in one instance (13). The anterior fontanel tends to remain open for a prolonged period. The forehead is high and broad. The frontal hair is upswept (cowlick) in 90% and its quality is soft, silky, and sparse in about 60%. There may be several hair whorls. The palpebral fissures frequently slant downward, less often upward, and the eyes appear deep set. The medial eyebrows flare. Hypertelorism, divergent strabismus (50%), epicanthic folds, and large corneae are common. The mouth is often kept open (facial hypotonia). The philtrum is long and the upper lip is thin. The lower lip is prominent and often there is drooling. Mild micrognathia and a high narrowly arched or cleft palate (1) are reported in 5% (Figs. 28–6 and 28–7). The teeth are usually crowded. Minor anomalies of the auricles are seen in about

Fig. 28–6. *FG syndrome*. (A) Broad forehead, downslanting palpebral fissures, strabismus, prominent lower lip, micrognathia. (B) Tall forehead, wide nasal bridge, downward slanting short palpebral fissures, long philtrum, open mouth. (From EM Thompson et al, Clin Genet 27:582, 1985.)



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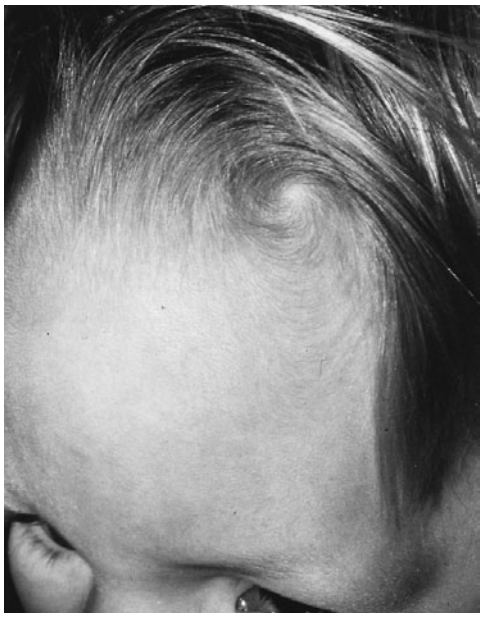

Fig. 28–7. *FG syndrome*. Frontal hair whorl. (From EM Thompson et al, Clin Genet 27:582, 1985.)

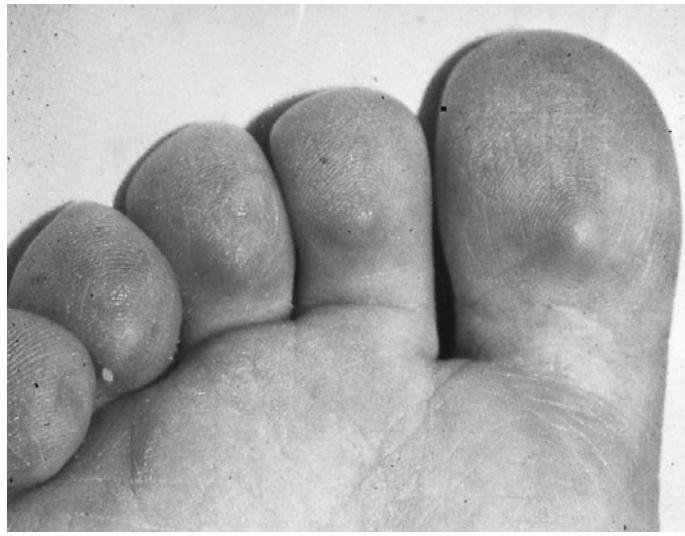

Fig. 28–8. *FG syndrome*. Toe padding. (From EM Thompson et al, Clin Genet 27:582, 1985.)

60%: small, simplified, occasionally protruding pinnae with mild posterior angulation and overfolded helix. Sensorineural hearing loss has been documented in 30% (11). Possibly parietal foramina are part of the syndrome (16).

Central nervous system. Mental retardation is constant and ranges from severe to mild but generally is moderate. Electroencephalographic disturbances are common but seizures are rare. The affect is one of hyperactivity (50%), affability, short attention span, and, occasionally, temper tantrums or aggression. Voice and speech are characteristic (9,25).

Partial absence, complete absence, or thinning of the corpus callosum has been reported (10,13,21–23). Thompson et al (23) reported necropsy findings consisting of simple convolutional patterning and large cavum septi pellucidi. Opitz et al (14) described midline fusion of mammillary bodies, heterotopia of neuroglial tissue in the seventh and eighth nerves, ependymal cell replacement by neuroglial tissue, and diffuse defect of neuronal cell migration.

In 90% there is severe congenital hypotonia, with secondary effects such as delayed motor development, feeding difficulties, and chronic bronchopulmonary problems. Other anomalies secondary to the central nervous system disorder include squint, ptosis, open mouth, malocclusion, variable degrees of congenital joint contractures (40%), winged scapulae, clinodactyly, pes planus, and genua recurvata.

Intestines. The most frequent intestinal and anogenital anomalies include severe constipation (70%), anal defect [imperforate, stenotic, anteriorly displaced, perianal skin tags (60%)], sacral dimple, malrotation of the bowel, small bowel atresia, absence of the mesentery, pyloric stenosis (10%), cryptorchidism (35%), hypospadias (25%), and inguinal and/or umbilical hernia (55%).

Other findings. There is a high fingertip whorl count (18) and there are fetal toe pads (Fig. 28–8). Broad thumbs and halluces are seen in 80% (10,15). Congenital heart defects are uncommon. Split hand has also been found (8).

Differential diagnosis. The dominantly inherited *Townes–Brocks syndrome* (imperforate anus, abnormalities of hands and feet, and sensorineural hearing loss) should be excluded. There is some overlap with the neurofaciodigitorenal syndrome (severe mental retardation, megalencephaly, high forehead, cowlick, groove of nasal tip, acrorenal field defect) (6). *Simpson–Golabi–Behmel syndrome* also needs to be excluded. Thompson et al (24) reported an X-linked mental retardation syndrome in which there was overlap with FG syndrome but without macrocephaly and with a different facies. Fryns et al (7) described two unrelated males with a syndrome overlapping FG syndrome but the small nose, relative microcephaly, and pre- and postnatal overgrowth make it distinctive. Another family that doesn't quite fit the FG syndrome is that of Stoll et al (2,20). Fetal toe pads are also seen in *Kabuki syndrome, Weaver syndrome*, and *del(18q) syndrome* (19).

References [FG syndrome (unusual facies, mental retardation, congenital hypotonia, and imperforate anus)]

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Kartagener syndrome (immotile cilia syndrome, primary ciliary dyskinesia)

The relationship between situs inversus viscerum and bronchiectasis was pointed out by Siewert (49) in 1904. Kartagener (29,30), in a series of papers from 1933 through 1935, added chronic rhinosinusitis, that is, nasal polyposis, chronic hyperplastic rhinitis, and ethmoidomaxillary sinusitis. Numerous investigators have also noted the absence or hypoplasia of the frontal sinuses. More than 500 cases have been recorded.

The syndrome exhibits autosomal recessive inheritance (1,33,54). Consanguinity has been found in about 25%. However, there is marked genetic heterogeneity (7,7a,22,36). Identical twins with discordant laterality have been noted (38).

Primary ciliary dyskinesia has at least one gene mapped to 19q13.3-qter (31). A gene for situs inversus viscerum is located at 14q32 (35). That this may be the site for one form of ciliary dyskinesia is bolstered by the finding of two brothers with a form of type I Usher syndrome which also maps to 14q32 (7). A familial situs ambiguus has been mapped to Xq26 (18). Inversion of the long arm of chromosome 11 has also been cited (24a) as well as 5p (38a).

Narayan et al (36) described a mother and five sons with three different fathers. Heterotaxia syndrome may have autosomal recessive, autosomal dominant, or even X-linked inheritance (4).

There is no racial predilection (54). The frequency of immotile cilia (primary ciliary dyskinesia) syndrome is about 1/16,000 population (45,54).

Abnormal cilia are considered the underlying cause of the anomalies observed in Kartagener syndrome (17,44). Most studies have found partial or total absence of dynein side arms (11,59) that would inhibit mucociliary transport. Transposed ciliary microtubules, missing radial spokes, and supernumerary microtubules have also been found (8,10,21,42,51–53,58). It has been suggested that ciliary defects may develop with age (24,41) since children may have normal nasal ultrastructure. An animal model has been found (15).

Respiratory tract. Sinusitis is a frequent finding (Fig. 28–9). Similarly, nasal polyps, found in about 20%, have been reported with situs inversus in the absence of bronchiectasis. Agenesis or diminution of the frontal sinuses is common (34,39) but also is rather frequently seen in bronchiectasis and sinusitis without situs inversus, indicating a relationship between the sinuses and the rest of the respiratory tract, but not necessarily with visceral inversion.

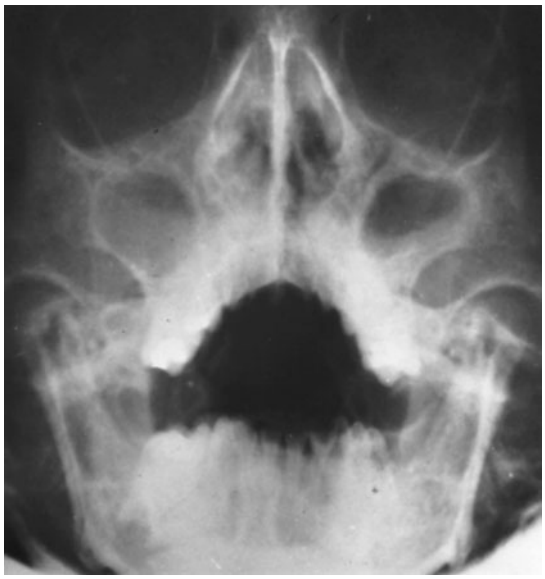


Fig. 28–9. *Kartagener syndrome*. Bilateral maxillary sinusitis, more pronounced on right side.

In early infancy, nasal discharge, frequent colds, and chronic bronchitis are observed, as well as recurrent bouts of pneumonia. Nasal catarrh and anosmia soon intervene and are followed in most cases by chronic cough productive of foul-smelling phlegm. Nasal mucosal cilia are defective (56). Bronchiectasis is found is about 30% of older children and adults. In some persons, however, bronchiectasis seems to precede involvement of the upper part of the respiratory tract. Occasionally, there are accompanying asthma, hemoptysis, and pulmonary osteoarthropathy. Life expectancy is normal.

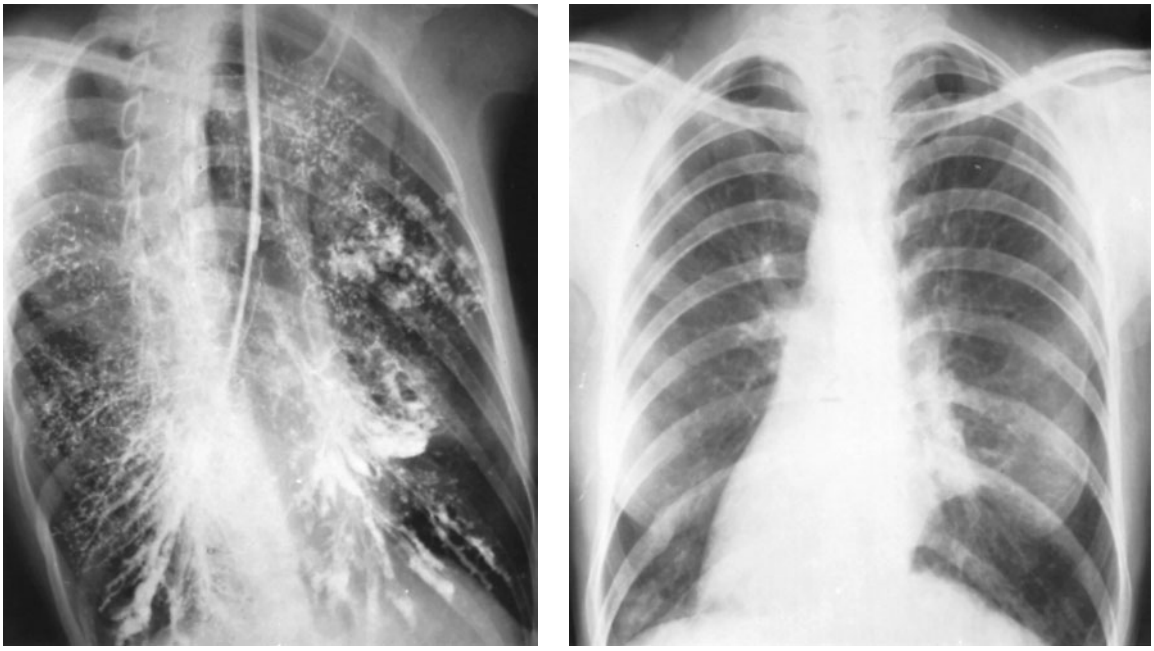
Among cases of situs inversus viscerum (see below), bronchiectasis is present in from 15% to 25% (34). This is far higher than the incidence among the general population (0.25%–0.50%) (30).

The bronchietasis is generally tubular or varicose, rather than cystic. There is still disagreement as to whether the bronchiectasis is of the acquired or congenital type (Fig. 28–10A).

Situs inversus viscerum. As an isolated phenomenon, situs inversus viscerum occurs once in about 8000 to 10,000 births (14,39). There is no unanimity of opinion concerning the relationship between visceral inversion and bronchiectasis, but possibly some factor predisposes the neonate with situs inversus to defective postnatal lung growth and atelectasis. About 50% of patients with immotile cilia syndrome manifest situs inversus (22,54). Ciliary orientation is more random than those in a control group (16,43). Rott (45) suggests that ciliary beats in the early embryo determine the type of laterality. Without the ciliary action, laterality develops randomly (16).

Dextrocardia, without further evidence of visceral inversion, has been frequently detected (56) (Fig. 28–10B), and corrected transposition has been reported once (50). Furthermore, investigators (20,47) have reported patients with Kartagener syndrome and features of the polysplenia field defect, suggesting a pathogenesis common to the two entities.

Fertility. Most males with Kartagener syndrome are infertile (2), due to an ultrastructural defect of sperm tails similar to that of respiratory cilia (16). There have been case reports of males with normal fertility (28) and normal spermatozoa (46). Female patients were originally considered to be normally fertile (3,6). However, Afzelius and Eliasson (2) found evidence that female fertility is also impaired, the Fallopian cilia being deficient in dynein arms (6,40).



A B

Fig. 28–10. *Kartagener syndrome*. (A) Bronchography showing bronchiectasis of left middle and both lower lobes. (B) Dextrocardia. Atelectasis of left middle lobe and right basal infiltration. (From A Glay, J Can Assoc Radiol 12:22, 1961.)

Other findings. Cases have been described with anomalous subclavian artery, malformation of retinal vessels, cardiac and renal anomalies, turricephaly, absence of the xiphoid process, thyrotoxicosis, spinal arteriovenous malformation (23), Paterson-Brown-Kelly syndrome (postcricoid web dysphagia, anemia, glossitis, cheilosis, and koilonychia) (55), mesangiocapillary glomerulonephritis (14), polysplenia (20,47) and extrahepatic biliary atresia (20).

Various associated eye anomalies have been reviewed by Segal et al (48). Chronic otitis media and hearing loss have been reported in several patients (26); Fischer et al (19) demonstrated that middle ear cilia were abnormal.

Valerius et al (57) noted depressed motility of polymorphonuclear leukocytes.

Differential diagnosis. Thick tenacious sinus and bronchial secretions, nasal polyposis, chronic sinusitis, and bronchiectasis also occur in cystic fibrosis. The histologic appearance of the respiratory epithelium, the bronchial plugging, and the absence of other stigmata (situs inversus viscerum) clearly distinguish cystic fibrosis from Kartagener syndrome. Ultrastructural defects may be seen in many individuals with repeated upper and lower respiratory infections (10). An especially good discussion of etiologies of familial bronchiectases is that of Davis et al (12).

Laboratory aids. Diagnosis can be achieved by studying mucociliary clearance (5) or ultrastructural examination of ciliary structures from samples obtained by nasal and bronchial brushing (32) (Fig. 28–11). Transmission EM with tannic acid staining is especially effective in demonstrating dynein abnormalities (27). Deficiencies in dynein arms on the outer microtubular doublets of cilia are most often (40%) evident. However, a host of other ultrastructural abnormalities have been reported [complete or incomplete absence of inner arms (6%), inner and outer arms (30%), radial spoke defect (10%), microtubular transposition, lack of central core structures, etc.] (1,9,13,52,54) (Fig. 28–12). Occasionally, no ciliary abnormalities are found (22). Abnormally long cilia have also been reported (37). Holtzmann et al (25) discussed a diagnostic approach.

References [Kartagener syndrome (immotile cilia syndrome, primary ciliary dyskinesia)]

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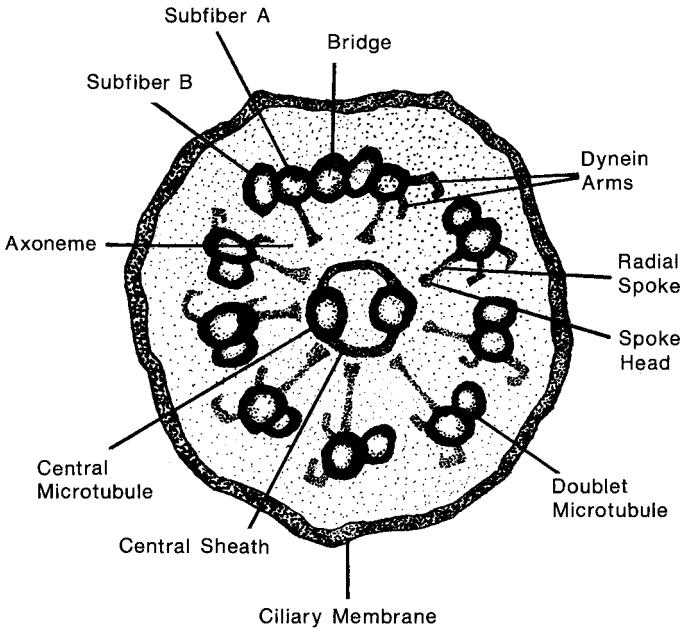
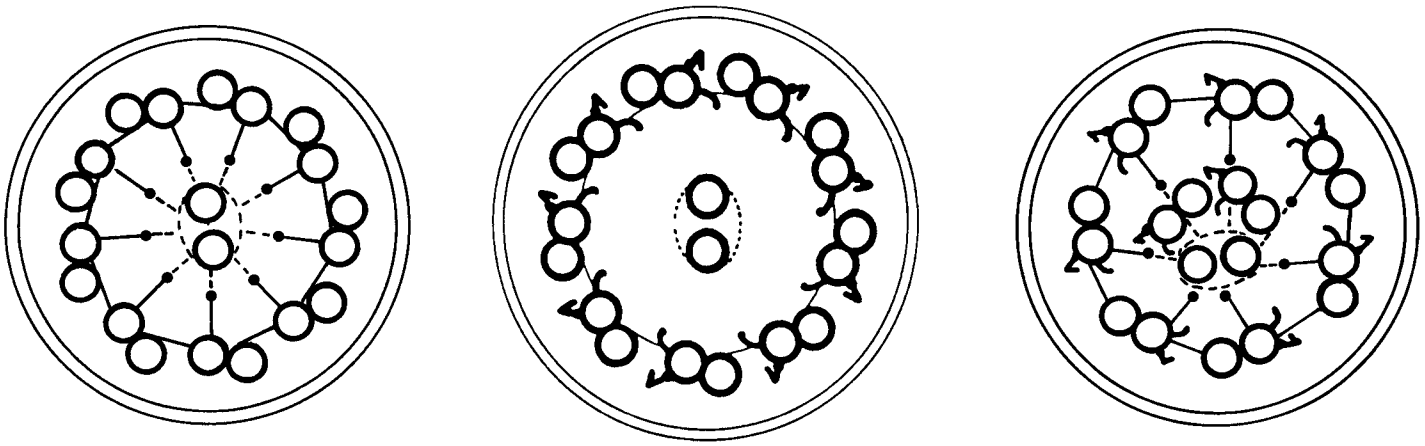
Fig. 28–11. *Kartagener syndrome*. Diagram of cross section of a cilium. Note nine outer microtubular doublets and two central microtubules held together by three kinds of connections: dynein arms, nexin links, and radial spokes. (From DJ Imbrie, Am J Otolaryngol 2:215, 1981.)





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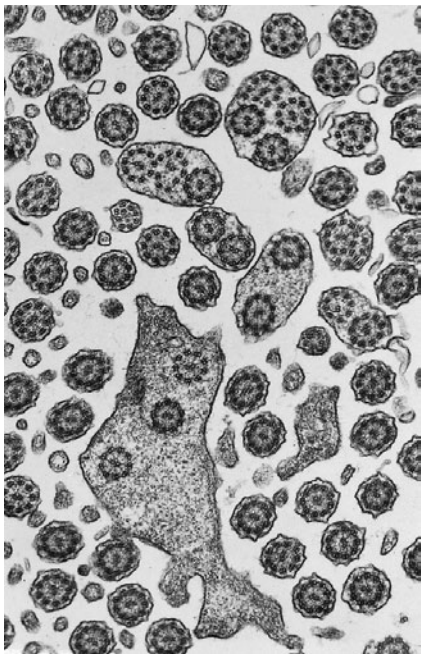

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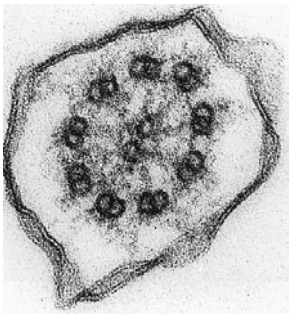

E

Fig. 28–12. *Kartagener syndrome*. Structural defects of cilia. (A) Total absence of dynein side arm. (B) Absence of radial spokes. (C) Microtubular transposition. (D) Electron photomicrograph of nasal mucosa in Kartagener syndrome showing megacilia, extra filaments, and disproportion of relationship of cytoplasm to axonemes. (E) Section illustrating complete dynein defect. (A–C from R Eliasson et al, N Engl J Med 297:1, 1977. D from AJ Lupin and GJ Misko, J Otolaryngol 7:95, 1978. E courtesy of JM Sturgess, Scarborough, Ontario, Canada.)

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Klippel-Feil anomaly

Klippel–Feil anomaly is characterized by faulty segmentation of two or more cervical vertebrae and, in its most severe form, consists of massive cervical vertebral "fusion," short neck, limitation of head movement, and low posterior hairline. The condition is morphologically and etiologically heterogeneous. Over 450 papers have been written on the subject (18), approximately 500 patients have been recorded to date (18,30), and extensive reviews are available (28,30).

Vertebral "fusion" is actually an inaccurate term, the condition resulting from failure of normal segmentation, which can be traced back to the third embryonic week when segmentation of mesodermal somites takes place (37). Although iniencephaly has been considered to be a severe form of Klippel-Feil anomaly (11,25,53), it has also been classified with anencephaly with retroflexion (52). Furthermore, little is gained by identifying iniencephaly with Klippel-Feil anomaly as the latter is neither a morphologic nor an etiologic entity.

Klippel–Feil anomaly was described as early as the sixteenth century, and involvement of the second and third cervical vertebrae has even been found in an Egyptian mummy of about 500 B.C.(26). In 1912, Klippel and Feil (34) described the postmortem findings of a 46-year-old French tailor who had a short immobile neck with massive fusion of cervical and upper thoracic vertebrae. Feil (22), in 1919, added 13 cases, 12 of which had been published previously. He defined three morphologic subtypes. Type I consisted of massive fusion of the cervical and upper thoracic vertebrae. In type II, fusion occurred at only one or two interspaces, but various anomalies such as hemivertebrae, occipitoatlantal fusion, and other defects could be present. Type III had both cervical and lower thoracic or lumbar fusion.

For type I, birth prevalence estimates have varied from a minimum of 0.025–0.03/1000 (36) to a maximum of 0.16/1000 (30). Sex predilection for females has been recorded by several authors (25,46), and Helmi and Pruzansky (30) have estimated the male:female ratio to be 1:1.3. Type II occurs more commonly, with a prevalence of 7.3/1000 (9,30), the most frequent sites of cervical fusion being at C_{2-3} and C_{5-6}.

Etiologic heterogeneity is evident and Gunderson et al (28) used Feil's (22) classification. For type I, almost all cases have been sporadic, although there have been a few familial examples (24,28). Autosomal recessive inheritance has been postulated (28), although among sporadic cases there has been female predilection, as indicated. Type II is transmitted as an autosomal dominant disorder and, in some instances, atlantooccipital fusion or other abnormalities may be observed (28). It has been suggested that type II is genetically heterogeneous with an autosomal recessive form also (33). For type III, an autosomal recessive mode of inheritance has been suggested (28). Da Silva (18) reported 12 cases of a newly recognized autosomal recessive disorder in an inbred kindred; patients had variable fusions of cervical, upper thoracic, and/or lumbar vertebrae, some presenting type I, others type III patterns. Raas-Rothschild et al (49) have opined that Klippel-Feil anomaly and sacral agenesis constitute a type IV. This and other examples have been represented by isolated cases (5,26,31). A dominant form associated with malformed larynx has been reported (13). In this form (vide infra), a gene has been mapped.

Clarke et al (14,15) reported a large family in which a chromosome inversion was found, suggesting that the gene is located at 8q22.2, the site of *SGM1.HOX* genes are involved in vertebral segmentation (40).

A large number of teratologic experiments in animals have resulted in vertebral malformations, suggesting that Klippel-Feil anomaly might occur on a teratogenic basis in humans. In this connection, Gunderson et al (28) reported a case of type I fusion in which the mother had attempted abortion with oral and parenteral agents on three occasions during the first trimester. The possibility of Klippel-Feil anomaly occurring on the basis of subclavian artery supply disruption has also been raised (8).

Bouwes Bavinck and Weaver (6) further suggested that a subclavian artery supply disruption to the developing embryo around the sixth week is responsible not only for Klippel-Feil anomaly, but Poland and Moebius anomalies, isolated terminal transverse limb defects, and Sprengel deformity.

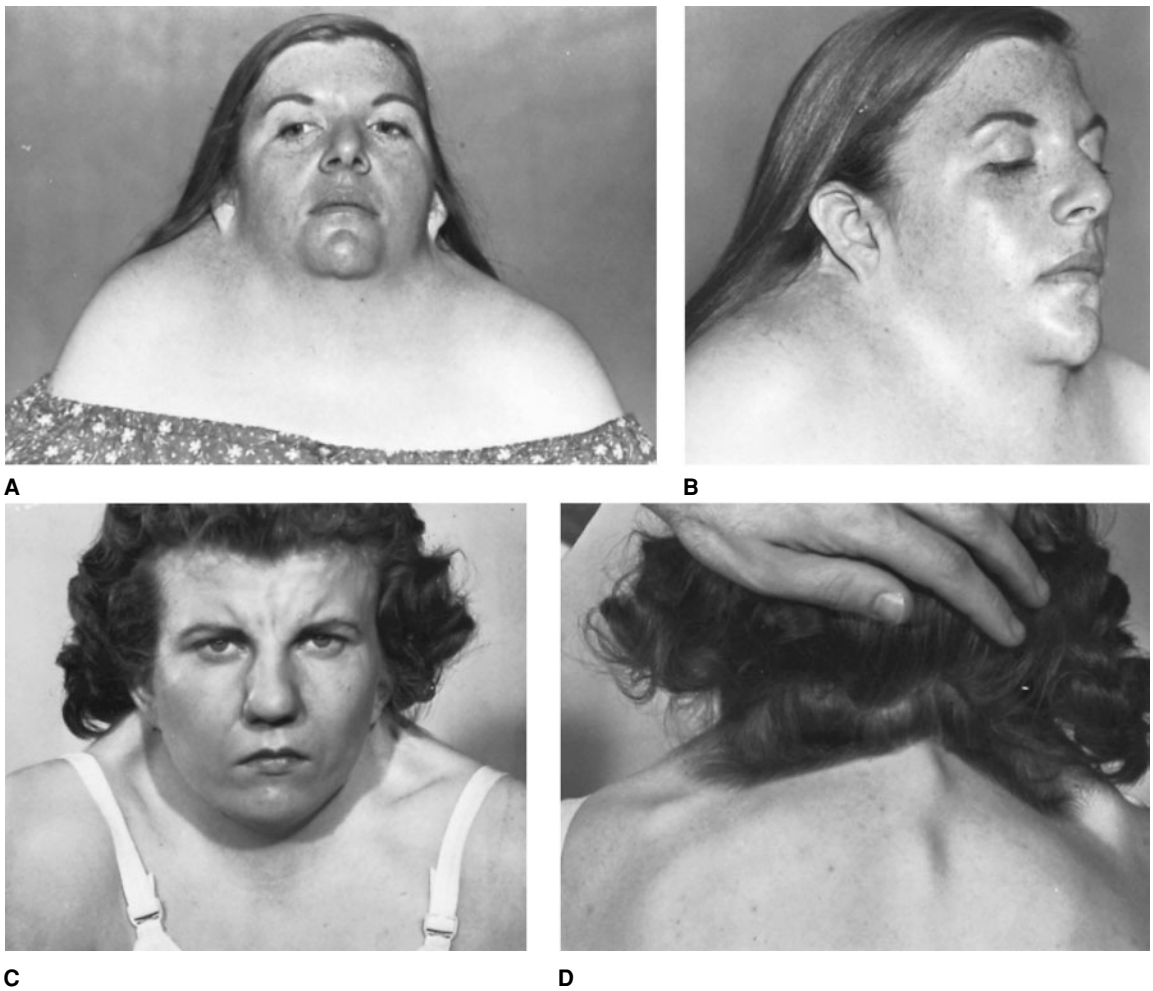


Fig. 28–13. *Klippel-Feil anomaly*. (A–D) Because of fusion of cervical vertebrae, the head appears to rest directly on the thorax, without an intervening neck. The pterygiumlike structures are actually the trapezius muscles. Note pulled-down slanted auricles in B and low-set posterior hairline in D.

Wildervanck syndrome consists of Klippel-Feil anomaly, abducens paralysis with retracted bulb, and sensorineural or conduction deafness (21). The appearance is striking, the head seeming to sit directly on the trunk with frequent facial asymmetry and/or torticollis. On medial gaze, the adducted globe becomes retracted as the eye slit narrows, a phenomenon known as Duane syndrome. Involvement may be unilateral or bilateral. Mental retardation has been noted on occasion. An overwhelming preponderance of females has been reported.

The MURCS association consists of *Mü*llerian duct aplasia, *R*enal aplasia, and *C*ervicothoracic *S*omite dysplasia. Vertebral defects occur especially from C_5 to T_1. Anomalies include Klippel-Feil anomaly, absent vagina, absence or hypoplasia of the uterus, renal agenesis, and a variety of low-frequency defects (1,7,10,29,41,43,47,57,63). This is the same as Rokitansky-Küster-Hauser syndrome. The corresponding disorder in males is characterized by azospermia (38,42,62,66). Hearing loss is found in 25% (17,57).

Chemke et al (12) described a patient with Klippel-Feil anomaly, torticollis, preauricular appendages, cleft palate, Sprengel deformity, absent ulna, and flexion contractures of the affected upper extremity.

Fragoso et al (23) reported a female with Klippel-Feil anomaly, ocular hypertelorism, broad nose, Sprengel deformity, and postaxial polydactyly. The patient may represent an example of craniofrontonasal dysplasia. However, no craniosynostosis was evident.

JW Hanson and MM Cohen Jr (personal observation, 1975) noted two male sibs with Klippel-Feil anomaly, mild ocular hypertelorism, downslanting palpebral fissures, prominent nasal bridge, micrognathia, submucous cleft palate, dislocated radial heads, positional foot deformities, and scoliosis.

Various authorities differ in their interpretation of what constitutes Klippel-Feil anomaly. The following description is confined to massive cervical vertebral fusion (type I) only.

Head and neck. The head seems to sit directly on the thorax, without an interposing neck. The flaring trapezius muscles extend from the mastoid areas to the shoulders, producing a pterygiumlike effect. Occasionally, there is facial asymmetry, with one eye situated lower than the other (44). Posteriorly, the hairline extends to the shoulders (Fig. 28–13).

Associated abnormalities (Table 28–1) have been especially well reviewed by Helmi and Pruzansky (30). The most common eye finding has been convergent strabismus (4). Less frequently found are horizontal nystagmus and chorioretinal atrophy. From 25% to 50% have exhibited hearing loss that may be sensorineural, mixed, or conductive (30,32,38a,39,50,56); many likely represent Wildervanck syndrome. Mondini type dysplasia has been found in some cases (64). Cleft palate is present in about 17% (1,16,30,46,55,59).

There have been several examples of partial duplication of the jaws in a Klippel-Feil-like syndrome (3,19,35) (Fig. 28–14).

Musculoskeletal system. Characteristically, several, occasionally all, cervical vertebrae are fused into a solid mass. In some instances, upper thoracic vertebrae may be involved. Scoliosis, cervical ribs, and/or the Sprengel deformity have been noted in about 30% (26,34,54). Other

Table 28–1. Klippel-Feil anomaly associated abnormalities

Abnormalities	Percentage ($n = 160$)
Neurological abnormalities	49
Mirror movements	(16)
Paralysis and palsy	(9)
Astereognosis	(4)
Syringomyelia	(1)
Paresthesia	(4)
Mental retardation	(9)
Meningocele	(4)
Occipital encephalocele	(4)
Hydrocephaly	(2)
Other neurological problems	(16)
Hearing deficits	24
Speech defects	17
Ocular abnormalities	21
Cleft palate	17
Congenital heart defects	9

(Based on C Helmi and S Pruzansky, Cleft palate J 17:65, 1980. Percentages are rounded off to nearest whole number. Percentages sum to greater than 100% because several abnormalities frequently occur in same patient.)

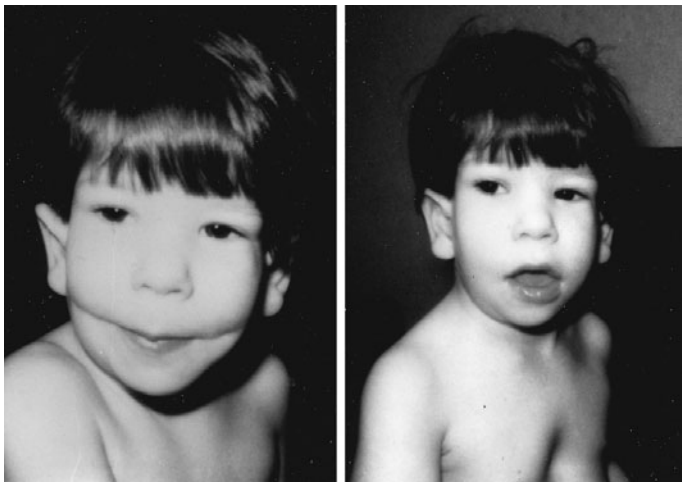
common findings include spina bifida occulta, fusion of the atlas with the occipital bone, cleft vertebrae, and hemivertebrae.

Central nervous system. A large number of associated neurologic disturbances have been recorded: spasticity or hyperreflexia, bimanual synkinesis or mirror movements (2,4,27), syringomyelia or syringobulbia (44,54), hemiplegia, paraplegia, triplegia, quadriplegia, and others. The neurological findings have been thoroughly reviewed by Mosberg (44). A case with neuroschisis of the cervical spinal cord has been noted (45).

Other findings. Congenital heart defects, usually ventricular septal defect, are occasionally reported (46,60). Situs inversus has been noted (12a) as well as Kallman syndrome (65).

Differential diagnosis. The flaring trapezius muscles give the patient an appearance that may simulate that in *Turner syndrome* or *Noonan syndrome*. The position of the head on the thorax may resemble that seen in tuberculosis of the cervical spine or in *Morquio syndrome*. Spondylothoracic dysplasia is genetically heterogeneous, consisting of dominant and recessive forms. The entire vertebral column is involved in fusions, hemivertebrae, scoliosis, etc. (10,48,61). In the *nevoid basal cell carcinoma syndrome*, cervical or upper thoracic vertebral fusion is observed in about 40%. In the *fetal alcohol syndrome*, cervical fusion occurs in approximately 40%, especially involving C_{2-3}. In *Crouzon syndrome*, approximately 30% have cervical fusion most commonly involving C_{2-3}. With *Apert syndrome* and with *Binder phenotype*, fusion of C_{5-6} (58%) or involvement of three or more vertebrae has been reported. Cervical vertebral anomalies and other defects of the spine may occur with *oculo-auriculo-vertebral spectrum* and in between 5% and 15% of those with cleft lip and palate (51). Mirror movements as an isolated finding may be inherited as an autosomal dominant trait (50). In addition, one must exclude the associations described in the introduction to this chapter such as *Wildervanck syndrome*, MURCS association, etc. For further discussion, see *Wildervanck syndrome*.

Fig. 28–14. *Klippel-Feil-like syndrome*. (A,B) With the mouth closed, indentations extend from the angle of the mouth toward the ears. When the mouth is agape, the child looks normal. One of us (RJG) is aware of three examples: those of H-R Wiedemann, GH Vance, and C Morris. The patients have mild cervical fusion, mild hearing loss, and partial duplication of the maxilla. (Courtesy of GH Vance, Indianapolis, Indiana.)



A B

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Opitz trigonocephaly syndrome (C syndrome)

In 1969, Opitz and co-workers (16) reported on a newly recognized syndrome in two sibs, naming it the "C syndrome of multiple congenital anomalies." The condition has subsequently been known as "Opitz trigonocephaly" syndrome (8,14). It comprises trigonocephaly, unusual facial appearance, wide alveolar ridges, multiple buccal frenula, limb defects, visceral anomalies, redundant skin, mental deficiency, and hypotonia.

To date, at least 40 published and 30 unpublished cases have been seen (2,4–8,10–13,15–21,23,24). It is unlikely that case 13 reported by Pfeiffer (17) also represents the disorder in two affected sibs; they more likely had Smith–Lemli–Opitz syndrome. Normal chromosomes, normal parents with multi-affected offspring, equal sex ratio of affected individuals, and consanguineous matings (2,12,16,21) suggest autosomal recessive inheritance. However, it is possible that we are dealing with heterogeneity.

Approximately half of the patients die within the first year of life. The patient reported by Golabi et al (11) was alive at 3 years.

Clinical features. The clinical findings are summarized in Table 28–2. Trigonocephaly, upslanting palpebral fissures, conspicuous epicanthic folds, strabismus, hypoplastic nasal root, anomalous and posteriorly angulated pinnae, glabellar capillary hemangioma, loose skin with cutis marmorata, and joint contractures and dislocations are observed in over 70% (Figs. 28–15 to 28–17).

Some abnormalities may change with age. Head size, for example, is normal at birth, but there is a tendency to develop microcephaly postnatally. In addition to the metopic suture, other sutures may be involved. Flatz et al (8) observed craniosynostosis involving the coronal, sagittal, and lambdoid sutures.

Wide alveolar ridges and deep midline palatal furrow are also common characteristics. Cleft palate was reported in one case (17). The ears are soft. Extracranial findings, seen in about 50%, include genital abnormalities, various congenital heart anomalies (2,8,10), and hemangiomas. Omphalocele has been noted (13).

Neurologic findings include hypotonia (30%), poor sucking reflex, and severe mental retardation (95%). Seizures (2), agenesis of corpus callosum (6,10,21,25), Dandy–Walker malformation (25), occipital meningocele (25), and medulloblastoma (15) have been observed in some cases. Normal (or nearly normal) intelligence has been noted by a few authors (13,24).

Low frequency findings include hypoplasia of middle and distal phalanges, renal cortical cysts, omphalocele (13), anal stenosis, microcornea (13), clitoral enlargement (2), and pectus (2,8,16).

Differential diagnosis and laboratory aids. Patients with Opitz trigonocephaly syndrome should be studied carefully for possible cytogenetic abnormalities. In two instances, patients originally diagnosed as having C syndrome were found to have abnormalities involving chromosome 3. One patient reported by Preus et al [18(case 2)] was later

Table 28–2. Opitz trigonocephaly syndrome (C syndrome)

Findings	Frequency
Performance	
Hypotonia	12/19
Mental deficiency	18/19
Seizures	5/19
Cranial	
Trigonocephaly	23/23
Postnatally developing microcephaly	13/21
Premature closure of other sutures	7/19
Cowlick	11/22
Facial	
Upslanting palpebral fissures	22/23
Epicanthic folds	20/22
Strabismus	16/22
Broad depressed nasal bridge	15/22
Long philtrum/small nose	21/23
Wide mouth	12/23
Wide alveolar ridges	10/18
Deep midline palatal furrow	16/21
Attached frenula	6/19
Micrognathia	15/22
Anomalous, posteriorly angulated ears	18/21
Neck	
Short neck	15/20
Limbs	
Polydactyly, postaxial	3/21
Bridged palmar creases	10/22
Ulnar deviation of fingers	4/21
Short limbs	5/22
Hip dysplasia	6/21
Dislocated knee	4/21
Equinovarus or valgus deformity	8/21
Contractures	7/21
Skin	
Redundant skin	14/20
Hemangiomas	9/17
Deep sacral dimple	5/17
Cardiovascular	
Congenital heart anomaly	11/22
Genital	
Cryptorchidism	7/9

Approximaly one-half of all patients die within the first year of life. Survivors develop microcephaly and mental deficiency. [From MM Cohen Jr (ed), Craniosynostosis, Diagnosis, Evaluation and Management, Raven Press, New York, 1986.]

found to have dup(3)(q23–qter);del(p25–pter) (19), and another studied by Sargent et al (21) had 46,XY,del(3)(pter–q27:). Preus et al (19) and McGaughran et al (13a) suggested that other C syndrome patients from the literature had a phenotype compatible with *dup(3q) syndrome*. The C syndrome patient reported by Golabi et al (11) had 47,XXY karyotype.

Differential diagnosis includes isolated trigonocephaly, other chromosomal syndromes with trigonocephaly such as *del(9p), del(11q)*, and *dup(13q)* (21). Monogenic syndromes with trigonocephaly include *Frydman trigonocephaly syndrome* (9) and *Say-Meyer trigonocephaly syndrome* (22).

Bohring et al (3), Addor et al (1), Oberklaid and Danks (14), Nakane et al (13b), and Brunner et al (3a) reported isolated examples of a syndrome that has considerable overlap with Opitz (C) trigonocephaly syndrome. However, they differed on the basis of intrauterine growth retardation, cleft lip/palate, exophthalmos, retinal involvement, flexion deformities of the upper limbs, dislocation of radial heads, situs abnormalities, nephroblastomatosis, and forehead hirsutism, seen in Bohring syndrome. This may be due to a 3q subtelomeric duplication (A Bohring, personal communication, 2000).

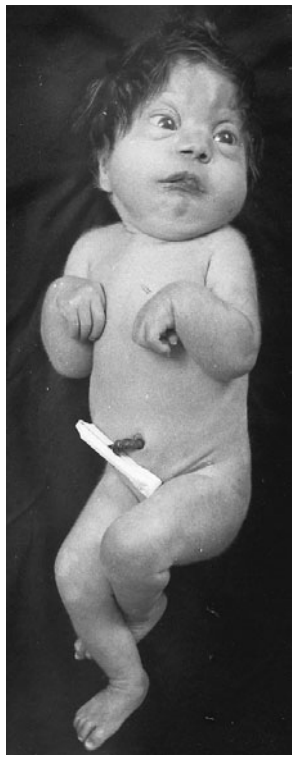

Fig. 28–15. *Opitz trigonocephaly syndrome*. Trigonocephaly, long upper lip, contractures at wrist. (From F Oberklaid and DM Danks, Am J Dis Child 129:1348, 1975.)

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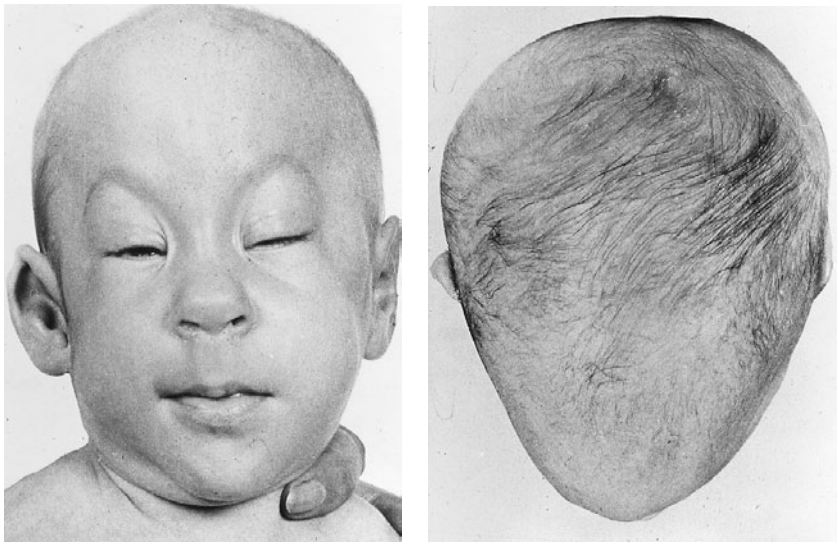

A B

Fig. 28–16. *Opitz trigonocephaly syndrome*. (A) Striking facies with metopic ridging, small head circumference, epicanthal folds, hypoplastic nose with anteverted nares. (B) Trigonocephaly. (From C Sargent et al, J Med Genet 22:39, 1985.)

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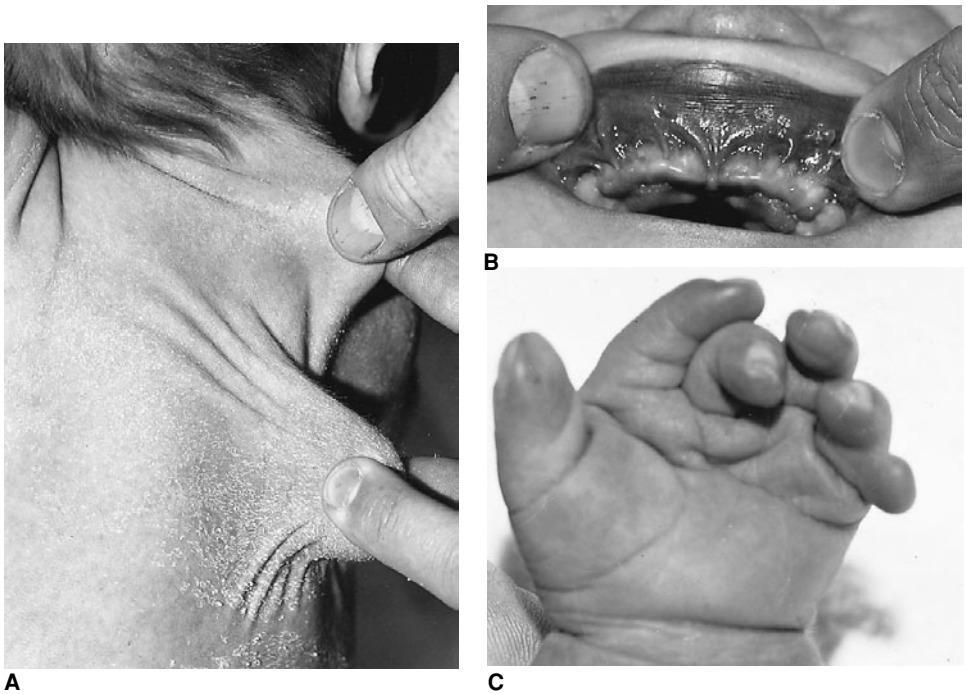
Smith-Lemli-Opitz syndrome

The syndrome, first defined by Smith et al (58), in 1974, is characterized by microcephaly, growth and mental retardation, soft-tissue syndactyly of toes 2–3, and genital abnormalities. Donnai et al (19) and Curry et al (13) drew attention to those at the severe end, that is, those affected with marked failure of masculinization of the external genitals in XY males or even "sex reversal." These infants also exhibited multiple visceral abnormalities and frequent neonatal lethality. For a while, it was thought there were two allelic forms, designated types I and II, but biochemical findings indicated that division was spurious (see below) (44,50). At least 350 patients have been described. Comprehensive review and bibliographies are those of Opitz et al (45–47). Excellent discussions are those of Kelley and Hennekam (29) and Ryan et al (54). The syndrome at various ages is described by Krajewska-Walasek et al (33).

Decreased fetal movement and oligohydramnios are often encountered, as is reduced or absent production of midtrimester estriol in affected fetuses. Breech presentation occurs in 50% and birth asphyxia is extremely common. Birthweight is less than 2500 g in approximately 35%.



A B C

Fig. 28–17. *Opitz trigonocephaly syndrome*. (A) Redundant skin. (B) Multiple frenula. (C) Postaxial polydactyly. [From JM Opitz et al, Birth Defects 5(2):161, 1969.]

Prematurity is noted in 25%. Neonatal feeding difficulties and irritability are seen in 90%. Prolonged high-pitched screaming has been described in 20%. Severely affected infants may die neonatally due to failure to thrive and hepatic dysfunction. Short stature is noted in those that reach childhood (33). Survival to adulthood is rare (49).

The syndrome has autosomal recessive inheritance (13,36,43). More males (70%) have been diagnosed, but we suspect that this is due to the frequent hypospadias. The gene has been mapped to 7q32.1 (2,3,56,63) and 11q12–q13 (64). The former reflects a defect in the Sonic Hedgehog pathway (see below). There is quite variable expression (13,39). Phenotypic expression has varied from 2–3 syndactyly of the toes to holoprosencephaly (12). Estimates of the occurrence of the syndrome in white North Americans have been between 1 per 20,000 and 1 per 40,000 births making it the third most common autosomal recessive disease after cystic fibrosis and phenylketonuria (60). An estimate of 1 per 60,000 has been made in the United Kingdom (54).

Tint et al (60,61), in 1994, found that patients with the syndrome have abnormally low levels of plasma and tissue cholesterol and extremely high levels of 7-dehydrocholesterol reflecting a defect in 3β-hydroxysterol-Δ^7–reductase (31,57,65). However, about 10% have normal cholesterol levels and would have been missed had not levels of 7-dehydrocholesterol been observed (12). A rapid ultraviolet spectrometric method for 7-dehydrocholesterol estimation has been described (23). Animal models have been created (17,35,67). Abnormal cell populations have been found at the rim of the developing forebrain and in the alar plate of the lower midbrain and hindbrain (17). Cholesterol is needed, inter alia, for morphogenetic signaling during embryogenesis (51). There is a presumed loss or defect of *Sonic Hedgehog* protein function in the syndrome (30). Tint et al (62) demonstrated that those with the more clinically severe syndrome had far lower levels of serum cholesterol, that is, the block was more complete. However, Cormier-Daire et al (11) and Cunniff et al (12) did not verify this correlation. Mutational analysis of 84 patients revealed that those with mutations in the transmembrane and c-terminal regions had the mildest phenotype (65,66). Rapid PCR-based assays have been used for the more common mutations (33a).

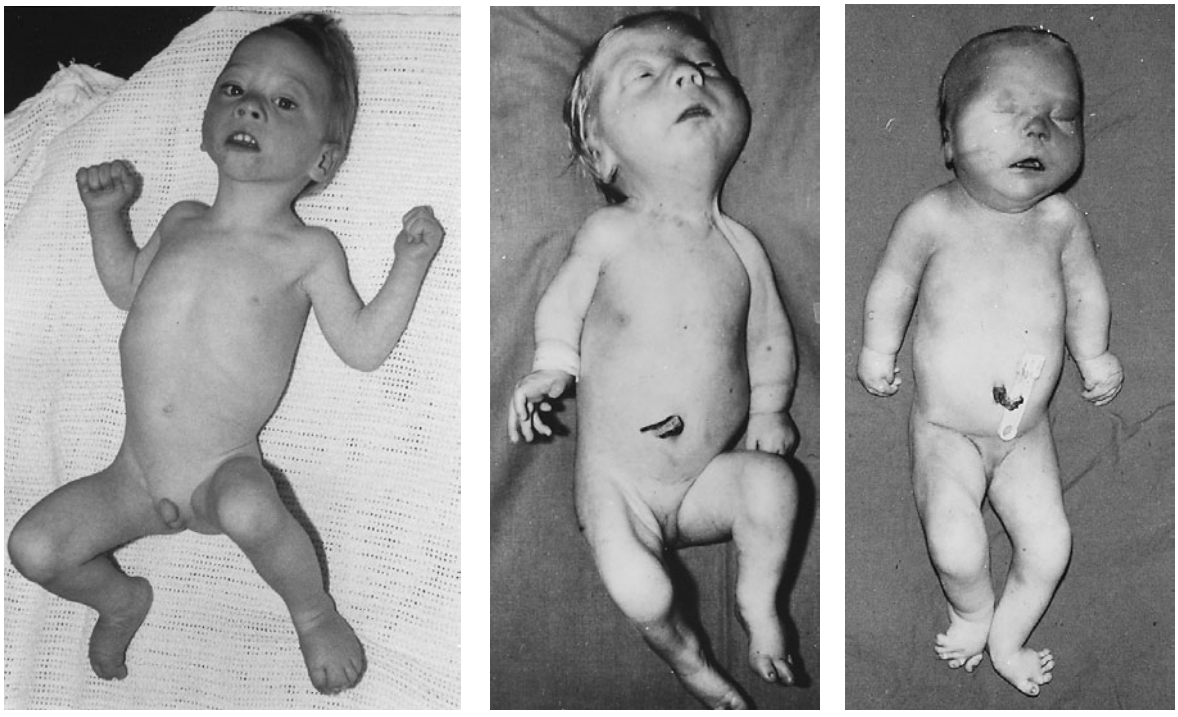
Facies. The face tends to be round with microcephaly (95%), ptosis (occasionally unilateral) (85%), strabismus (40%), epicanthal folds (40%), wide nasal bridge (50%), anteverted nares (75%), low-set and/or retroverted (35%) or outstanding pinnae (60%), micrognathia (80%), and short neck with redundant skin folds (5,43,58) (Figs. 28–18 and 28–19). A nevus flammeus over the glabella may be noted. The facies normalizes with age (15), but the lips become thick and pouting (33). Diagnosis becomes difficult during adolescence (33).

Eyes. Ptosis (60%), convergent strabismus (40%), epicanthus (40%), and hypertelorism (25%) have been documented. Cataracts are noted in 10% in those at the milder end of the spectrum (7) and in 45% of those with more severe expression (13,19,21,36).

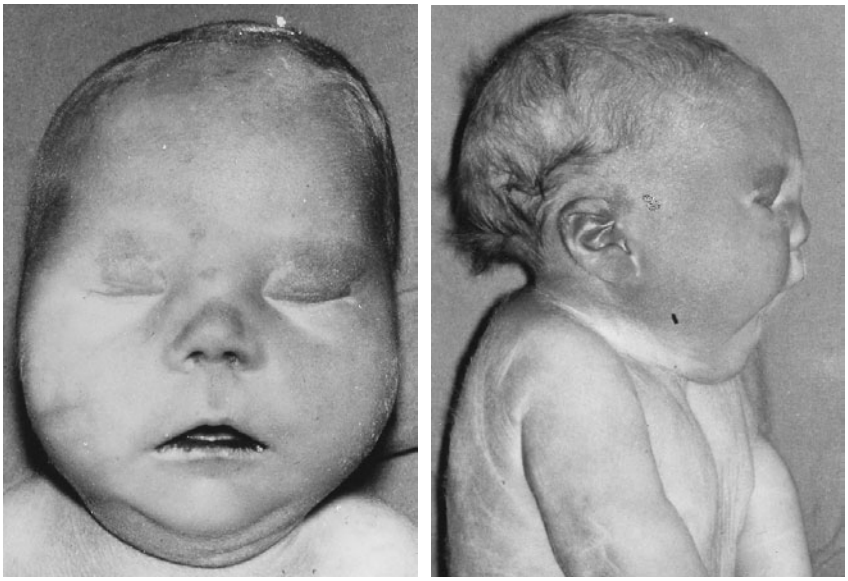
Central nervous system. The most extreme form is holoprosencephaly (12,30). Microcephaly is found in over 90%, with 40% having abnormal skull shape. Patients have a wide range of developmental defects of the brain (ventricular dilatation, seizures, partial agenesis of cerebellar vermis and/or corpus callosum, hypoplasia of frontal lobes), associated with severe retardation (10,43). During the neonatal period, hypotonia is noted in about 50%, while, later in life, hypertonia is documented in 30%. Aggressive behavior and self-injuries are often noted in those that survive (54). There is markedly reduced myelination of both brain and peripheral nervous system. Reflexes are brisk (41). Motor skills seem to improve with age (33). Abnormal sleep patterns have been noted in 70% (54). An excellent summary of the behavior phenotype is that of Tierney et al (59a).

Limbs. Postaxial polydactyly of hands or feet ranges from 25% in milder examples (7) to 75% in severely affected (13,36). A short first metacarpal with secondary short thumb has been seen in nearly all (54). A peculiar short first metatarsal and valgus foot positioning are frequent. About 50% of the infants have dislocated hips. Transverse palmar creases are frequent (36). Soft-tissue syndactyly of the second and

Fig. 28–18. *Smith-Lemli-Opitz syndrome*. (A) Note microcephaly, small upturned nose, epicanthal folds, abnormal genitalia, soft tissue syndactyly of second or third toes. (B,C) Unusual facies, superficial angiomas, limb shortening, inguinal skin creases, postaxial polydactyly. Note apparent female genitalia in 46,XY patients. (A,C courtesy of D Donnai, Manchester, England. B from CJR Curry et al, Am J Med Genet 28:45, 1987.)



A B C



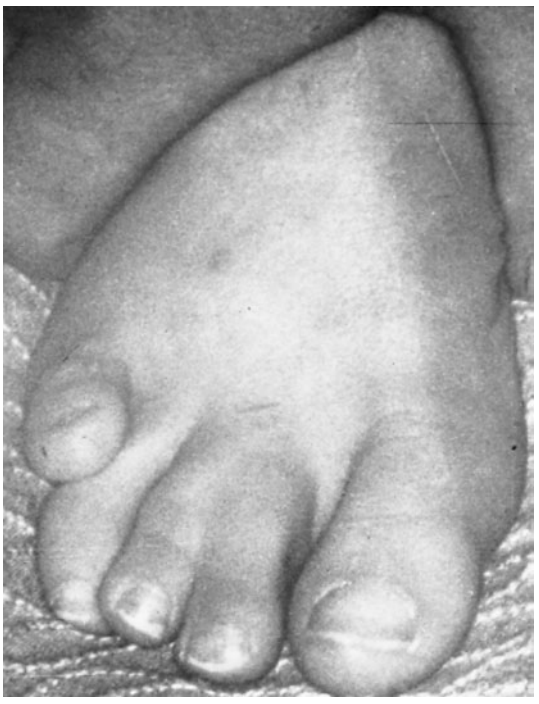
A B

Fig. 28–19. *Smith-Lemli-Opitz syndrome*. (A,B) Facial angiomas, short nose, micrognathia, short neck. (Courtesy of D Donnai, Manchester, England.)

third toes has been noted in about 80% (43) (Fig. 28–20). The thumbs are often short (54). The proximal limbs are short without evidence of primary bone dysplasia (Fig. 28–21). Positional foot abnormalities are common: metatarsus adductus, pes equinovarus, and metatarsus varus. Other findings have included clinodactyly of fingers, hallucal hammertoe, proximally placed thumbs, and long tapered fingers. Rare patients have ectrodactyly and/or preaxial polydactyly (18). Dermatoglyphics may be abnormal and diagnostic with high absolute and relative total ridge count, interdigital and hypothenar patterns with increased *atd* angle, distal triradii, and occasional zygodactyly.

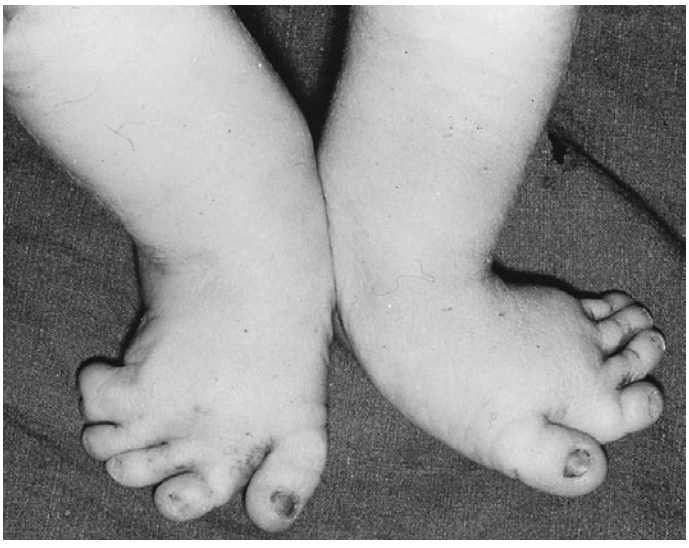
Genitalia. In males, genital changes, found in 70%, range from mild abnormality to genital ambiguity or "sex reversal" or male pseudohermaphroditism (perineoscrotal hypospadias with perineal urethral opening); most common are bilateral cryptorchidism (50%) and hypospadias (50%) (7). Microphallus and/or chordee have been documented in 20% (Fig. 28–22). No male with more severe expression has had normal genitalia; the majority have been assigned female gender and, among the rest, sex assignment has been unclear. Features noted in XY males have included hypoplastic labia majora, absent labia, scrotalization of the labia, prominent clitoris, third degree hypospadias, micropenis, and bifid scrotum (see Fig. 28–18B,C). Autopsies in severely ambiguous XY infants have revealed intraabdominal or inguinal testes, and, in most, Müllerian duct remnants. A few XY infants have had hypoplastic vagina and uterus (13,36). Occasionally, males have normal female genitalia (22,48). Females have hypoplastic labia.

Fig. 28–20. *Smith-Lemli-Opitz syndrome*. Soft-tissue syndactyly of second and third toes. Note short fifth toes with tibial clinodactyly. (From CG Judge et al, Med J Aust 2:145, 1971.)



Kidney. Upper urinary tract changes, found in 55%, have been reported in 45% of those at the mild end: ureteropelvic obstruction, hypoplasia, renal duplication, hydrocephalus, cystic and dysplastic alterations. Renal cysts and hypoplastic kidney are frequent in severe examples (7,19,22,28,32,38).

Fig. 28–21. *Smith-Lemli-Opitz syndrome*. Valgus deformity of feet, short halluces, polysyndactyly. (Courtesy of D Donnai, Manchester, England.)



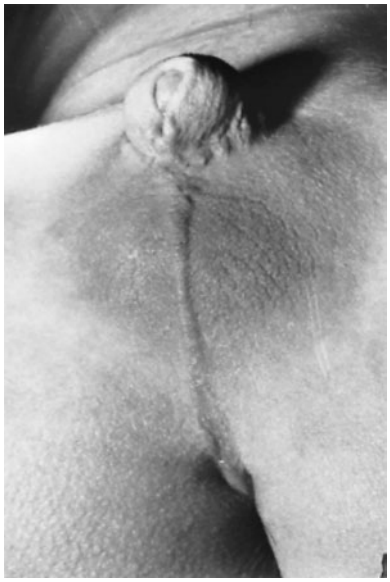


Fig. 28–22. *Smith-Lemli-Opitz syndrome*. Hypospadias and hypoplastic scrotum. (From CG Judge et al, Med J Aust 2:145, 1971.)

Heart. Various congenital heart anomalies (PDA, VSD, tetralogy of Fallot, aberrant right subclavian artery, ASD) have been reported in 20% to 100%, depending on severity of expression (10,22,43,48,52,55). The most comprehensive study is that of Lin et al (37). They found that 45% had cardiovascular malformations, the most frequent being secundum type ASD, PDA, AV canal, and anomalous pulmonary venous return. We have seen coarctation of the aorta in an 11-year-old male.

Oral manifestations. Cleft palate has been found in about 50% (7,13,22,36,48) and broad maxillary alveolar ridges in over 60%. However, the maxilla is relatively small and the anterior spine may be absent. The tongue tends to be small. There may be redundant sublingual tissue (Fig. 28–23). Lingual cysts have been found in a few cases (36).

Miscellaneous. At autopsy, unusual findings have included pancreatic islet cell "giant cell" hyperplasia, unilobate lungs, pyloric stenosis, and Hirschsprung disease (8,22,36,48,69). Photosensitivity has been noted in about 65% (4,54).

Differential diagnosis. Differential diagnosis of Smith-Lemli-Opitz syndrome can be quite extensive. A chromosome anomaly should clearly be ruled out. In severe examples of SLO syndrome, major diagnostic confusion can exist with *Meckel syndrome*. Some patients initially diagnosed and published as examples of Meckel syndrome likely represent such cases. Sibs published by Casamassima et al (9) have features of both Smith-Lemli-Opitz syndrome and Meckel syndrome. They had cerebellar findings similar to those of Joubert syndrome but this disorder seems to stand as a distinct condition (24,59). There are some similarities with *Pallister-Hall syndrome*. However, the presence of a hypothalamic hamartoblastoma appears to be unique in the latter syndrome. *Hydrolethalus syndrome* may present occasional diagnostic difficulty in the hydrocephalic patients. In *Meckel syndrome*, there is a characteristic cystic kidney dysplasia. SLO syndrome may possibly be the same as *genito-palato-cardiac* or *Gardner-Silengo-Wachtel syndrome*. In SLO the testes are present; in *genito-palato-cardiac syndrome*, there is gonadal dysgenesis. We are uncertain how to classify the disorder reported by Rutledge et al (53), but that also may be SLO. Joint contractures, cerebellar hypoplasia, and tongue cysts seem to distinguish it from SLO syndrome. An apparently unique condition resembling *Raine syndrome* and, to some degree, that of SLO is due to desmosterolosis (20).

Laboratory aids. Prenatal diagnosis in SLO has been accomplished sonographically (27) and by finding accumulation of 7-dehydrocholesterol in amniotic fluid (1,14,40) and in chorionic villus specimens (26,34). Increased nuchal translucency was found on ultrasound (25).

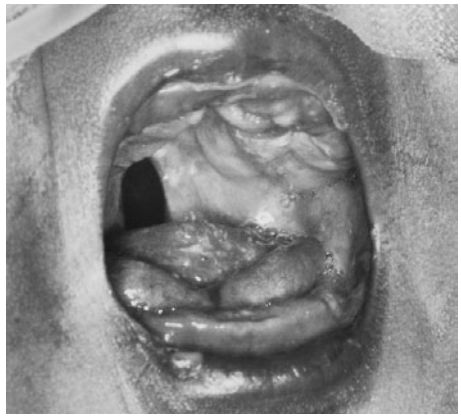


Fig. 28–23. *Smith-Lemli-Opitz syndrome*. Palatal cleft, small tongue, redundant sublingual tissue. (From CJR Curry et al, Am J Med Genet 28:45, 1987.)

Cholesterol values in Smith-Lemli-Opitz syndrome are often less than 1.00 mmol/l (normal 4.83 ± 0.8), while 7-dehydrocholesterol, normally less than 0.002 mmol/l, may reach 0.800 in those with Smith-Lemli-Opitz syndrome (16). Cholesterol determination/fractionation can aid in diagnosing atypical cases (56), and old specimens (42). Newborn screening cords can be used for definitive diagnosis. Filter paper blood specimens using secondary ion mass spectrometry has been advocated (68).

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Chapter 29
Other Miscellaneous Syndromes

Acro-renal-mandibular syndrome

Halal et al (3) reported two French-Canadian female sibs whose parents were consanguineous. Both exhibited severe split hand and foot malformations, renal (polycystic kidneys, renal agenesis, and absent ureters) and genital (septate uterus, unicornuate uterus, and single tube) abnormalities, and very severe micrognathia (Fig. 29–1). Although split hand and foot occurs in the classic acro-renal syndrome, no patient has had micrognathia as severe as that observed in Halal's patients. Moreover, all known instances of acro-renal syndrome have been isolated males with no history of parental consanguinity. They have had unilateral renal agenesis, crossed renal ectopy, hypospadias, and/or cryptorchidism. The female reported by Fitch and Lachance (2) did not have micrognathia. The three sibs described by Evans et al (1) were more severely affected. Hennekam et al (4) also noted sibs with a similar phenotype.

Inheritance is autosomal recessive.

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Aberrant oral frenula, cataracts, and growth retardation

Wellesley et al (1), in 1991, described a mother and her son and daughter with posterior polar cataracts, numerous aberrant frenula, growth retardation, and unusual facies.

Growth retardation was below the third centile. Facial changes included epicanthic folds, short upslanting palpebral fissures, small nose with upturned tip, and posteriorly angulated ears with a creased lobule. The scalp hair was coarse, blond, and curly. The son exhibited unilateral ptosis, the daughter, a cavernous hemangioma at the corner of her mouth.

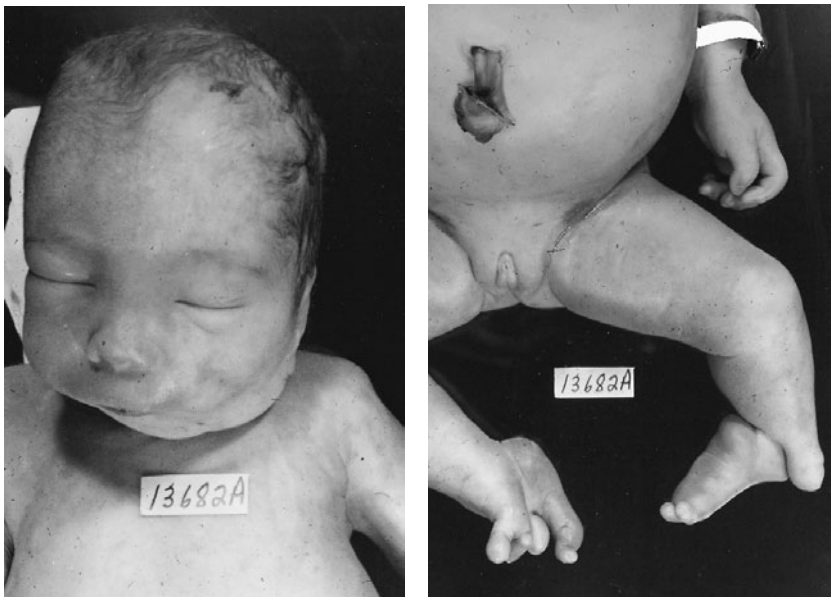
Inheritance is presumably autosomal dominant.

Reference (Aberrant oral frenula, cataracts, and growth retardation)

1. Wellesley D et al: Cataracts, aberrant oral frenula, and growth retardation: A new autosomal dominant syndrome. Am J Med Genet 40:341–342, 1991.

Agenesis of salivary and lacrimal glands

Major salivary glands and lacrimal glands have been reported to be symmetrically aplastic or severely hypoplastic. Early examples are those of Bradbury (3) in 1879, Ramsay (18) in 1924, and Blackmar (2) and Raison (17) in 1925. At least 30 case reports are available. Duct orifices are often missing, but ducts may be present (1,16). The lacrimal points may be missing or hypoplastic (1,2,5,9,13,14,23). Early cases of isolated absence



A B

Fig. 29–1. *Acro-renal-mandibular syndrome*. (A) Note severe mandibular hypoplasia and mild Potter facies. (B) Bilateral split foot anomaly. Cleft involves lower third of leg. Note hypoplastic toes. Sib was similarly affected. (From F Halal et al, Am J Med Genet 5:277, 1980.)

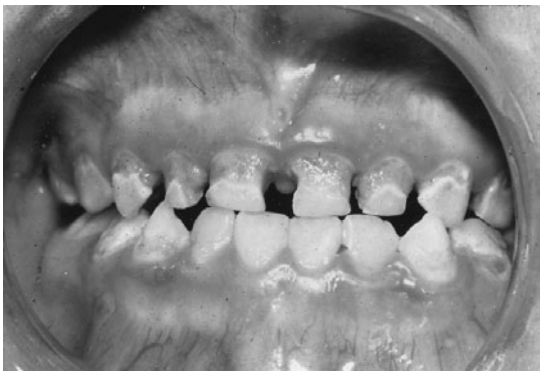


Fig. 29–2. *Agenesis of salivary and lacrimal glands*. Severe lack of saliva results in extensive dental caries.

of glands have been reviewed (20,23,25). The resultant lack of secretions causes severe dryness of the oral and conjunctival mucosae. The lips are often cracked. The teeth decay and fracture at the neck (Fig. 29–2). Mastication is extremely difficult (7).

There are several reports of the disorder affecting two or more generations (4,5,6a,18,20,26). Others have been isolated examples (8,11,15,19,21–23). There are also numerous reports of dominantly inherited isolated deficiency of lacrimal glands or atresia of the lacrimal puncta (12). The literature has been reviewed by Caccamise and Townes (4) and McDonald et al (10). Computerized tomography, MRI, and (99m) Tc-pertechnetate scintigraphy have been used in diagnosis (14,22,26,27).

Aplasia of salivary glands may be an isolated finding or may be seen in *lacrimo-auriculo-dento-digital (LADD) syndrome*, in *oculo-auriculo-vertebral spectrum* (24), or in the rare example of *hypohidrotic ectodermal dysplasia* (6). It has been noted in association with cleft lip and palate (9a).

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Achalasia, alacrima, and adrenal deficiency (triple A syndrome, Allgrove syndrome)

To be separated from *familial dysautonomia* is the syndrome of achalasia, alacrima, and adrenal deficiency because the first two symptoms are seen in that disorder. The syndrome was first reported by Allgrove et al (1) in 1978. At least 50 examples have been described (10).

Growth and psychomotor development are mildly to moderately retarded (2,5,9).

Inheritance is clearly autosomal recessive (5,6,9,15). The gene, *ALADIN*, maps to 12q13 (19).

Achalasia. Achalasia of the cardia, that is, functional obstruction due to increased lower esophageal sphincter pressure, absent esophageal peristalsis, and failure of the lower sphincter to relax in swallowing, is rare in children (18). In this syndrome, it most often presents at 3–4 years but may not be evident until the second decade (3,6,10,16).

Lacrimal glands. There is defective tear formation from birth. It is the most consistent early finding (1,6).

Adrenal insufficiency. Allgrove et al (1) and others (7,8) reported acquired glucocorticoid deficiency, which may lead in some cases to hypoglycemic shock or even death. In some families, however, adrenal function is normal (7,9,12–14). Hyperpigmentation of the skin is common.

Neurologic findings. In addition to autonomic dysfunction and moderate psychomotor retardation, some exhibit dysdiadochokinesis (9), epilepsy (5,9), cerebellar ataxia (2,12), stiff gait (9), speech disorder (7), optic atrophy (2), microcephaly (2,7), peripheral neuropathy (5,16), clumsiness (5), anisocoria (5), brisk deep tendon reflexes (5), and velopharyngeal insufficiency (4,13).

Autonomic dysfunction is variable, presenting in adolescence with postural hypotension and heart rate variability during deep breathing. Alacrima, achalasia, and, possibly, adrenal hypofunction are the result of parasympathetic failure.

Laboratory findings. Histamine skin testing is negative. Cardiac autonomic tests are abnormal. EMG shows slowed motor conduction velocities and reduced amplitude of sensory action potentials. Some patients have normal adrenal function (9), most have reduced glucocorticoids and, less often, mineralocorticoids (1,2,4–7,12–14,16,17). Microscopic examination of the adrenal glands shows absence of the zona fascicula with normal zona glomerulosa of the adrenal glands.

Diagnosis. In *familial dysautonomia*, there are deficient fungiform and circumvallate papillae, and hypomotility, atony, and dilatation of the esophagus. Achalasia usually occurs as an isolated finding and may be found in families. Achalasia and gastric hyposecretion (10,11) may occur with Sjögren syndrome.

References [Achalasia, alacrima, and adrenal deficiency (triple A syndrome, Allgrove syndrome)]

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Noonan-like/multiple giant cell lesion syndrome (including cherubism and polyarticular pigmented villonodular synovitis)

Falace (12) described the combination of polyarticular pigmented villonodular synovitis, "jaw cysts," cardiac defects, mild developmental delay, and distinctive facies. In their review of the literature, Cohen and Gorlin (7) found several additional cases (4,8,16,18,21,25,26,28). The combination of Noonan syndrome and cherubism (or multiple giant cell lesions) has been reported by Addante and Breen (1), Chuong et al (6), Bianchi (5), Hoyer and Neukam (14), Dunlap et al (11), Salinas et al (20), Levine et al (17), Bertola et al (3a), and others (see *Noonan syndrome*).

Facial features include mild hypertelorism, oculomotor defect (26,28), and low-set ears (26,28) (Fig. 29–3). In one family, multiple lentigines were found (28). Although jaw lesions were stated to be fibrous dysplasia (28) and giant cell granuloma (18,23a), we believe that they really represented cherubism. In addition, cavernous hemangioma of the lip (16) and orbit (J Hoza, personal communication, 1989) has been documented.

As in *Noonan syndrome* and *LEOPARD syndrome*, pulmonic stenosis (4,16,18,26), mitral valve prolapse (28), mild growth retardation, peripheral lymphedema, and developmental delay have been evident (4,18,25,26). It should be noted that Noonan syndrome maps to chromosome 12q (15). A few patients exhibited pectus (26,28).

In contrast to monoarticular villonodular synovitis, which occurs in adults in their third to fifth decades, in this syndrome the villonodular synovitis is polyarticular, and patients are less than 10 years old. Most often the knees and ankles are involved, less often the wrists or elbows.

Inheritance may be autosomal dominant (28), but the vast majority are isolated examples.

Cherubism usually is a lone finding with autosomal dominant inheritance (13,29). It maps to 4p16.3 (19,22). Extraoral bone involvement has been described by many authors cited by Cohen and Gorlin (7). Bianchi et al (5) and Weldon and Cozzi (27) have noted pulmonary stenosis in patients with cherubism or multiple giant cell lesions of the jaws. Pulmonary stenosis may also be found with *Noonan syndrome* and with *neurofibromatosis* in binary combination and with *gingival fibromatosis, hypertrichosis, mental and somatic retardation, and epilepsy (Ramon syndrome)*. Cherubism has been described with short stature and optic atrophy (2). De Pina-Neto et al (9,10) suggested that some members of the family they investigated had juvenile rheumatoid arthritis. Could this have been polyarticular pigmented villonodular synovitis? RJ Gorlin believes that these associations are examples of contiguous gene syndromes. Multiple central giant cell granulomas have been noted in hyperparathyroidism (24) and in *neurofibromatosis* (3). A possibly aleatory combination of craniosynostosis, cherubism, and drum-stick terminal phalanges was reported Stiller et al (22a).

References [Noonan-like/multiple giant cell lesion syndrome (including cherubism and polyarticular pigmented villonodular synovitis)]

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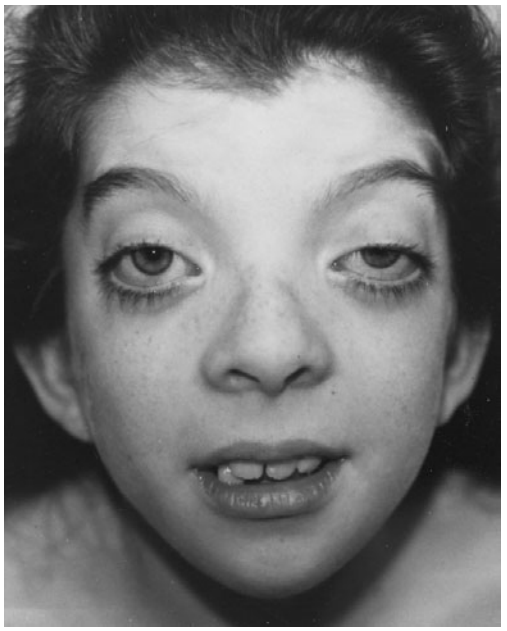

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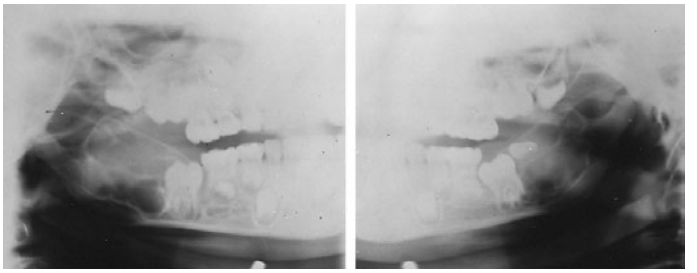

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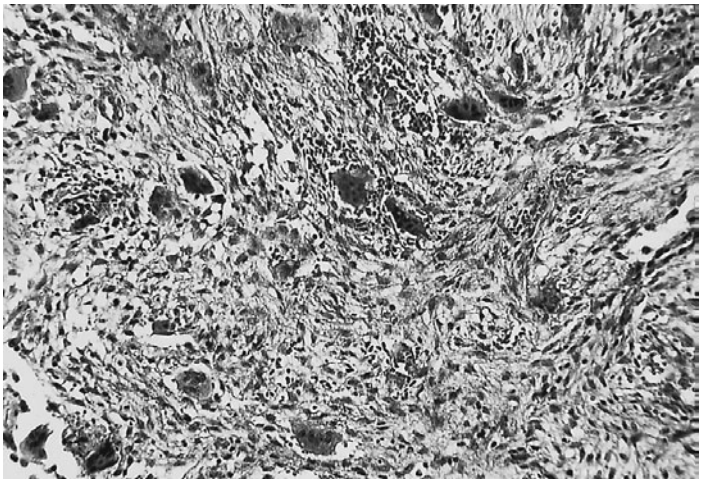

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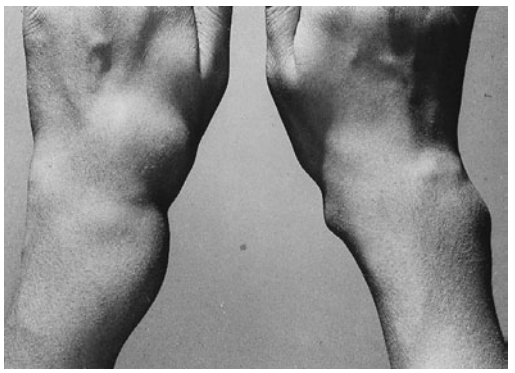

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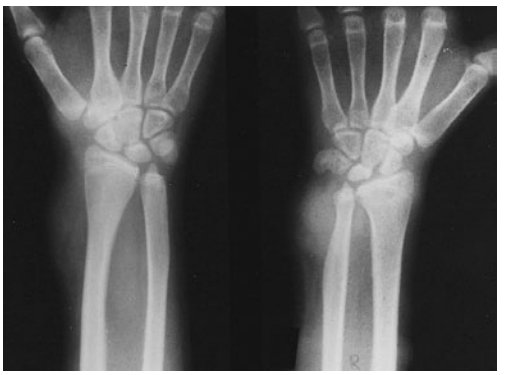

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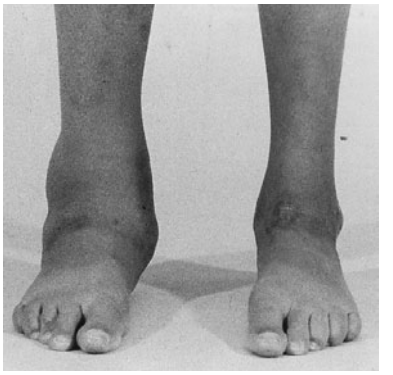

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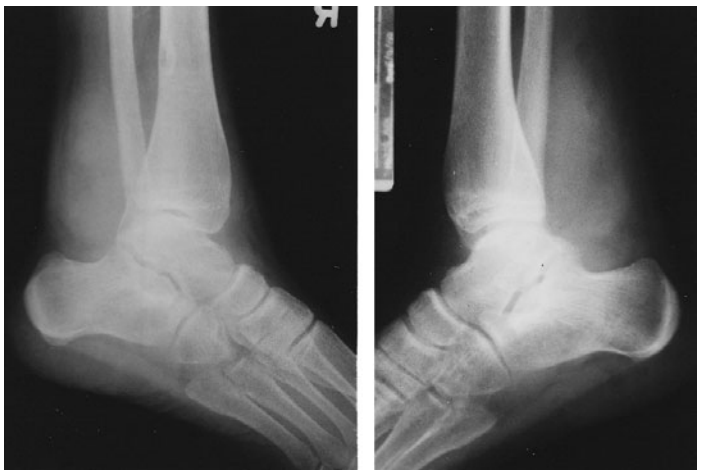

G

Fig. 29–3. *Noonan-like syndrome, cherubism, and polyarticular pigmented villonodular synovitis*. (A) Note widow's peak, ptosis, hypertelorism, exorbitism, and sclera exposed below the iris. (B) Retromolar radiolucent multilocular lesions in all four quadrants is typical of cherubism. (C) Loose connective tissue with multinucleated giant cells. (D,E) Involvement of the wrists. (F,G) Similar involvement of the ankles. (A courtesy of P Falace, Lexington, Kentucky. D–G from ML Wagner and JS Percy, AJR Am J Roentgenol 136:821, 1981.

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Noonan-like phenotype, myopathy and malignant hyperthermia (King syndrome)

King et al (6), in 1972, reviewed children who exhibited predisposition to malignant hyperthermia and noted a distinct phenotype. There have been approximately 16 cases reported to date. Nearly all were males. Inheritance is debatable. All have been isolated examples (1–7,9–14). In a few cases, first-degree relatives have been stated to have subtle features (2). Chitayat et al (1) suspect that King syndrome represents a heterogeneous phenotype. At least one gene for malignant hyperthermia maps to 19q13 (9a). We believe that the patient of Kousseff and Nichols (8) has still a different condition, because of the presence of multiple severe contractures, skin dimpling, axillary webbing, and hypoplastic nipples.

Normal intelligence has usually been found. Short stature has been associated with spinal anomalies in 90%. Delayed motor development is a common finding.

Craniofacial changes include ptosis or blepharophimosis (75%), downslanting palpebral fissures (75%), malar hypoplasia (70%), cleft palate (5,11), micrognathia (100%), and webbed neck (2). Musculoskeletal abnormalities include pectus carinatum or excavatum (90%), scoliosis (100%), lumbar lordosis (10%), and scapular winging (2,4–6,9,11). The muscles are often weak. The myopathy is exhibited by elevated creatinine kinase, abnormal electromyograms, abnormal muscle biopsy, and malignant hyperthermia.

Malignant hyperthermia may be associated with several myopathies, principally central core disease. It may be dominantly inherited and at least six susceptibility loci have been identified (2). To be excluded is *Noonan syndrome*. Also see *hyperthermic embryopathy*. A recessive disorder, Native American (Lumbee), myopathy consists of short stature, ptosis, cleft palate, scoliosis, congenital joint contractures, camptodactyly, and talipes equinovarus. Inheritance is autosomal recessive. Death has occurred during the first year of life in 35% from severe pulmonary hypoplasia and apnea.

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Bifid mandibular condyle, polythelia, and postaxial hexadactyly

Zohar and Laurian (1) described an unusual group of findings in a female patient: bifid mandibular condylar head, polythelia, bilateral postminimum digits, and clinodactyly.

It is possible that these findings were of chance occurrence.

Reference (Bifid mandibular condyle, polythelia, and postaxial hexadactyly)

1. Zohar Y, Laurian N: Bifid condyle of the mandible with associated polythelia and manual anomalies. J Laryngol Otol 101:1315–1319, 1987.

Facio-audio-symphalangism

Maroteaux et al (11), in 1972, and Herrmann (5), in 1974, reported kindreds with multiple synostoses and conductive hearing loss. The face is characteristic and symphalangism of the fingers and toes occurs together with other skeletal anomalies. Several papers on the subject have appeared (1,2,6,7,14,16,17,19). Less certain are other cases in which facial features (8,12,13) or hearing loss (10,15) were not mentioned. The case of Tsuruta et al (19) is unusual. The question of whether multiple synostoses without facial and audiological abnormalities should be treated differently is discussed by Sugiura and Inagaki (18). Besides facio-audio-symphalangism, the term *WL syndrome* has been used (5,6).

Autosomal dominant inheritance is evident. The gene maps to 17p22 (9). It is related to the *Noggin (NOG)* gene (3).

Features of the syndrome are summarized in Table 29–1. The nose is long and thin and has minimal alar flare, that is, it is hemicylindrical (Fig. 29–4). Progressive conductive hearing loss is characteristic (5–7,11). Ankylosis of the stapedial footplate and malformation of the stapes and the incus have been recorded (5,11,16). Even though the patient is of normal height, proportions appear abnormal. The gait is waddling; the patient often walks on the outer border of the feet without resting on the heels.

The upper arms are short. There is cubitus valgus with dislocation of the head of the radius and limitation of pronation, supination, and extension at the elbow.

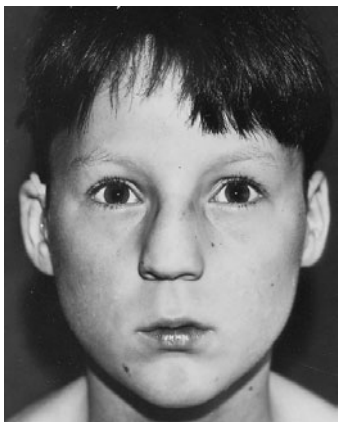
The fingers are short. There is absence of creases over all proximal interphalangeal joints of fingers and over the fifth, or less often the fourth, distal interphalangeal finger joints (Fig. 29–5). One or more fingernails and/or toenails may be hypoplastic. One or more terminal portions of

Table 29–1. *Facio-audio-symphalangism:* clinical findings

Findings	Frequency F=>50% I=<50%
Craniofacial	
Conductive hearing loss	F
Broad, hemicylindrical nose	F
Narrow upper lip	F
Internal strabismus	I
Spinal anomalies	I
Upper extremities	
Short arms	I
Dislocated radial head	F
Cubitus valgus	F
Brachydactyly	F
Clinodactyly	I
Symphalangism 2,3,4	F
Cutaneous syndactyly 2,3,4	F
Hypoplastic/aplastic middle phalanx	F
Hypoplastic/aplastic distal phalanx	F
Correspondingly aplastic/hypoplastic nail	F
Absence of creases over PIP	F
Absence of creases over DIP	I
Lower extremities	
Short legs	I
Pes planovalgus	I
Short foot	F
Short hallux	F
Increased gap between hallux and second toe	I
Cutaneous syndactyly 2,3	F
Absent distal phalanges	F
Correspondingly absent/hypoplastic toenail	F
Proximal symphalangism 2,3,4	F
Musculoskeletal	
Good muscle development	I
Prominent chondrocostal junction	F
Pectus excavatum	F
Short sternum	I
Anteriorly positioned shoulders	I

(Based on review of 14 cases by SA Hurvitz et al, Clin Genet 28:61, 1985.)

Fig. 29–4. *Facio-audio-symphalangism syndrome*. (A,B) Facies characterized by thin upper lip, broad cylindrical nose. [A from J Herrmann, Birth Defects 10(5):23, 1974. B from SA Hurvitz et al, Clin Genet 28:61, 1985.]



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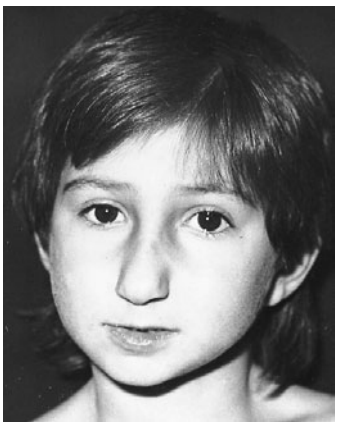

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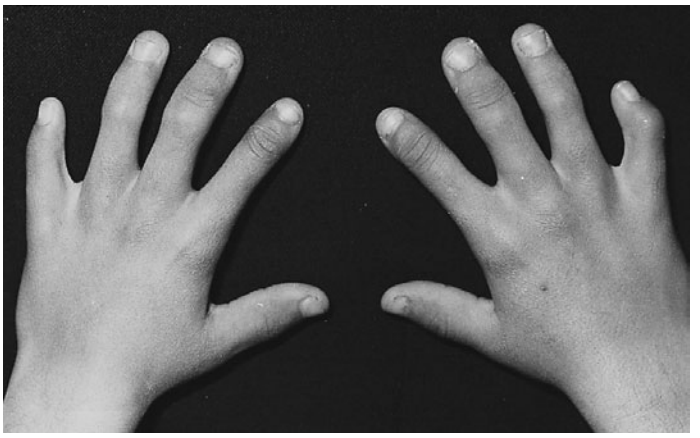

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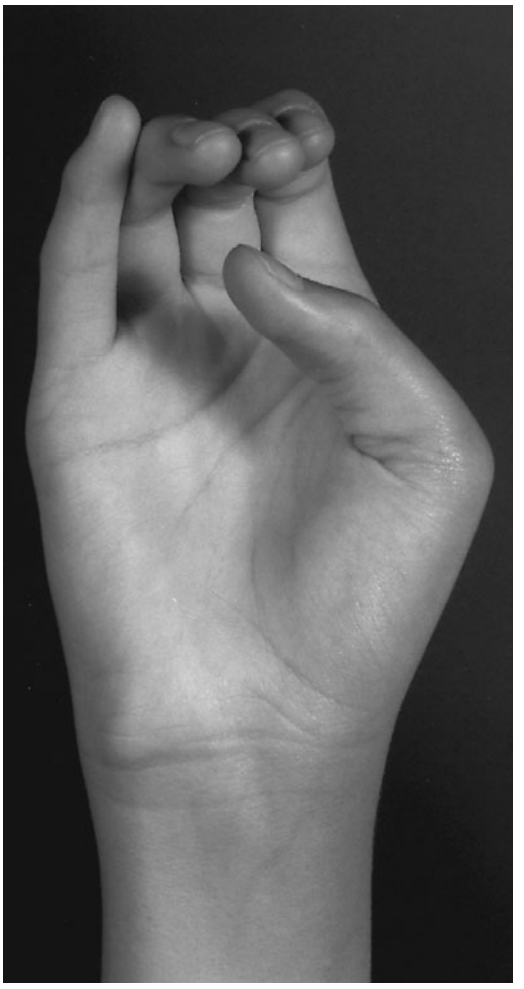


B

Fig. 29–5. *Facio-audio-symphalangism syndrome*. (A) Clinodactyly, mild syndactyly, brachydactyly, and absence of digital creases suggesting symphalangism. (B) Note finger contractures, palmar thumb. (A from SA Hurvitz et al, Clin Genet 28:61, 1985. B courtesy of K North, Boston, Massachusetts.)

fingers (rarely the third) and/or toes may be missing. The fifth finger may exhibit clinodactyly. The hallux is often short; there may be an increase in the space between the hallux and second toe.

The hands and feet are most severely affected. Starting in childhood, there is progressive coalition of the lesser multangular-capitate-hamate and triquetral bones, short and broad first metacarpal, progressive

proximal symphalangism of the second, third, fourth, and fifth digits, and progressive distal symphalangism of the fifth and often the fourth digits. One or more distal phalanges may be hypoplastic and one or more metacarpals and proximal phalanges may be overtubulated (Fig. 29–6).

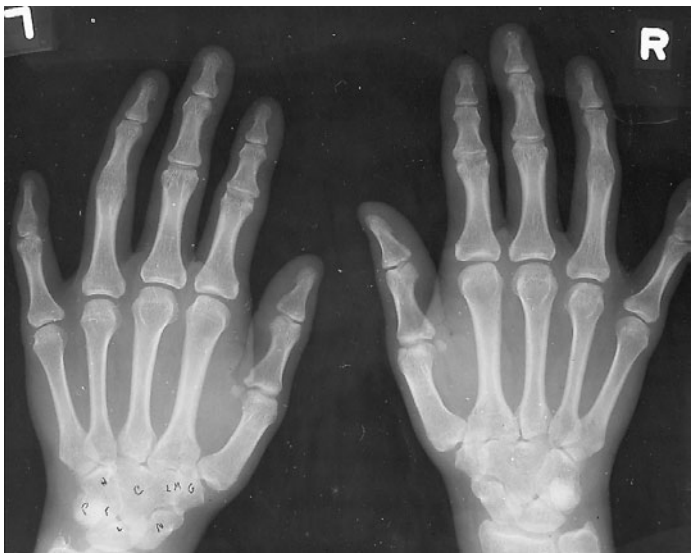
The forefoot is short and shows coalition of the talus and navicular bone, fusion between second and third cuneiforms, and coalition between both the first two cuneiforms and the tarsometatarsal joints. There are progressive hallux valgus and proximal symphalangism of the second, third, and fourth digits, and hypoplastic or absent middle and distal phalanges of the fourth and/or fifth digits. The first metatarsal is often short and, like the other metatarsals, may be overtubulated.

The metaphyses of long bones are broad and irregular. The diaphyses may be somewhat bowed. Radiohumeral synostosis, malformed distal humerus and proximal radius, and subluxation of the radial head are common findings.

Spinal anomalies include hypoplastic spinal processes of cervical vertebrae, fused arches, spinal canal stenosis, and osteolytic defects in the anterior superior portions of the lower thoracic and upper lumbar vertebrae (2a). The patient of Pfeiffer et al (16) had block fusion of C_2–C_3, C_5–C_7, and T_4–T_{10}.

Single palmar creases are a common finding. The absence of some digital triradii and the presence of two palmar axial triradii have been observed (11). Strabismus has been noted (5).

Symphalangism and conductive hearing loss can be excluded since facial appearance is not altered. Furthermore, the skeletal findings are limited to the hands and feet and aplasia/hypoplasia of the terminal phalanges and nails does not occur (4).



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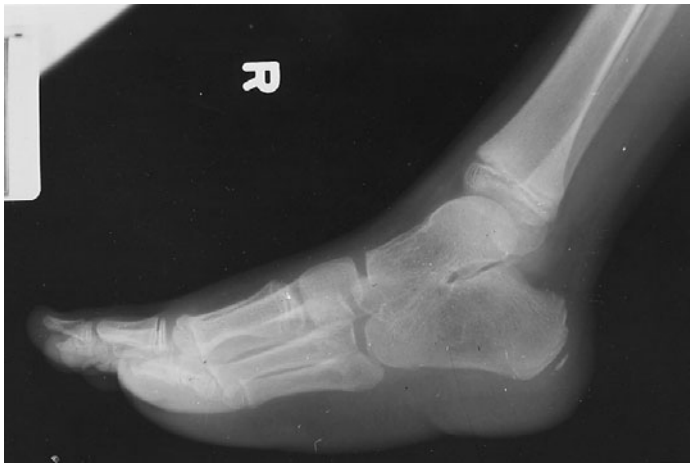

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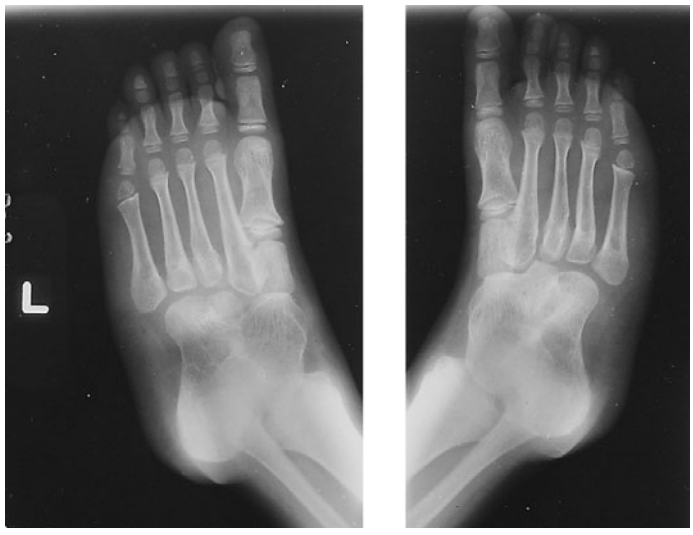

C

Fig. 29–6. *Facio-audio-symphalangism syndrome*. Radiographs showing (A) symphalangism and extensive fusion of carpal bones, bilateral brachydactyly of the middle phalanx of the fifth digit with clinodactyly, and (B,C) fusion of calcaneus, cuboid, talus, and navicular bones, reduction in number of cuneiform bones.

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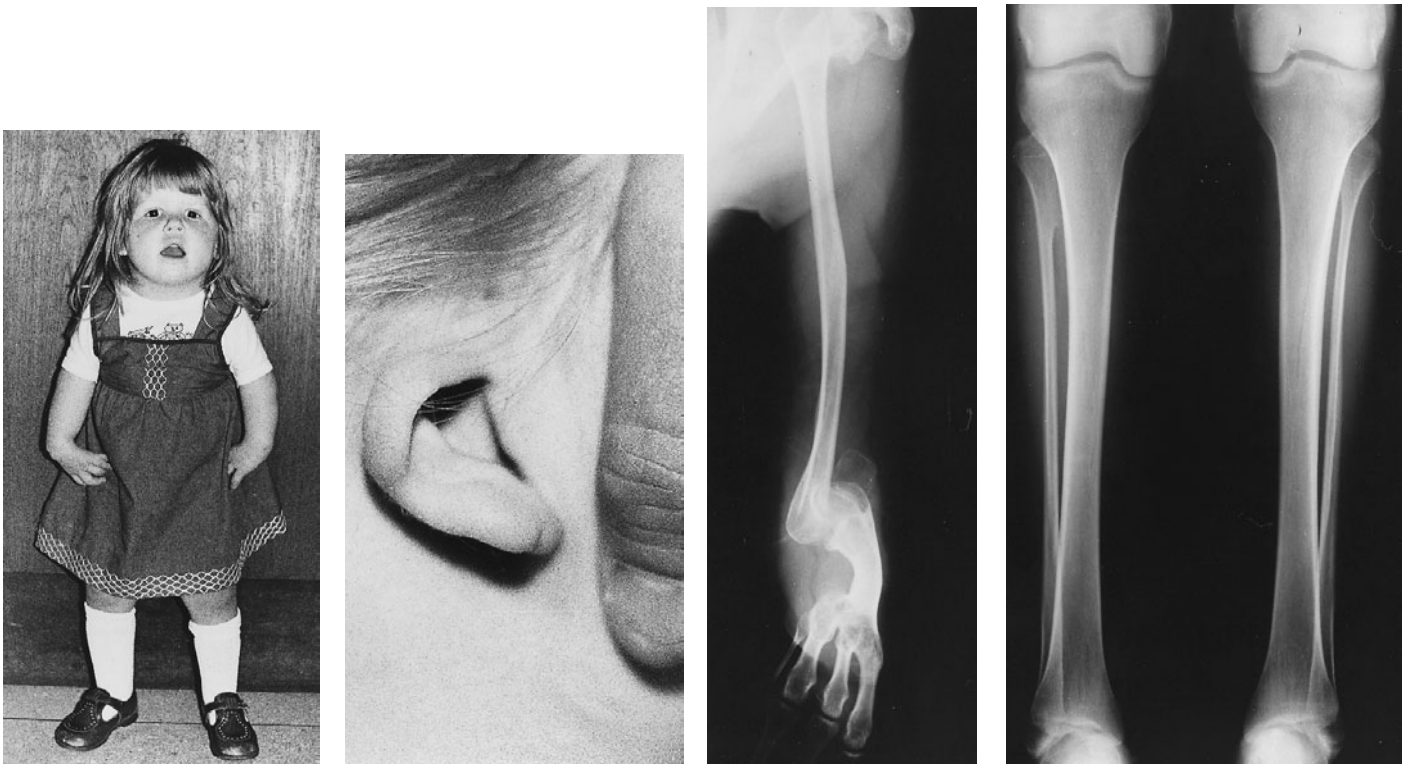

A B C D

Fig. 29–7. *Facio-auriculo-radial dysplasia*. (A) Midface hypoplasia, downslanting palpebral fissures, long philtrum. Bilateral mesomelic shortening of arms and rudimentary thumbs. (B) Pinna is microtic. (C) Arm of mother of patient shown in A. Note absent radius, shortening and bowing of ulna, absent thumb, rudimentary second metacarpal. (D) Proximal shortening of fibulae with exostosis at one metaphysis. (From AE Harding et al, J Med Genet 19:110, 1982.)

Facio-auriculo-radial dysplasia

Harding et al (1), in 1982, described the association of unusual facies, asymmetrical radial dysplasia, abnormal pinnae, and conductive hearing loss in a mother and daughter. They pointed out that a similar family had been reported by Stoll et al (2) in 1974. There was midfacial hypoplasia. The pinnae were dysplastic. The philtrum was long and prominent. Aplasia of thumbs and index fingers, hypoplastic thumbs, aplastic or hypoplastic radii, radioulnar synostosis, somewhat hypoplastic fibulae, and minor changes in the vertebrae were found (Fig. 29–7).

Inheritance is autosomal dominant with variable expression. There is overlap with the VATER association and with *oculo-auriculo-vertebral spectrum*.

References (Facio-auriculo-radial dysplasia)

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Facio-cardio-renal syndrome (Eastman-Bixler syndrome)

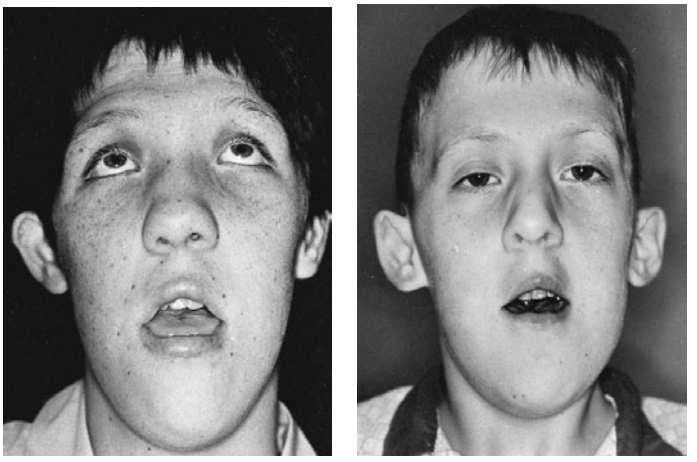
Eastman and Bixler (1) reported three sibs with characteristic facies, severe mental retardation, congenital heart anomalies, and horseshoe kidneys. There were plagiocephaly, broad nasal root, malar hypoplasia, stiff outstanding pinnae, hypoplastic philtrum, nasal alae, and thin vermilion. The antegonial notch of the mandible was prominent. One child had cleft palate (Fig. 29–8).

Various heart anomalies, including endocardial fibroelastosis, were found in all three children. All were subject to cyanotic and respiratory problems at birth and, later, to bronchopneumonia. The musculature was poorly developed. The heel cords were tight, the gait waddling, and there was limitation of motion in ankles and knees. The halluces were broad, and the thumbs were clinodactylous. The nails were hypoplastic.

Inheritance is probably autosomal recessive.

The facies is similar to that of *cleft lip, microbrachycephaly, long thin face, ptosis, hypotelorism, lumbosacral/pelvic anomalies, and*

Fig. 29–8. *Facio-cardio-renal syndrome*. (A,B) Facies of two of three affected sibs. In addition to severe mental retardation, all had plagiocephaly, long face with malar hypoplasia, broad nasal root, poorly developed philtrum, and prominent relatively inflexible pinnae. (From JR Eastman and D Bixler, Clin Genet 11:424, 1977.)



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mental retardation. Nevin et al (2) described a boy under the title "facio-cardio-renal (Eastman-Bixler) syndrome." While, indeed, the child had several of the same features (moderate mental retardation, broad nasal root, prominent ears, cleft palate, and horseshoe kidneys), he had tricuspid valve prolapse, isolated growth hormone deficiency, and a quite different facies.

Cleft lip-palate, urogenital anomalies, somatic and mental retardation (Malpuech syndrome) has some overlapping findings but clearly is a different entity.

References [Facio-cardio-renal syndrome (Eastman-Bixler syndrome)]

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2. Nevin NC et al: Facio-cardio-renal (Eastman-Bixler) syndrome. Am J Med Genet 40:31–33, 1991.

Facio-cardio-musculo-skeletal syndrome

Quadrelli et al (1), in 2000, described three male patients from a single family with brachyturricephaly, a somewhat pugilistic facial appearance, muffled voice, cardiomyopathy, marked muscular hypertrophy, broad hands, wide feet with progressive pes cavus, dislocation of toes, variable congenital hip dislocation, and scoliosis. Three other males in the family, now deceased from heart disease, appeared to have had the same disorder.

X-linked recessive inheritance is clearly evident.

Reference (Facio-cardio-musculo-skeletal syndrome)

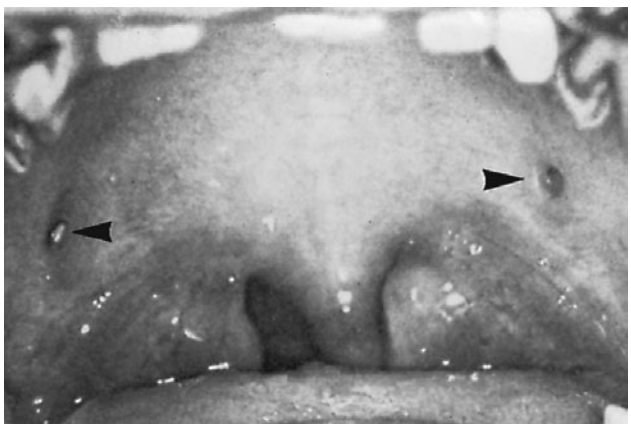
1. Quadrelli R: Uruguay facio-cardio-musculo-skeletal syndrome: A novel X-linked recessive disorder. Am J Med Genet 95:247–265, 2000.

Fistulas of lateral soft palate and associated anomalies

A number of cases of bilateral symmetrical defects of the soft palate have been reported (1–19). The reader is referred to the paper of Campbell (3) for review of early cases. Several examples have been found in association with other anomalies such as absence or hypoplasia of one or both palatine tonsils (3,5,7,9,16), preauricular fistulas (9), hearing loss (4), and strabismus (3). We are truly mystified by the apparent disappearance of this anomaly in the recent literature.

Though usually bilateral, the defects may be unilateral (3,7,9,16). The disorder may be familial, having been seen in two brothers (9) (Fig. 29–9).

Fig. 29–9. *Fistulas of lateral soft palate and associated anomalies*. Arrows point to bilateral fistulas, often associated with agenesis of one, or both, of the palatine tonsils. (From O Neuss, Z Laryngol Rhinol 35:411, 1956.)



The defect appears to be related to irregularity in development of the second pharyngeal pouch (12). Several early cases were attributed to infection, either primary or secondary to surgical complications.

References (Fistulas of lateral soft palate and associated anomalies)

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Keutel syndrome (calcification of cartilages, brachytelephalangy, multiple peripheral pulmonary stenoses, and mixed hearing loss)

Keutel et al (9,10), in 1971–72, reported a syndrome of multiple peripheral pulmonary stenoses, brachytelephalangy, diffuse calcification and/or ossification of cartilages, and mixed hearing loss in two sibs. Approximately 12 patients have been documented to date (2,5,9,10,11,15,16,19).

Affected sibs (10,11) and parental consanguinity (2,3,10,11) clearly indicate autosomal recessive inheritance. The gene has been mapped to 12p12.3–13.1. Mutations in the gene encoding human matrix Gla protein cause the syndrome (13).

Stature has been at or below the 25th centile in all, and below the 3rd centile in a few (5,11,15). Increased miscarriage has been noted (6).

The face is somewhat flattened with a small depressed nose, small alae nasi, and mild midface hypoplasia, becoming more pronounced with age. The pinnae are somewhat large and prominent, and are pale, stiff, and hard in consistency (Fig. 29–10). The cartilaginous ossification begins within the first three years of life and is progressive (2,9,11). Hearing loss is noted prior to admission to school. Sensorineural, mixed, or conductive hearing loss of 30–75 dB, being greater at higher frequencies, has been found in nearly all affected (2,5,9,11,12,16,19). The conductive component is probably related to recurrent middle-ear infections.

Some patients have normal intelligence (2,9,11), whereas others have been mildly retarded (5,6,16).

Variable shortening of the terminal phalanges of the hands (brachytelephalangy) has been a constant finding. The halluces also tend to be short.

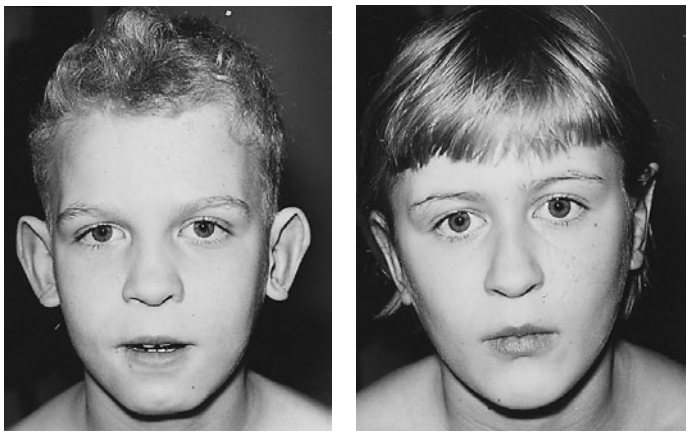

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Fig. 29–10. *Keutel syndrome*. (A,B) Sibs with syndrome. Facies is essentially normal except for calcified pinnae. (Courtesy of G Jörgensen, Göttingen, Germany.)

Radiographic studies show calcification of the pinnae (Fig. 29–11A), cartilaginous portions of ribs, and laryngotracheal, bronchial, and nasal cartilages (Fig. 29–11B,C). The mastoid processes are abnormally dense. Variable shortening of the terminal phalanges of the fingers and halluces and premature fusion of the epiphyses of these phalanges are evident (Fig. 29–12).

Peripheral pulmonary stenosis and pulmonary artery hypoplasia have been found in at least 50% (5,9,11,12,17,18). Angiography has revealed systolic pressure elevation in the right ventricle and in the main pulmonary artery and lowered diastolic pressure in the pulmonary vein together with a systolic pressure gradient—a picture compatible with multiple peripheral pulmonary stenoses.

Recurrent bronchitis, chronic sinusitis, and otitis media have occurred in nearly all the patients (12).

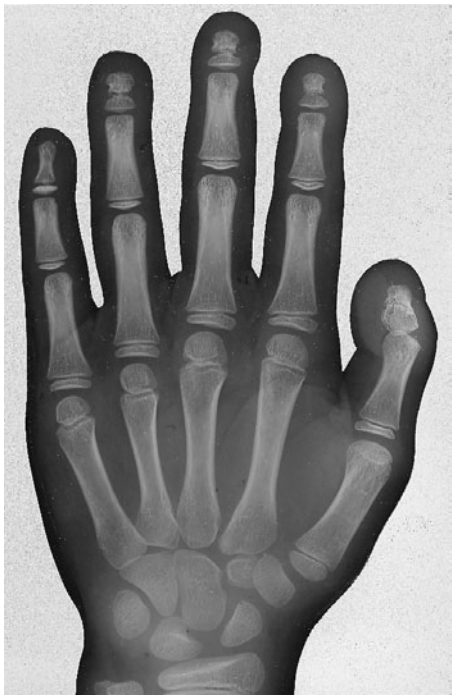
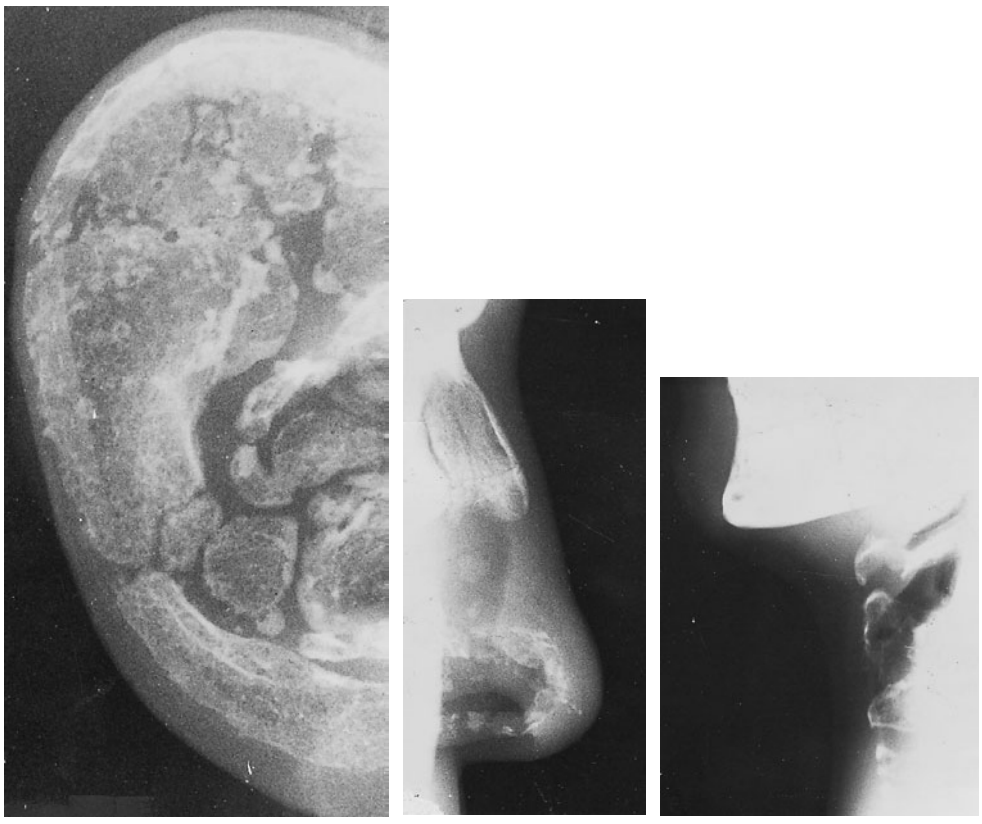


Fig. 29–12. *Keutel syndrome*. Radiograph showing abbreviation of terminal phalanges of several fingers. (Courtesy of R Walbaum, Roubaix, France.)

Multiple pulmonary stenoses and associated hearing loss have been reported (1). Gyllenswärd et al (7) noted "malformation of the external ears" in two patients with multiple peripheral pulmonary stenoses, but further definition was not made. Multiple peripheral pulmonary stenoses can been seen in combination with supravalvular aortic stenosis and in *Williams syndrome* (6).



A B C

Fig. 29–11. *Keutel syndrome*. (A–C) Calcification of cartilages of ear, nose, and trachea. (From G Jörgensen, Arch Klin Exp Ohren Nasen Kehlkopfheilkd 202:1, 1972.)

Calcification and/or ossification of the auricular cartilage can follow frostbite, physical trauma, perichondritis, and in *diastrophic dysplasia* (4,12). Auricular ossification has also been reported as a dominant trait (11), and Primrose (14) described a mentally deficient male with ossification of the ear cartilages who had hearing loss. Ectopic calcification, in general, has been discussed under *chondrodysplasia punctata*.

References [Keutel syndrome (calcification of cartilages, brachytelephalangy, multiple peripheral pulmonary stenoses, and mixed hearing loss)]

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13. Munroe PB et al: Mutations in the gene encoding the human matrix Gla protein cause Keutel syndrome. Nat Genet 21:142–144, 1999.
14. Primrose DA: A slowly progressive degenerative condition characterized by mental deficiency, wasting of limb musculature and bone abnormalities including ossification of the pinnae. J Ment Defic Res 26:101–106, 1982.
15. Say B et al: Unusual calcium deposition in cartilage associated with short stature and peculiar facial features. Pediatr Radiol 1:127–129, 1973.
16. Teebi AS et al: Keutel syndrome: Further characterization and review. Am J Med Genet 78:182–187, 1998.
17. Walbaum R: Les brachydactylies. J Genet Hum 31:167–181, 1983.
18. Walbaum R et al: Le syndrome de Keutel. Pediatrie 30:303–314, 1975.
19. Ziereisen F et al: The Keutel syndrome. Pediatr Radiol 23:314–315, 1993.

Macrocephaly, short stature, and mental retardation (Atkin syndrome)

Atkin et al (1), in 1985, reported a new mental retardation syndrome of macrocephaly, short stature, and coarse facial features. Additional families have been documented (2–5).

The facies is characterized by macrocephaly, prominent forehead, heavy supraorbital ridges, hypertelorism, broad nasal tip, anteverted nostrils, and thick lips.

Intelligence varies from moderate to severe retardation.

Skeletal changes are mostly minor: hyperextensible joints, tapering fingers, genua valga and recurvata, scoliosis, and hyperkyphosis.

Inheritance is either autosomal dominant or X-linked dominant. There is some similarity to *Coffin-Lowry syndrome*.

References [Macrocephaly, short stature, and mental retardation (Atkin syndrome)]

1. Atkin JF et al: A new X-linked mental retardation syndrome. Am J Med Genet 21:697–705, 1985.
2. Baraitser M et al: Nonspecific X-linked mental retardation with macrocephaly and obesity. Am J Med Genet 57:370–373, 1995.
3. Clark RD, Baraitser M: A new X-linked mental retardation syndrome. Am J Med Genet 26:13–15, 1987.
4. Fryns JP et al: Mental retardation, short stature and craniofacial dysmorphism in three sisters. Clin Genet 33:293–298, 1988.
5. Gragg GW: Familial megalencephaly. Birth Defects 7(1):228–230, 1971.

Martsolf syndrome (cataract-mental retardation-hypogonadism)

In 1978, Martsolf et al (3) reported two brothers with unusual facies, severe mental retardation, short stature, cataracts, and hypogonadism.

Sanchez et al (6) described male sibs with similar problems. Hennekam et al (2) and Harbord et al (1) described an affected brother and sister. Another possible example is that of Strisciuglio et al (7). Inheritance is autosomal recessive.

In addition to the severe mental retardation, frequently there are feeding problems in infancy. Height, weight, and head circumference are usually below the third percentile. The facies is characterized by an aged appearance, brachycephaly, cataracts, epicanthal folds, low nasal bridge, broad nasal tip, maxillary retrusion, short philtrum, pouting lips, and micrognathia (Fig. 29–13).

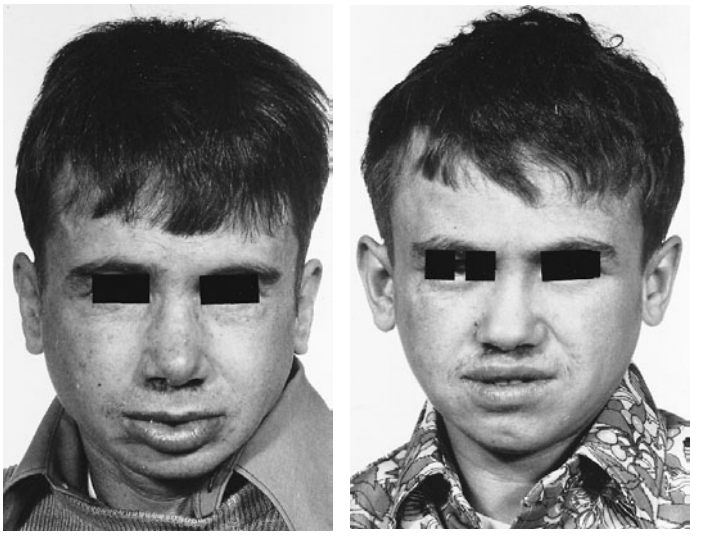
Various other anomalies have included prominent nipples, lumbar hyperlordosis, thin limbs, broad fingertips, short palms, lax finger joints, various foot anomalies including abnormal toenails, hypogonadism, and cryptorchidism.

There are several similarities to *Cohen syndrome* and Mirhosseini-Holmes-Walton (4,5) syndrome, a disorder of short stature, mental retardation, microcephaly, maxillary hypoplasia, cataracts, mottled retinal pigmentation, short philtrum, narrow hands and feet with long digits, delayed puberty, and hyperextensible joints. There is also resemblance to *COFS*.

References [Martsolf syndrome (cataract-mental retardation-hypogonadism)]

1. Harbord MG et al: Microcephaly, mental retardation, cataracts, and hypogonadism in sibs: Martsolf's syndrome. J Med Genet 26:397–406, 1989.
2. Hennekam RCM et al: Martsolf syndrome in a brother and sister: Clinical features and pattern of inheritance. Eur J Pediatr 147:539–543, 1988.

Fig. 29–13. *Martsolf syndrome*. (A,B) Prominent antitragi, mild maxillary hypoplasia, short philtrum, pouty lower lip, sparse facial hair in 28- and 25-year-old brothers. (From JT Martsolf et al, Am J Med Genet 1:291, 1978.)



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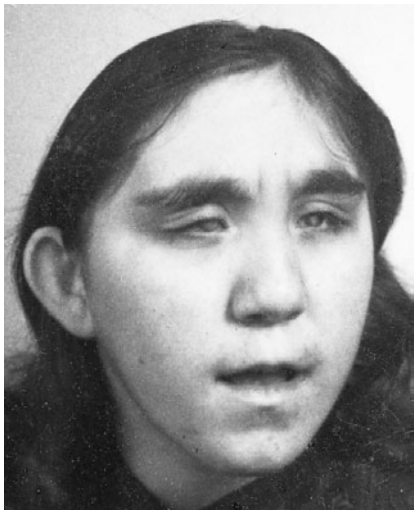


Fig. 29–14. *Midface hypoplasia, corneal clouding, subvalvular aortic stenosis, and mental and somatic retardation*. Note round and hypoplastic face, bilateral microcornea with diffuse clouding, internal strabismus. (From JP Fryns and H Van den Berghe, Eur J Pediatr 131:179, 1979.)

3. Martsolf JT et al: Severe mental retardation, cataracts, short stature, and primary hypogonadism in two brothers. Am J Med Genet 1:291–299, 1978.
4. Mendez HM et al: The syndrome of retinal pigmentary degeneration, microcephaly, and severe mental retardation (Mirhosseini-Holmes-Walton syndrome): Report of two patients. Am J Med Genet 22:223–228, 1985.
5. Mirhosseini SA et al: Syndrome of pigmentary retinal degeneration, cataract, microcephaly and severe mental retardation. J Med Genet 9:193–196, 1972.
6. Sanchez JM et al: Two brothers with Martsolf's syndrome. J Med Genet 22:308–310, 1985.
7. Strisciuglio P et al: Martsolf's syndrome in a non-Jewish boy. J Med Genet 25:267–269, 1988.

Midface hypoplasia, corneal clouding, subvalvular aortic stenosis, and mental and somatic retardation

Fryns and Van den Berghe (1), in 1979, described male and female sibs with microcornea with diffuse clouding (Peters anomaly), glaucoma, and internal strabismus. The face was round and hypoplastic. The nose was relatively small with anteversion of the nostrils and a broad nasal bridge (Fig. 29–14).

Membranous subvalvular aortic stenosis was detected during infancy. Hands and feet were short and stubby. Mental and growth retardation were more marked in the sisters.

Haney and Falls (2) reported Peters anomaly in association with hypertelorism, upslanting palpebral fissures, brachydactyly, and mental and somatic retardation in two sibs, but we believe that this condition represents a different disorder.

References (Midface hypoplasia, corneal clouding, subvalvular aortic stenosis, and mental and somatic retardation)

1. Fryns JP, Van den Berghe H: Corneal clouding, subvalvular aortic stenosis and midfacial hypoplasia associated with mental deficiency and growth retardation—a new syndrome? Eur J Pediatr 131:179–183, 1979.
2. Haney WP, Falls HF: The occurrence of congenital keratoconus posterior circumscriptus. Am J Ophthalmol 52:53–57, 1961.

Mietens-Weber syndrome

Four of six children of consanguineous normal parents were reported by Mietens and Weber (2) in 1966 with a syndrome of marked growth

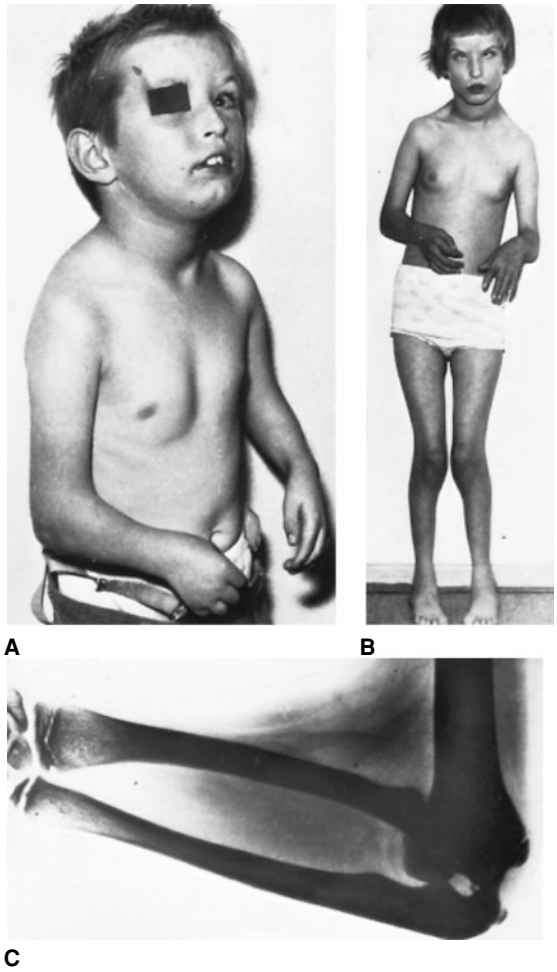


Fig. 29–15. *Mietens-Weber syndrome*. (A,B) Two of four affected sibs with convergent strabismus, narrow pointed nose, short forearms, contraction at elbows, atrophic calves. (C) Short radius and ulna; radial head dislocated, its epiphysis absent. (From C Mietens and H Weber, J Pediatr 69:624, 1966.)

retardation (−3 SD) and mild mental retardation (IQ 70–80). A child of unrelated parents was documented by Waring and Rodrigues (4). There was bilateral microsclerocornea and absent left fibula. Intelligence was normal. Resemblance to the kindred reported by Mietens and Weber is otherwise marked. Other cases have been described (1,3).

Clinical appearance was striking, the facies being marked by convergent strabismus and a small, narrow, pointed nose. Disclike central opacities of the cornea, located mainly in the superficial layers, were noted bilaterally. Short forearms and flexion of the elbows with proliferation and contraction of the connective tissues on the volar aspect were also marked. Calf muscles were atrophic, and pes valgus planus was evident (Fig. 29–15).

Radiographically, the ulna and radius were abbreviated. The head of the radius was dislocated and its epiphysis was absent bilaterally.

The disorder has autosomal recessive inheritance.

References (Mietens-Weber syndrome)

1. Carnevale A et al: Mietens-Weber syndrome. Rev Invest Clin 28:347–352, 1976.
2. Mietens C, Weber H: A syndrome characterized by corneal opacity, nystagmus, flexion contraction of the elbows, growth failure and mental retardation. J Pediatr 69:624–629, 1966.
3. Nagano A et al: Mietens' syndrome. Arch Orthop Unfallchir 89:81–86, 1977.
4. Waring GO III, Rodrigues MM: Ultrastructure and successful keratoplasty of sclerocornea in Mietens' syndrome. Am J Ophthalmol 90:469–475, 1980.

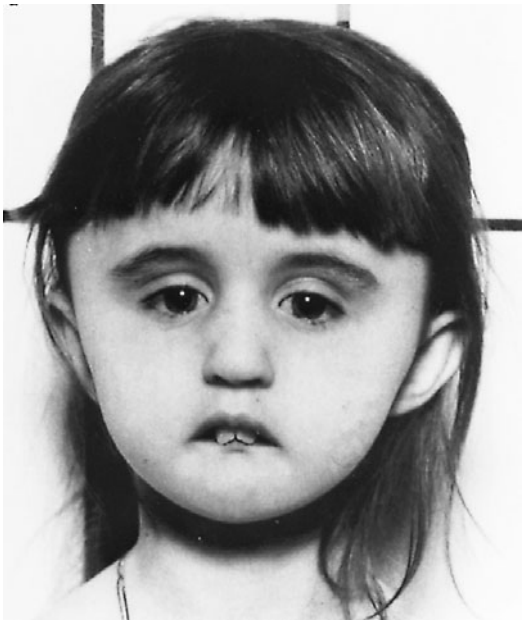


Fig. 29–16. *Short stature, auditory canal atresia, mandibular hypoplasia, and skeletal anomalies (SAMS syndrome)*. Deep-set eyes, downslanting palpebral fissures, hypotelorism, malar hypoplasia, and small mouth. (From EG Lemire et al, Am J Med Genet 75:256, 1998.)

Short stature, auditory canal atresia, mandibular hypoplasia, and skeletal abnormalities (SAMS syndrome)

Lemire et al (1) reported a female Mennonite child with *S*hort stature, *A*tresia of the external auditory canals, *M*andibular hypoplasia, and *S*keletal anomalies. The mnemonic SAMS was suggested.

The facies was characterized by deep-set eyes, hypotelorism, downslanting palpebral fissures, malar hypoplasia, and small mouth (Fig. 29–16).

Skeletal defects consist of bilateral humeral hypoplasia, delayed ossification of pubic rami, and humero-scapular synostosis (Fig. 29–17).

She was the product of a consanguineous union. Autosomal recessive inheritance is likely.

Reference [Short stature, auditory canal atresia, mandibular hypoplasia, and skeletal abnormalities (SAMS syndrome)]

1. Lemire EG et al: SAMS: Provisionally unique multiple congenital anomaly syndrome consisting of short stature, auditory canal atresia, mandibular hypoplasia, and skeletal abnormalities. Am J Med Genet 75:256–260, 1998.

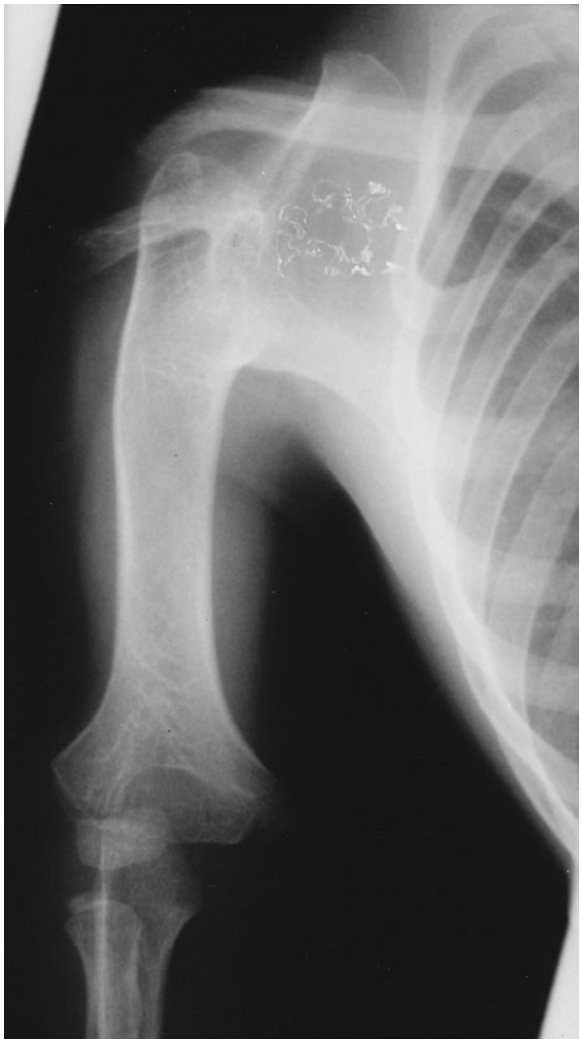
Ptosis-aortic coarctation syndrome

Cornel et al (2), in 1987, reported autosomal dominant inheritance of eyelid ptosis with coarctation of the aorta. Noted in a four-generation pedigree, the syndrome is characterized by congenital bilateral ptosis, sensorineural hearing deficit, coarctation of the aorta, and asthma. Larned et al (3) noted the nonspecific association of congenital ptosis and congenital heart defects. The combination of ptosis and congenital heart defects may also be observed with *Turner syndrome* and *Noonan syndrome*. Bazopoulou-Kyrkanidou et al (1) reported an affected mother.

References (Ptosis-aortic coarctation syndrome)

1. Bazopoulou-Kyrkanidou E et al: Familial bilateral blepharoptosis and subvalvular aortic stenosis. Genet Couns 6:227–232, 1995.

2. Cornel G et al: Familial coarctation of the aortic arch with bilateral ptosis: A new syndrome? J Pediatr Surg 22:724–726, 1987.



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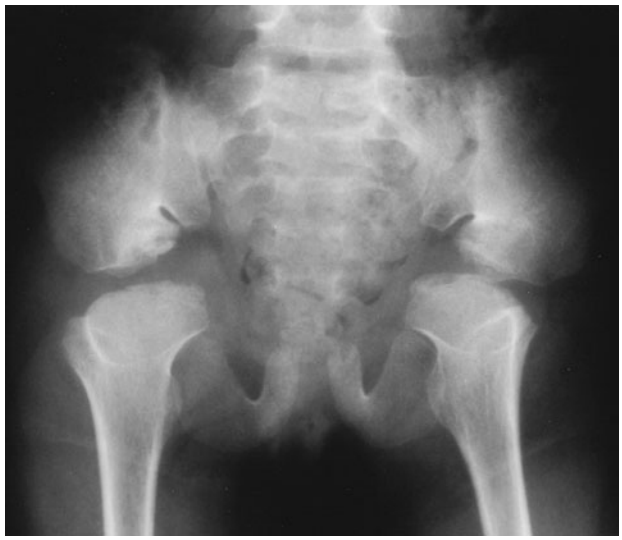


B

Fig. 29–17. *Short stature, auditory canal atresia, mandibular hypoplasia, and skeletal anomalies (SAMS syndrome)*. (A) Shortened humerus with scapulohumeral synostosis and distal metaphyseal flare. (B) Absent ossification of pubic bones, small sacrosciatic notches, central dislocation of hips, poorly ossified and flattened femoral epiphyses, wide femoral necks. (From EG Lemire et al, Am J Med Genet 75:256, 1998.)

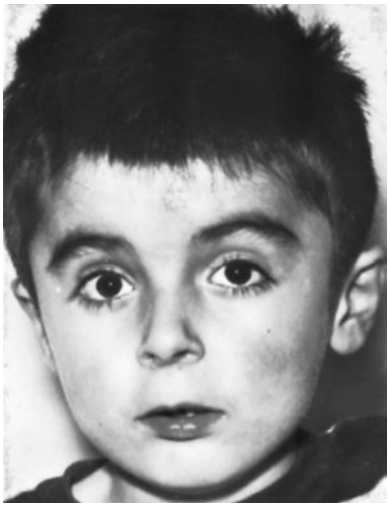


Fig. 29–18. *Craniodigital syndrome*. Brachycephaly, pointed nose, and startled expression. (From CR Scott et al, J Pediatr 78:658, 1971.)

3. Larned DC et al: The association of congenital ptosis and congenital heart disease. Ophthalmology 93:492–494, 1986.

Craniodigital syndrome

In 1971, Scott et al (2) reported a newly recognized craniodigital syndrome in three affected brothers who were said to resemble patients with *Saethre–Chotzen syndrome* but who differed significantly by having growth deficiency, moderate to severe mental retardation, and brachycephaly with absence of craniosynostosis. Other features included thick scalp hair, temporal and sideburn hair extension, prominent eyebrows, long dark eyelashes, startled facial expression, small pointed nose, micrognathia, soft-tissue syndactyly between the second, third, and fourth fingers, and soft-tissue syndactyly between the second and third toes (Fig. 29–18). A similarly affected male child was described by Lorenz et al (1). The mother had 2–3 syndactyly of the toes. A new family (personal communication, CR Scott, 1997) confirms the inheritance pattern. Unaffected sisters each had an affected son.

The mode of inheritance is X-linked.

References (Craniodigital syndrome)

1. Lorenz P et al: The craniodigital syndrome of Scott: Report of a second family. Am J Med Genet 37:224–226, 1990.

2. Scott CR et al: A new craniodigital syndrome with mental retardation. J Pediatr 78:658–663, 1971.

Singleton-Merten syndrome

A syndrome consisting of calcification of the aortic arch and aortic valve, hypoplastic tooth buds, and osteoporosis and widening of the metacarpals, carpals, and phalanges was described in two unrelated female children by Singleton and Merten (4). Additional patients were reported by McLoughlin et al (3), Gay and Kuhn (2), and Feigenbaum et al (1).

The deciduous teeth become carious at any early age and are lost prematurely, producing decreased vertical height. The permanent teeth are dysplastic, some never develop, and others erupt late (Fig. 29–19A,B).

Cardiac enlargement with calcification of the thoracic aorta was seen in all children in mid or later childhood (Fig. 29–19C). Death results from calcific aortic stenosis leading to heart failure usually in the teen years.

Severe to moderate muscular weakness becomes manifest in the first or second year of life following a febrile illness. There are secondary hip and foot deformities. Stature is small. Osteoporosis of the cranial vault and all long bones is significant, being most marked in the hand bones (Fig. 29–19D). A psoriasiform skin eruption was reported by Gay and Kuhn (2).

References (Singleton-Merten syndrome)

1. Feigenbaum A et al: Singleton-Merten (S-M) syndrome. Am J Hum Genet 43(Suppl):A48, 1988.

2. Gay BB Jr, Kuhn JP: A syndrome of widened medullary cavities of bone, aortic cavitation, abnormal dentition, and muscular weakness (the Singleton-Merten syndrome). Radiology 118:389–395, 1996.

3. McLoughlin MJ et al: Idiopathic calcification of the ascending aorta and aortic valve in two young women. Br Heart J 36:96–100, 1974.

4. Singleton EB, Merten DF: An unusual syndrome of widened medullary cavities of the metacarpals and phalanges, aortic calcification and abnormal dentition. Pediatr Radiol 1:2–7, 1973.

Unusual facies, congenital corneal anesthesia with retinal abnormalities, sensorineural hearing loss, patent ductus arteriosus, and mental retardation

Ramos-Arroyo et al (1) and Saksena et al (2) described male and female sibs with failure to thrive and deficient stature and weight. In addition to mental retardation and persistent ductus arteriosus, the facial and ocular findings included broad flat face, upslanting palpebral fissures, ocular hypertelorism, frontal bossing, depressed nasal root and bridge, and midface hypoplasia. Keratitis, absence of peripapillary choriocapillaris, absence of retinal pigment epithelium, and poor visual acuity were noted. Both exhibited sensorineural hearing loss and patent ductus arteriosus (Fig. 29–20). The mother had mild to moderate sensorineural hearing loss, retinal changes, and similar facial features. Inheritance appears to be autosomal dominant.

References (Unusual facies, congenital corneal anesthesia with retinal abnormalities, sensorineural hearing loss, patent ductus arteriosus, and mental retardation)

1. Ramos-Arroyo MA et al: Congenital corneal anesthesia with retinal abnormalities, deafness, unusual facies, persistent ductus arteriosus, and mental retardation: A new syndrome? Am J Med Genet 26:345–354, 1987.

2. Saksena SS et al: Craniofacial pattern profile (CFPP) evaluation of facial dysmorphology in a familial syndrome with corneal anesthesia and multiple congenital anomalies. Am J Phys Anthropol 74:465–471, 1987.

Unusual facies, mental retardation, cataracts, muscle wasting, and skeletal abnormalities

Primrose (4), in 1982, described a slowly progressive degenerative disorder characterized by mental deficiency, wasting of limb musculature, bone abnormalities, and ossification of the pinnae. A virtually identical example was described by Collacott et al (1).

Relative macrocephaly, large calcified pinnae, sensorineural hearing loss, cataracts, and torus palatinus were found (Fig. 29–21A,B). Body build in the two males was markedly feminine. There was distal muscle wasting with contractures of fingers, hips, and knees (Fig. 29–21C).

Radiographically, generalized osteoporosis was noted. The skull was large with basilar impression and midface hypoplasia. The chest was narrow with downward-sloping ribs. The lumbar spine showed kyphosis with endplate irregularities, posterior scalloping of vertebral bodies, and collapse-wedging of lumbar vertebrae. There were well-defined radiolucencies in the proximal femoral and humeral shafts and in both patellae. The iliac wings were narrow. The terminal phalanges were short and there were erosions at the bases of the proximal phalanges of the index and middle fingers.

The disorder appears to be different from *Keutel syndrome* (2,3) in which patients have normal or low normal intelligence, brachytelephalangy, diffuse cartilage calcification, and peripheral pulmonary stenosis. Calcified pinnae may result from trauma.

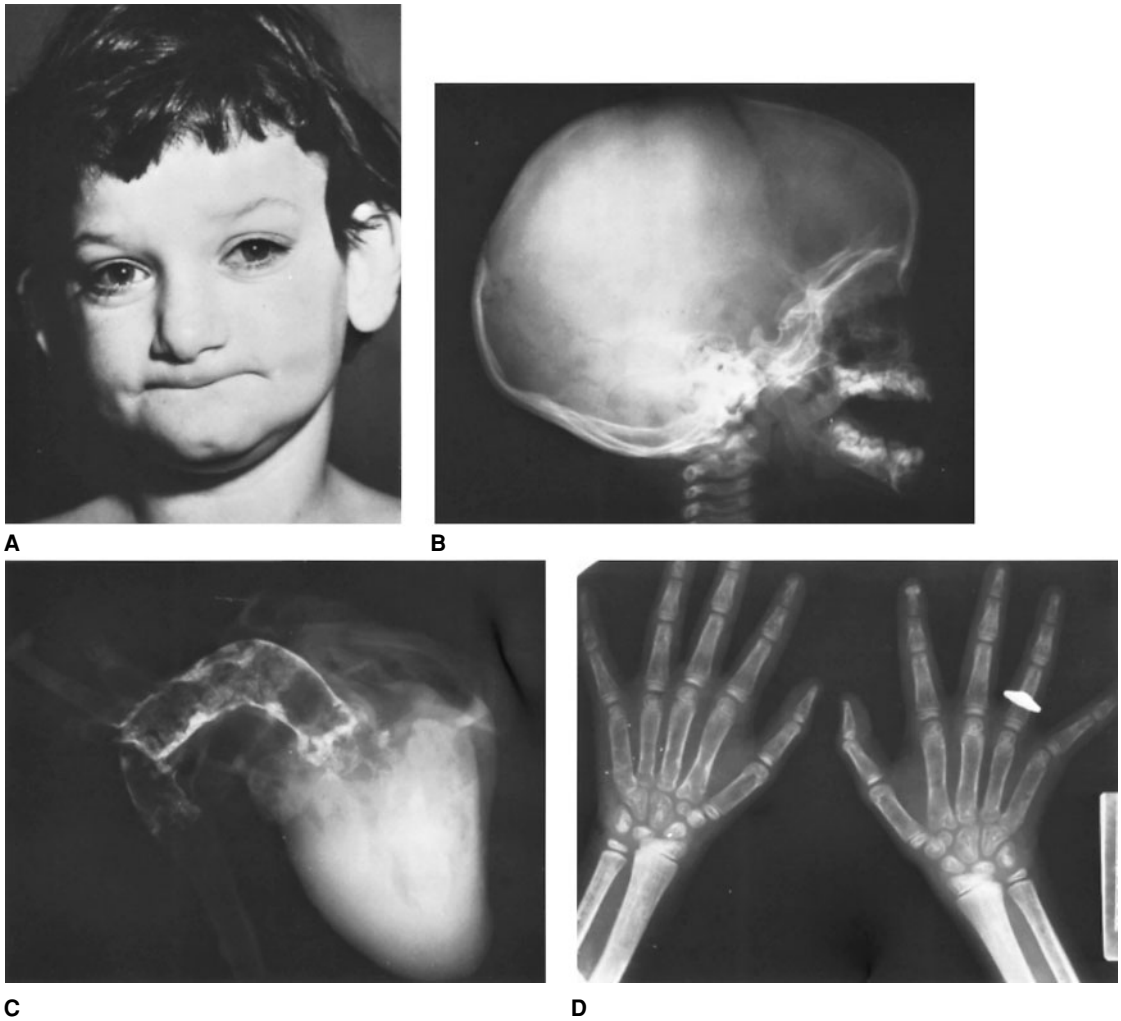


Fig. 29–19. *Singleton-Merten syndrome*. (A) Loss of vertical height in lower face due to unerupted teeth makes child look older than 10 years of age. (B) Radiograph shows mild maxillary hypoplasia, mild diffuse osteoporosis, and multiple unerupted teeth. (C) Extensive calcification of aortic arch and aortic valve. (D) Marked osteoporosis of hand bones, subungual calcification of second finger. (From EB Singleton and DF Merten, Pediatr Radiol 1:2, 1973.)

References (Unusual facies, mental retardation, cataracts, muscle wasting, and skeletal abnormalities)

1. Collacott RA et al: The syndrome of mental handicap, cataracts, muscle wasting and skeletal abnormalities. Report of a second case. J Ment Defic Res 30:301–308, 1986.
2. Fryns JP et al: Calcification of cartilages, brachytelephalangy and peripheral pulmonary stenosis. Confirmation of Keutel syndrome. Eur J Pediatr 42:201–203, 1984.
3. Keutel J et al: A new autosomal recessive syndrome: Peripheral pulmonary stenosis, brachytelephalangism, neural hearing loss and abnormal cartilage calcifications/ossification. Birth Defects 8(5):60–68, 1972.
4. Primrose DA: A slowly progressive degenerative condition characterized by mental deficiency, wasting of limb musculature and bone abnormalities including ossification of the pinnae. J Ment Defic Res 26:101–106, 1982.

Unusual facies, short limbs, and congenital heart disease

Barrow and Fitzsimmons (1) described an apparently unique lethal disorder in a male infant. The child had severe rhizomelic shortening of the limbs, more marked in the upper extremities, and mild talipes equinus.

There were posterior sloping of the forehead, prominent nasal bridge, epicanthal folds, narrow palpebral fissures with mild upslant, capillary hemangiomas involving the glabellar area and both lips, thin vermilion, micrognathia, and short neck (Fig. 29–22).

Postmortem examination revealed a single ventricle leading into the truncus arteriosus that divided into right and left pulmonary arteries and continued as the aorta. The testes were intraabdominal.

Reference (Unusual facies, short limbs, and congenital heart disease)

1. Barrow M, Fitzsimmons JS: Short limbs, abnormal facial appearance and congenital heart defect. Am J Med Genet 18:431–433, 1984.

Cerebro-oculo-nasal syndrome

Richieri-Costa and Guion-Almeida (3) in 1993, reported two unrelated girls with bilateral anophthalmia, abnormal nares and central nervous system anomalies (Fig. 29–23A–C). A third example, also a female, was provided by Ercal and Say (1). Case 1 of Temple et al (4) has similar nose and microphthalmic left eye but otherwise appears different. Two additional examples were added by Guion-Almeida et al (2). Another patient was reported by C Booth to MM Cohen, Jr (personal communication, 1998).

All patients were mentally retarded. Hydrocephalus was constant. Encephalocele and craniosynostosis were reported in one patient each (3).

The facies is striking. All had frontal prominence and bilateral anophthalmos. Eyebrows and eyelashes were sparse and irregularly placed.

Fig. 29–20. *Unusual facies, congenital corneal anesthesia with retinal abnormalities, sensorineural hearing loss, patent ductus arteriosus, and mental retardation*. Affected sibs with frontal bossing, hypertelorism, depressed nasal bridge, midfacial hypoplasia. Female has tarsorrhaphies. (Courtesy of ME Hodes, Indianapolis, Indiana.)

Two had a midline nasal appendage (1,3) (Fig. 29–23D). The nose was short with an elevated bridge and anteverted nostrils. The mouth is down-turned. Cleft palate was found in one case as was single maxillary central incisor (3) (Fig. 29–23E). The pinnae were low set and outstanding.

Dermal pigmentation over the neck was noted in one case (1).

References (Cerebro-oculo-nasal syndrome)

1. Ercal D, Say B: Cerebro-oculo-nasal syndrome: Another case and review of the literature. Clin Dysmorphol 7:139–141, 1998

2. Guion-Almeida ML et al: Clinical variability in cerebro-oculo-nasal syndrome: Report on two additional cases. Clin Dysmorphol 9:253–257, 2000.

3. Richieri-Costa A, Guion-Almeida ML: Mental retardation, structural anomalies of the central nervous system, anophthalmia and abnormal nares: A new MCA/MR syndrome of unknown cause. Am J Med Genet 47:702–706, 1993.

4. Temple IK et al: Midline facial defects with ocular colobomata. Am J Med Genet 37:23–27, 1990.

CHANDS syndrome

Baughman (1), in 1971, and Toriello et al (6), in 1979, reported a rather large inbred kindred of Dutch extraction with *C*urly *H*air, *A*nkyloblepharon filiforme, *N*ail *D*ysplasia from which the acronym CHANDS was created. Additional examples were contributed by Ohishi et al (3) and Toriello (5).

Inheritance is clearly autosomal recessive.

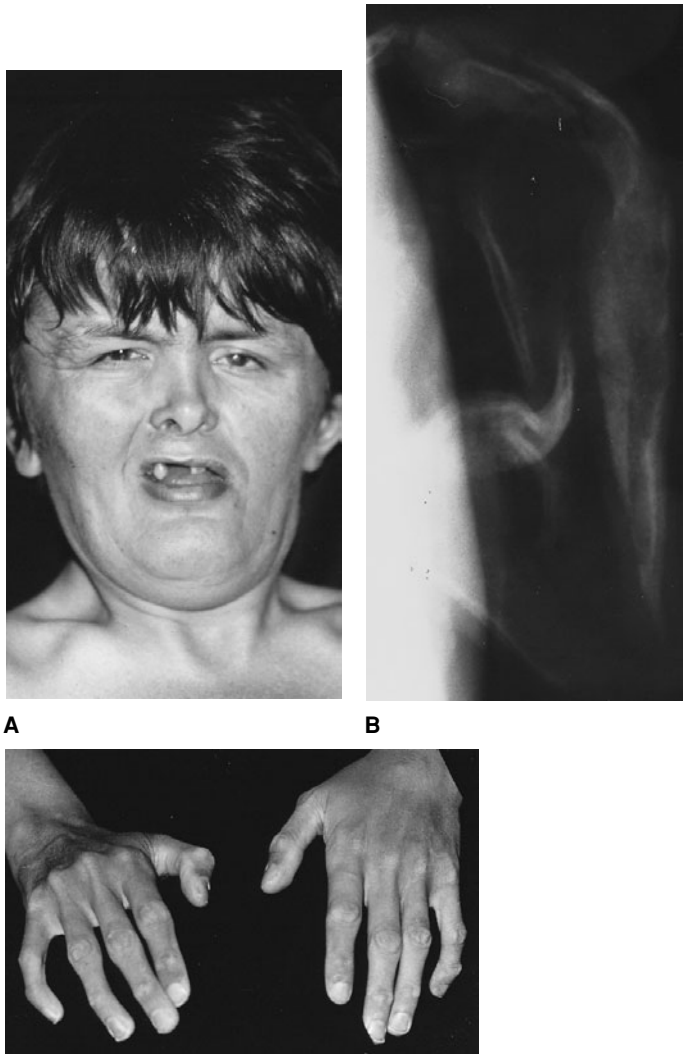
Commisural lip pits were noted by Ohishi et al (3).

There is overlap with *Hay-Wells syndrome* (2). The relationship to the syndrome reported in sibs by Seres-Santamaria et al (4) consisting of cleft palate, ankyloblepharon, alveolar synechiae, nail dystrophy, coarse hair and pits of the lower lip is not known. See *EEC syndrome*.

References (CHANDS syndrome)

1. Baughman FA Jr: CHANDS: The curly hair- ankyloblepharon-nail dysplasia syndrome. Birth Defects 7(8):100–102, 1971.

2. Bertola DR et al: AEC syndrome and CHAND syndrome. Further evidence of clinical overlapping in the ectodermal dysplasias. Pediatr Dermatol 17:218–222, 2000.



A B C

Fig. 29–21. *Unusual facies, mental retardation, cataracts, muscle wasting, and skeletal abnormalities*. (A) Macrocephaly, large calcified pinnae, and cataracts. (B) Radiograph showing calcification of pinnae. (C) Distal muscle wasting with contracture of fingers. (From RA Collacott et al, J Ment Defic Res 30:301, 1986.)

3. Ohishi M et al: Alveolar synechiae, ankyloblepharon and ectodermal disorders: An autosomal recessive disorder? Am J Med Genet 38:13–15, 1991.

4. Seres-Santamaria A et al: Two sibs with cleft palate, ankyloblepharon, alveolar synechiae, and ectodermal defects: A new recessive syndrome? J Med Genet 30:793–795, 1993.

5. Toriello HV: Alveolar synechia-ankyloblepharon-ectodermal defects likely CHANDS. Am J Med Genet 49:348, 1994.

6. Toriello HV et al: Reevaluation of CHANDS. J Med Genet 16:316–317, 1979.

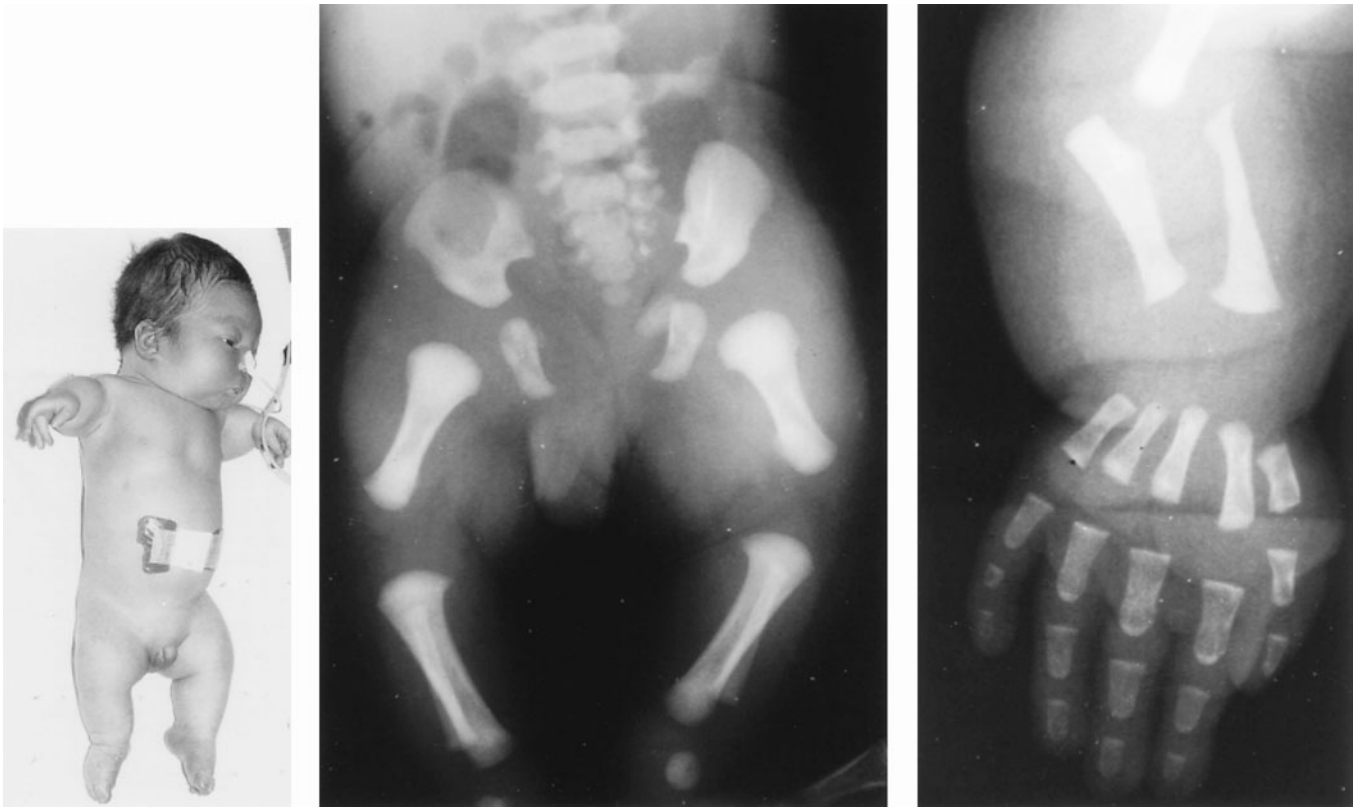
Cerebro-facio-thoracic syndrome

Pascual-Castroviejo et al (3), in 1975, were the first to describe a syndrome of abnormal facies, costovertebral abnormalities, and mental retardation with hypoplasia of the corpus callosum in three unrelated children. They entitled the syndrome *cerebro-facio-thoracic dysplasia*. To date, six examples have been documented.

Inheritance is autosomal recessive (3,4).

Birthweight above the 90th centile was noted in three cases (1,3).

Craniofacial anomalies included macrocephaly, brachycephaly, low hairline, narrow forehead, hypertelorism, epicanthic folds, synophrys,



A B C

Fig. 29–22. *Unusual facies, short limbs, and congenital heart disease*. (A) Rhizomelic shortening of upper limbs more severe than of lower limbs, micrognathia, short neck, talipes equinus. (B,C) Shortened and thickened long bones. Femora and humeri especially shortened. (From M Barrow and JS Fitzsimmons, Am J Med Genet 18:431, 1984.)

short broad nose, hypoplastic maxilla, low-set posteriorly rotated pinnae, and short neck. Three of six had cleft lip–palate (1,4) (Fig. 29–24).

All exhibited mental retardation but were affable. CT studies revealed hypoplastic corpus callosum in two of five patients. A large septum pellucidum was noted in three. The petroclinoid ligament was calcified.

The thorax and shoulders were narrowed, and the scapulae elevated. Costovertebral anomalies (bifid and fused ribs, fused or wedged vertebrae, hemivertebrae) resembling those in *cerebro-costo-mandibular syndrome* were a constant feature.

One must exclude autosomal recessive spondylocostal dysostosis; Moerman et al (2) described a syndrome of macrocrania, spondylocostal anomalies, and agenesis of the corpus callosum, but there were other findings: congenital heart and renal anomalies and severe growth retardation.

References (Cerebro-facio-thoracic syndrome)

1. Guion-Almeida ML et al: Cerebrofaciothoracic syndrome. Am J Med Genet 61:152–153, 1996.

2. Moerman P et al: A new lethal chondrodysplasia with spondylocostal dysostosis, multiple internal anomalies and Dandy-Walker cyst. Clin Genet 27:160–164, 1985.

3. Pascual-Castroviejo K et al: Cerebro-facio-thoracic dysplasia: Report of three cases. Dev Med Child Neurol 17:343–357, 1975.

4. Philip N: Cerebrofaciothoracic dysplasia: A new family. J Med Genet 29:497–499, 1992.

Coarse facies, mental retardation, and heavy breathing (Pitt-Hopkins syndrome)

Pitt and Hopkins (1), in 1978, described a syndrome, the common findings of which were mental retardation, coarse face, and abnormal breathing pattern. Other examples have been reported by Singh (2) and van Balkom et al (3).

All share poor motor development and voluntary overbreathing. Facially, all exhibit a wide nasal bridge, prominent nose, flared nares, macrostomia, thick fleshy lips, and dysmorphic pinnae. Skeletal changes were minimal but all exhibited clubbing of fingers and most had club foot. Short great toes were noted in two (1,3) (Fig. 29–25).

All cases have been isolated.

Differential diagnosis should exclude Joubert syndrome and Rett syndrome.

References [Coarse facies, mental retardation, and heavy breathing (Pitt-Hopkins syndrome)]

1. Pitt DB, Hopkins I: A syndrome of mental retardation, wide mouth and intermittent overbreathing. Aust Paediatr J 14:182–184, 1978.

2. Singh HA: Mental retardation, macrostomia, and hyperpnoea syndrome. J Paediatr Child Health 29:156–157, 1993.

3. van Balkom IDC et al: Mental retardation, "coarse" face, and hyperbreathing: Confirmation of the Pitt-Hopkins syndrome. Am J Med Genet 75:273–276, 1998.

Facio-skeleto-genital syndrome

Mollica et al (2) reported an infant, the daughter of consanguineous parents. The child had tetramelic limb deficiency, bilateral cleft lip–palate, athelia, low umbilicus, bladder exstrophy, no external genitalia, and anteriorly displaced anus.

The authors suggested resemblance to limb/pelvis-hypoplasia/aplasia syndrome of Al-Awadi et al (1) and Raas-Rothschild et al (3).

References (Facio-skeleto-genital syndrome)

1. Al-Awadi S et al: Profound limb deficiency, thoracic dystrophy, unusual facies, and normal intelligence: A new syndrome. J Med Genet 22:36–38, 1985.

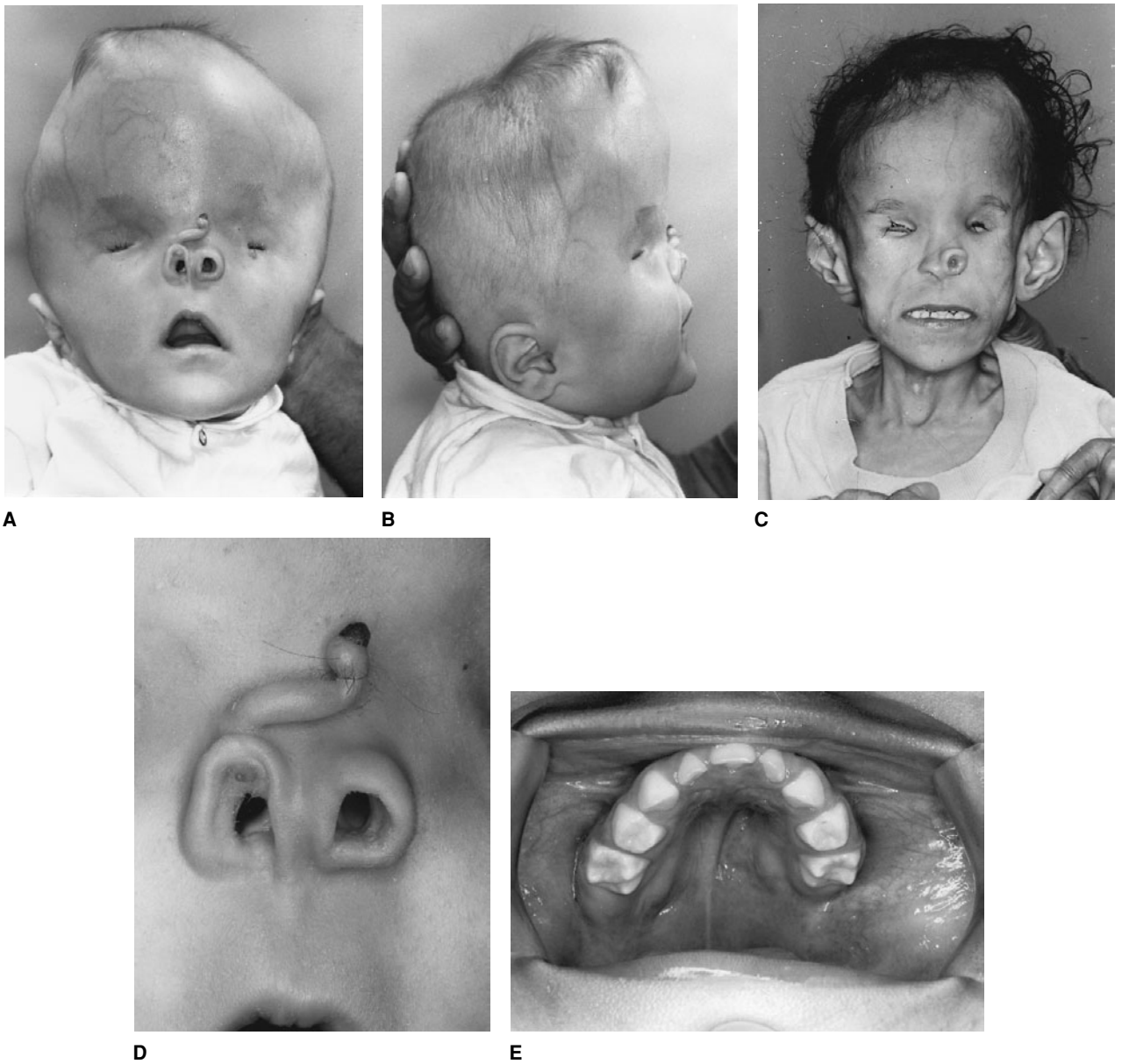


Fig. 29–23. *Cerebro-oculo-nasal syndrome*. (A–C) Hydrocephaly, prominent forehead, anophthalmos, and abnormal nares in two similarly affected patients. Patient in A and B had craniosynostosis. (D) Nasal appendage. (E) Single maxillary central incisor. (From A Richieri-Costa and ML Guion-Almeida, Am J Med Genet 47:702, 1993.)

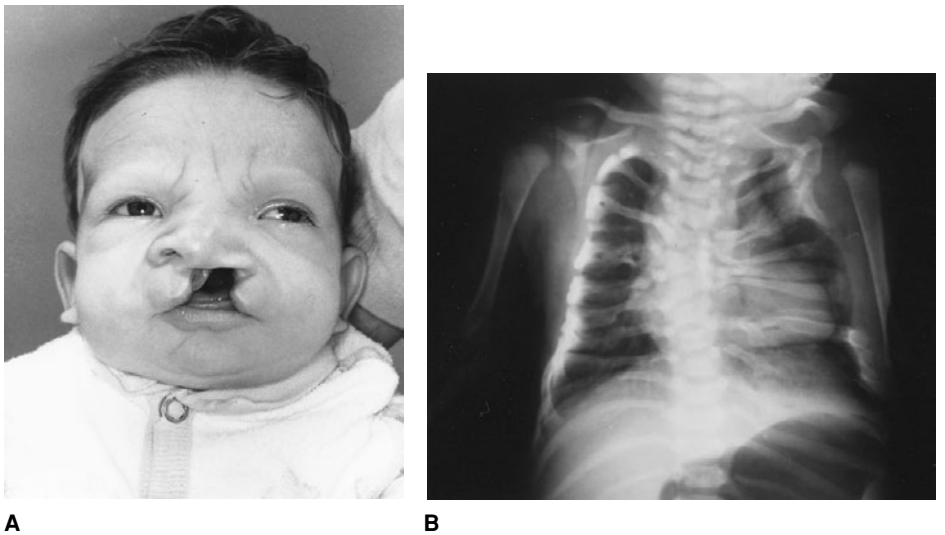


Fig. 29–24. *Cerebro-facio-thoracic syndrome*. (A) Hypertelorism, sparse eyebrows, upslanting palpebral fissures, short broad nose, and cleft lip-palate. (B) Costovertebral anomalies. (From ML Guion-Almeida et al, Am J Med Genet 61:152, 1996.)

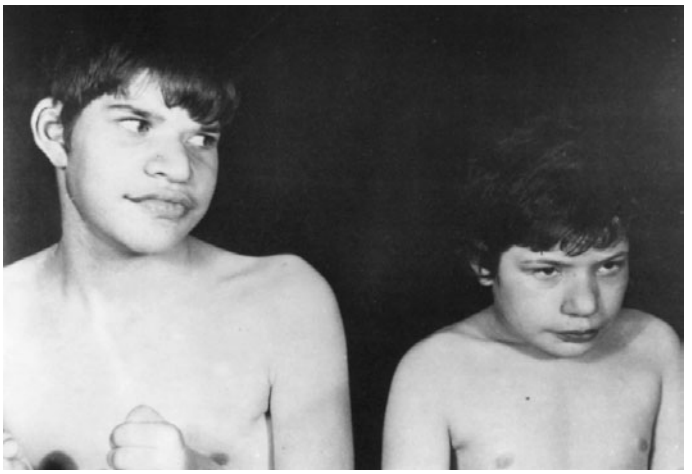


Fig. 29–25. *Coarse facies, mental retardation, and heavy breathing (Pitt-Hopkins syndrome)*. Note wide nasal bridge, prominent nose, flared nares, macrostomia, and thick fleshy lips. (From DB Pitt and I Hopkins, Aust Paediatr J 14:182, 1978.)

2. Mollica F et al: Severe case of Al-Awadi/Raas-Rothschild syndrome or new, possibly autosomal recessive facio-skeleto-genital syndrome. Am J Med Genet 56:168–172, 1995.

3. Raas-Rothschild A et al: Pathological features and prenatal diagnosis in the newly recognized limb/pelvis-hypoplasia/aplasia syndrome. J Med Genet 25: 687–697, 1988.

Faciodigitogenital syndrome, Kuwaiti type

Teebi et al (2), in 1988, reported what they called a new autosomal recessive faciodigitogenital syndrome. They contrasted it with Aarskog syndrome, which it resembles but has X-linked inheritance. The highly inbred family, of Bedouin Kuwaiti origin, consisted of three male and two female affected sibs.

In addition to short stature, common features included skull bossing, triangular facies, coarse dry hypopigmented scalp hair, widow's peak, hypertelorism, short stubby nose with anteverted nostrils, flat nasofrontal angle, dysmorphic pinnae, long deep philtrum, wide mouth, pouty lower lip, small broad hands, clinodactyly of fifth fingers, bulbous toes, and shawl scrotum in males. There was no ptosis of eyelids, nor were there downslanting palpebral fissures.

Teebi and Al-Awadi (1) increased the number of observed examples to 16.

Aarskog syndrome must be excluded.

References (Faciodigitogenital syndrome, Kuwaiti type)

1. Teebi AS, Al-Awadi SA: Kuwait type faciodigitogenital syndrome. J Med Genet 28:805–808, 1991.

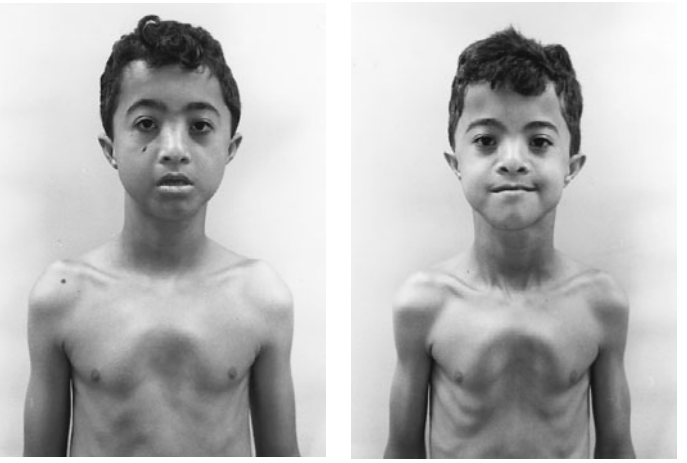
2. Teebi AS et al: New autosomal recessive faciodigitogenital syndrome. J Med Genet 25:400–406, 1988.

Faciothoracoskeletal syndrome

In 1994, Richieri-Costa et al (1) noted two Brazilian brothers, born to consanguineous parents, presenting with long thin face, hypertelorism, short upslanting palpebral fissures, malar hypoplasia, small pinnae with hypoplastic lobules, long neck, pectus excavatum, winged scapulae, brachycamptodactyly, sacral dimple, and seizures (Figs. 29–26 and 29–27).

Inheritance is probably autosomal recessive.

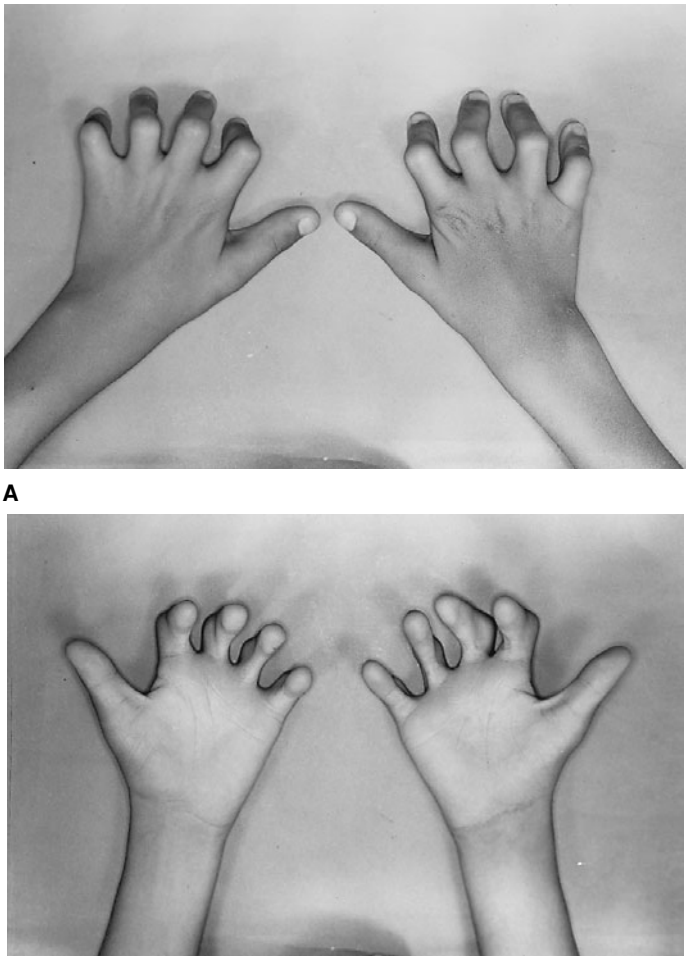
To be excluded are various camptodactyly syndromes.



A B

Fig. 29–26. *Faciothoracoskeletal syndrome*. (A,B) Two brothers with long thin face, hypertelorism, short upslanting palpebral fissures, malar hypoplasia, long neck, and pectus excavatum. (From A Richieri-Costa et al, Am J Med Genet 49:224, 1994.)

Fig. 29–27. *Faciothoracoskeletal syndrome*. (A,B) Brachycamptodactyly. (From A Richieri-Costa et al, Am J Med Genet 49:224, 1994.)



A

B

Reference (Faciothoracoskeletal syndrome)

1. Richieri-Costa A et al: Newly recognized autosomal recessive faciothoracoskeletal syndrome. Am J Med Genet 49:224–228, 1994.

Craniofacial dysostosis, limb malformations, and omphalocele

Gardner et al (1) reported a combination of a craniofacial dysostosis, unusual facies, limb malformations, and omphalocele.

The face was remarkably striking with severe hypertelorism and frontal bossing. The mouth was very small and in-drawn. The nasal bridge was depressed. A nevus flammeus extended from the glabellar area to the forehead. A tag was present in the philtral area. Colobomata were evident in the lower eyelids and nasal alae. The eyes bulged, the corneas were cloudy, and the sclera encroached on the cornea. A bald patch was noted at the vertex of the scalp. The palate was cleft (Fig. 29–28).

The limbs were asymmetrically shortened, and the hands were in ulnar deviation. Fingers 3–4 on one hand were fused and overlapped by other digits. Talipes and variable syndactyly of toes were present. The thorax was small and the sternum short.

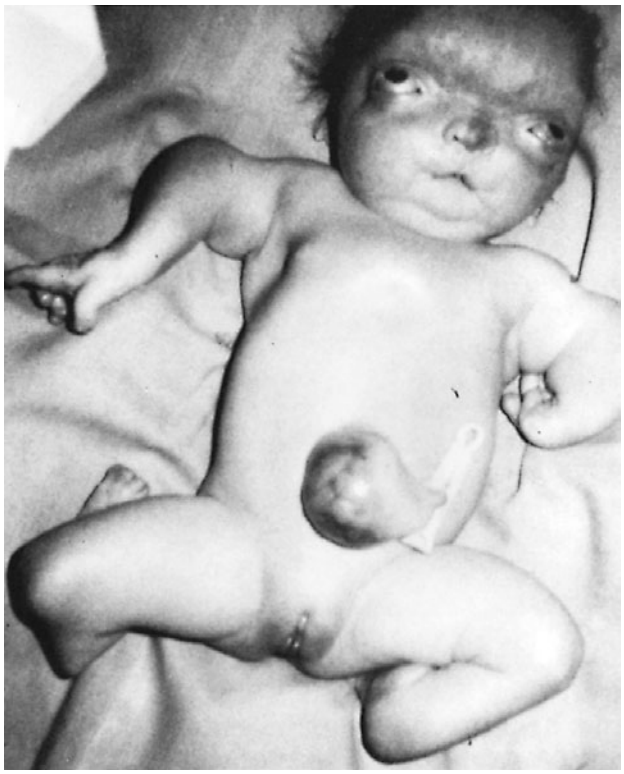
Other anomalies were omphalocele, anteriorly displaced anus, and bicornuate uterus.

Radiographic changes included indented occiput, poorly ossified skull, variably sized vertebral bodies, irregular ribs, and variably deformed long bones.

Reference (Craniofacial dysostosis, limb malformations, and omphalocele)

1. Gardner RJM et al: Syndrome of a craniofacial dysostosis, limb malformation, and omphalocele. Am J Med Genet 36:133–136, 1990.

Fig. 29–28. *Craniofacial dysostosis, limb malformations, and omphalocele*. Note marked hypertelorism, frontal bossing, small mouth, depressed nasal bridge, nevus flammeus of glabellar area, colobomata of lower eyelids, and exophthalmos. Limbs are asymmetrically shortened, and hands show ulnar deviation. Talipes is marked. (From RJ Gardner et al, Am J Med Genet 36:133, 1990.)



Giannotti syndrome

A progeroid syndrome with unusual facies and hand anomalies was described in a father and son by Giannotti et al (1) in 1997.

The phenotype appeared quite distinctive with sparse subcutaneous fat, prominent veins, blepharophimosis, extremely prominent nose, short philtrum, thin lips, and prominent ears. The son exhibited microcephaly, congenital heart anomaly, and bilateral conductive hearing loss.

In the son, the fingers were long with partial cutaneous syndactyly of fingers 2–3 and clinocamptodactyly of 5. Hallux valgus was also noted. In the father, radial deviation of the third fingers with ulnar deviation of the fourth fingers and camptodactyly of the fifth fingers were observed.

Reference (Giannotti syndrome)

1. Giannotti A et al: Progeroid syndrome with characteristic facial appearance and hand anomalies in father and son. Am J Med Genet 73:227–229, 1997.

Brachycephaly, hearing loss, cataracts, and mental retardation (Fine-Lubinsky syndrome)

In 1993, Suthers et al (8) reported a single patient with brachycephaly without craniosynostosis, hearing loss, cataract, dysmorphic face, and developmental delay. Aymé and Philip (1,2) reported a similar patient and suggested that the cases reported by Fine and Lubinsky (3) and Preus et al (7) had the same entity. Gripp et al (4,5) described two other cases as having a possible "new" syndrome. All cases were singletons, no consanguinity was reported, and chromosome studies were normal.

Clinical features include borderline growth, both prenatal and postnatal, small or large head circumference, and a remarkable "Down syndrome-like" face (Fig. 29–29): flat, brachycephalic, flat nasal bridge that becomes prominent later on, shallow orbits, hypertelorism, upward-slanting palpebral fissures in infancy but downward-slanting at older ages, small nose, thin nares, long philtrum, thin upper vermilion border, small mouth, and small, low-set, and posteriorly rotated ears. Two patients had cleft palate (3,7). The auditory canals may be very narrow. All had bilateral congenital hearing loss, and most, a congenital dense zonular cataract.

The thorax may show pectus carinatum superiorly and excavatum inferiorly. One patient had diaphragmatic hernia and idiopathic pericardial effusions (4), another, pyloric stenosis and unilateral hydronephrosis (8). Inverted and widely set nipples (1,7), underdeveloped breast in adolescence (1), and shawl scrotum (8) have been reported. Other features are radioulnar synostosis, camptodactyly of fifth fingers, and dystrophic nails. Central nervous system anomalies include enlarged cerebral ventricles with normal pressure, EEG anomalies, and agenesis of callosal body (3). All were hypotonic and had mild to severe mental retardation. Radiologic changes include fusion and sclerosis along the metopic sutures, no true craniosynostosis, very large frontal sinuses (1), slender long bones, carpal synostosis, and brachydactyly. Two patients (4) developed idiopathic chondrolysis of the hip.

The differential diagnosis includes *Martsolf syndrome* (6), *Tuomaala-Haapanen syndrome* (9), *maxillonasal dysplasia*, and Insley-Astley syndrome.

References [Brachydactyly, hearing loss, cataracts, and mental retardation (Fine-Lubinsky syndrome)]

1. Aymé S, Philip N: Fine-Lubinsky syndrome: A fourth patient with brachycephaly, deafness, cataract, microstomia, and mental retardation. Clin Dysmorphol 5:55–60, 1996.

2. Aymé S, Philip N: Apparently new syndrome of congenital cataracts, sensorineural deafness, Down syndrome-like facial appearance, short stature, and mental retardation. Am J Med Genet 70:333, 1997.

3. Fine BA, Lubinsky M: Craniofacial and CNS anomalies with body asymmetry, severe retardation, and other malformations. J Clin Dysmorphol 1(4):6–9, 1983.

4. Gripp KW et al: Apparently new syndrome of congenital cataracts, sensorineural deafness, Down syndrome-like facial appearance, short stature, and mental retardation. Am J Med Genet 61:382–386, 1996.

A B C

Fig. 29–29. *Fine-Lubinsky syndrome*. (A,B) Note triangular face, high frontal hairline, hypertelorism, flat midface, and microstomia. (C) Note brachycephaly, verticalization of skull base, and lifting of orbital roof. (A,B courtesy of S Aymé, Villejuif, France. C from S Aymé and N Philip, Clin Dysmorphol 5:55, 1996.)

5. Gripp KW et al: Reply to Aymé and Philip. Am J Med Genet 70:334–335, 1997.
6. Hennekam RCM et al: Martsolf syndrome in a brother and a sister: Clinical features and pattern of inheritance. Eur J Pediatr 147:539–543, 1988.
7. Preus M et al: Sensorineural hearing loss, small facial features, submucous cleft palate, and myoclonic seizures. J Clin Dysmorphol 2:30–31, 1984.
8. Suthers GK et al: A distinctive syndrome of brachycephaly, deafness, cataracts, and mental retardation. Clin Dysmorphol 2:342–345, 1993.
9. Tuuomaala P, Haapanen E: Three siblings with similar anomalies in the eyes, bones, and skin. Acta Ophthalmol 46:365–371, 1968.

Hypertelorism, tetralogy of Fallot, and hypospadias

Farag and Teebi (1) reported an autosomal recessive syndrome in an inbred Arab family. The syndrome, present in four members of the extended kindred (three male sibs and female cousin), consisted of early cyanosis, feeding problems, hypertelorism, epicanthic folds, narrow palpebral fissures, flat nasal bridge, dysmorphic pinnae, hypospadias, tetralogy of Fallot and other cardiac defects, and mild mental retardation.

One must exclude *Opitz BBB/G syndromes*.

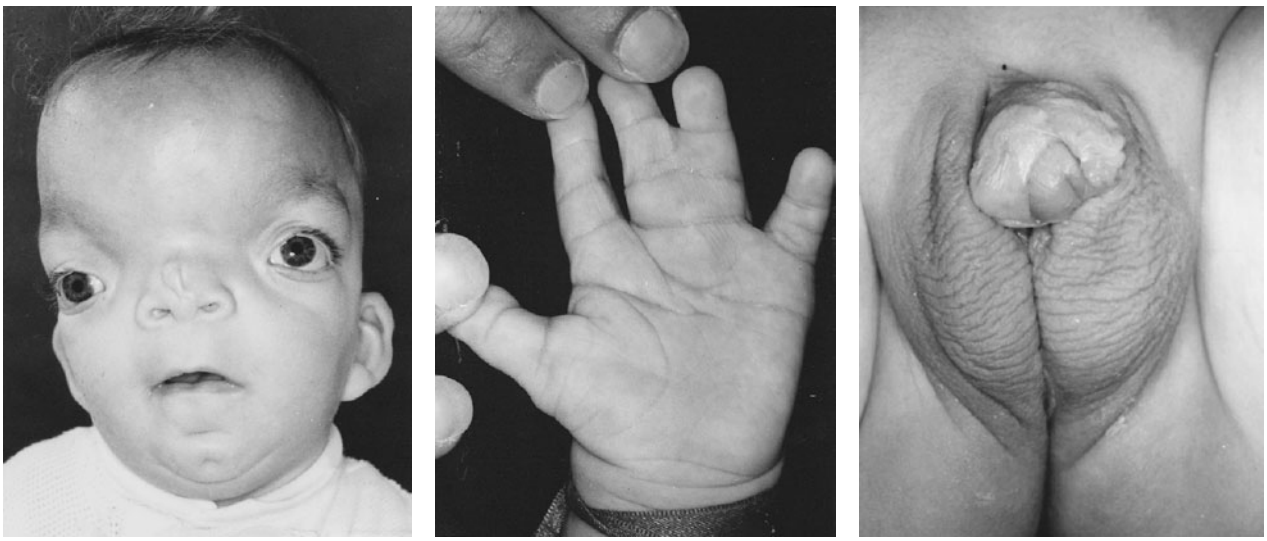
Reference (Hypertelorism, tetralogy of Fallot, and hypospadias)

1. Farag TI, Teebi AS: Autosomal recessive inheritance of hypertelorism, hypospadias and tetralogy of Fallot? Am J Med Genet 35:516–518, 1990.

Hypertelorism, hypospadias, polydactyly syndrome (Naguib and Richieri-Costa syndrome)

Naguib (1), in 1988, reported three sibs with marked hypertelorism, downslanting palpebral fissures, ptosis of eyelids, broad nasal bridge and tip with midline groove, dysmorphic pinnae, variable soft tissue syndactyly of fingers 2– 4, hypospadias, shawl scrotum, and normal psychomotor development. There was parental consanguinity.

Richieri-Costa et al (2), in 1989, reported an unusual form of acrofronto-facial-nasal dysostosis in which sibs exhibited microbrachycephaly, wide forehead, marked hypertelorism, broad nose with midline groove, soft tissue syndactyly of fingers 3–4, broad thumb and hallux, hypospadias and shawl scrotum (Fig. 29–30). There was parental consanguinity.



A B C

Fig. 29–30. *Hypertelorism, hypospadias, polydactyly syndrome (Naguib and Richieri-Costa syndrome)*. (A–C) Note wide forehead, marked hypertelorism, broad nose with midline groove, syndactyly of fingers 3–4, and hypospadias with shawl scrotum.

Teebi (3) suggested that they had the same disorder. There is some resemblance to *Aarskog syndrome*.

Inheritance is autosomal recessive.

References [Hypertelorism, hypospadias, polydactyly syndrome (Naguib and Richieri-Costa syndrome)]

1. Naguib KK: Hypertelorism, proptosis, ptosis, polysyndactyly, hypospadias and normal height in 3 sibs, a new syndrome? Am J Med Genet 29:35–41, 1988.
2. Richieri-Costa A et al: Autosomal recessive acro-fronto- facio-nasal dysostosis associated with genitourinary anomalies. Am J Med Genet 33:121–124, 1989.
3. Teebi AS: Naguib–Richieri-Costa syndrome: Hypertelorism, hypospadias, and polydactyly. Am J Med Genet 44:115–116, 1992.

Hyperparathyroidism and multiple ossifying fibromas of the jaws

The association of hyperparathyroidism and multiple ossifying fibromas of the jaws was first pointed out by Jackson (5) in 1958. Originally thought to be related to MEN1, no pancreatic islet cell or pituitary lesions were found. Several other families have been described (1,2,4,6–15).

Solitary (rarely multiple) parathyroid adenomas with associated hypercalcemia is the rule. The adenomas generally present in the fourth decade giving rise to hypercalcemia and renal stones. However, they have been reported in children as young as 10 years (11). Occasionally, they may recur (5,8,9). Some are cystic (9). Parathyroid carcinomas have been reported in 6 of 16 families (1,7,10,12,13,15). Ultrasonography and scintigraphy can be utilized in diagnosis (4).

Multiple ossifying fibromas are located in the premolar and molar areas of the mandible and, less often, the maxilla. They present usually during adolescence and have been detected in approximately 50% of the affected. Unrelated to the "brown tumors" of hyperparathyroidism, the multiple ossifying and/or cementifying fibromas appear and enlarge even though the hypercalcemia is corrected by surgical removal of parathyroid adenomas.

Microscopically, the jaw lesions are multiple and fibroosseous with irregular trabeculae. Multinucleated giant cells are absent, in contrast to the "brown tumors," which are usually single and loaded with giant cells. The fibroosseous lesions do not heal after the parathyroid adenoma has been removed.

Other aspects are severe recurring pancreatitis (6). Wilms tumor may be associated, presenting as late as 50 years (4,7,11–13). Renal hamartomas and cystic kidney disease have been described (12).

Inheritance is autosomal dominant (6). The *HRPT2* gene maps to 1q21–q31 (3,11–13).

Differential diagnosis would include multiple endocrine neoplasia syndromes, types 1 and 2A.

References (Hyperparathyroidism and multiple ossifying fibromas of the jaws)

1. Dinnen JS et al: Parathyroid carcinoma in familial hyperparathyroidism. J Clin Pathol 30:966–975, 1977.
2. Firat D, Stutzman L: Fibrous dysplasia of the bone: Review of twenty-four cases. Am J Med 44:421–429, 1968.
3. Hobbs MR et al: Hyperparathyroidism-jaw tumor syndrome: The HRPT2 locus is within a 0.7cM region on chromosome 1q. Am J Hum Genet 64:518–525, 1999.
4. Inoue H et al: Familial hyperparathyroidism associated with jaw fibroma: Case report and literature review. Clin Endocrinol 43:225–229, 1995.
5. Jackson CE: Hereditary hyperparathyroidism associated with recurrent pancreatitis. Ann Intern Med 49:829–836, 1958.
6. Jackson CE et al: Hereditary hyperparathyroidism and multiple ossifying jaw fibromas: A clinically and genetically distinct syndrome. Surgery 108:1006–1013, 1990.
7. Kakinuma A et al: Familiar primary hyperparathyroidism complicated with Wilms tumor. Intern Med 33:123–126, 1994.
8. Kennett S, Pollick H: Jaw lesions in familial hyperparathyroidism. Oral Surg 31:502–510, 1971.
9. Mallette LE et al: Familial cystic parathyroid adenomatosis. Ann Intern Med 107:54–60, 1987.
10. Rosen IB, Palmer JA: Fibroosseous tumors of the facial skeleton in association with primary hyperparathyroidism: An endocrine syndrome or coincidence? Am J Med Genet 142:494– 498, 1981.
11. Szabó J et al: Hereditary hyperparathyroidism-jaw tumor syndrome: The endocrine tumor gene HRPT2 maps to chromosome 1q21–q31. Am J Med Genet 56:944–950, 1995.
12. Teh BT et al: Autosomal dominant primary hyperparathyroidism and jaw tumor syndrome associated with renal hamartomas and cystic kidney disease. Linkage to 1q21–q32 and loss of the wild type allele in renal hamartomas. J Clin Endocrinol Metab 81:4204–4211, 1996.
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15. Yamaguchi K et al: Familial hyperparathyroidism. Jap J Clin Med 53:895–898, 1995.

Mutilating keratopachydermia, hypotrichosis, acrodermatitis enteropathica-like lesions, and sensorineural hearing loss (Olmsted syndrome)

Olmsted (15), in 1927, first described a syndrome of infantile onset of progressive hyperkeratosis of palmar and plantar surfaces and flexor areas of extremities. About 20 examples have subsequently been reported (1–22).

Beginning in early childhood, hyperkeratosis is noted around body orifices, periorally, in the groin, and on the inner thighs resembling acrodermatosis enteropathica (22). Oral and perioral hyperkeratosis may be marked (4,17,21) (Fig. 29–31A,B). The keratoses are diffuse, symmetric, and sharply marginated. They lead to flexion contractures of the fingers (Fig. 29–31C,D). There is associated hypohidrosis. Linear papules are observed at friction sites. Nail dystrophy may be mild to severe. The distal phalanges of the extremities undergo dissolution (Fig. 29–31E,F). Hypotrichosis or generalized alopecia may be present from birth (1,9,13,17,19). The joints may be excessively lax (Fig. 29–31G).

Hearing loss has been noted at higher frequencies.

It has been suggested that there is an alteration in keratin expression (failure of switching from keratins 5 and 14 to keratins 1 and 10 (11).

Involvement of a mother and son (1,10) and identical twins (3) suggests autosomal dominant inheritance.

Most examples have been misdiagnosed as acrodermatitis enteropathica or any of various keratopachydermias. Vohwinkel syndrome must be excluded.

References [Mutilating keratopachydermia, hypotrichosis, acrodermatitis enteropathica-like lesions, and sensorineural hearing loss (Olmsted syndrome)]

1. Atherton DJH et al: Mutilating palmoplantar keratoderma with periorificial keratotic plaques (Olmsted syndrome). Br J Dermatol 122:245–252, 1990.
2. Barnett JH, Estes SA: Multiple epitheliomata cuniculate occurring in a mutilating keratoderma. Cutis 35:345–347, 1985.
3. Cambiagi S et al: Olmsted syndrome in twins. Arch Dermatol 131:738–739, 1995.
4. Costa OG: Acroceratoses, Minas Geraes, Belo Horizonte, Brazil, 1962.
5. Frias-Iniesta J et al: Olmsted syndrome. Br J Dermatol 136:935–938, 1997.
6. Georgü A et al: Olmsted-Syndrom. Hautarzt 40:708–712, 1989.
7. Harms M et al: Syndromes de Olmsted. Dermatologica 171:140–141, 1985.
8. Hausser J et al: Olmsted-Syndrom. Erfolgrische Therapie durch Behandlung mit Etretinate. Hautarzt 44:394–400, 1993.
9. Judge MR et al: Palmoplantar and periorificial keratoderma with corneal epithelial dysplasia: A new syndrome. Br J Dermatol 125:186–188, 1991.
10. Keir M: Keratodermia palmaris et plantaris. J R Soc Med 79:419–421, 1967.

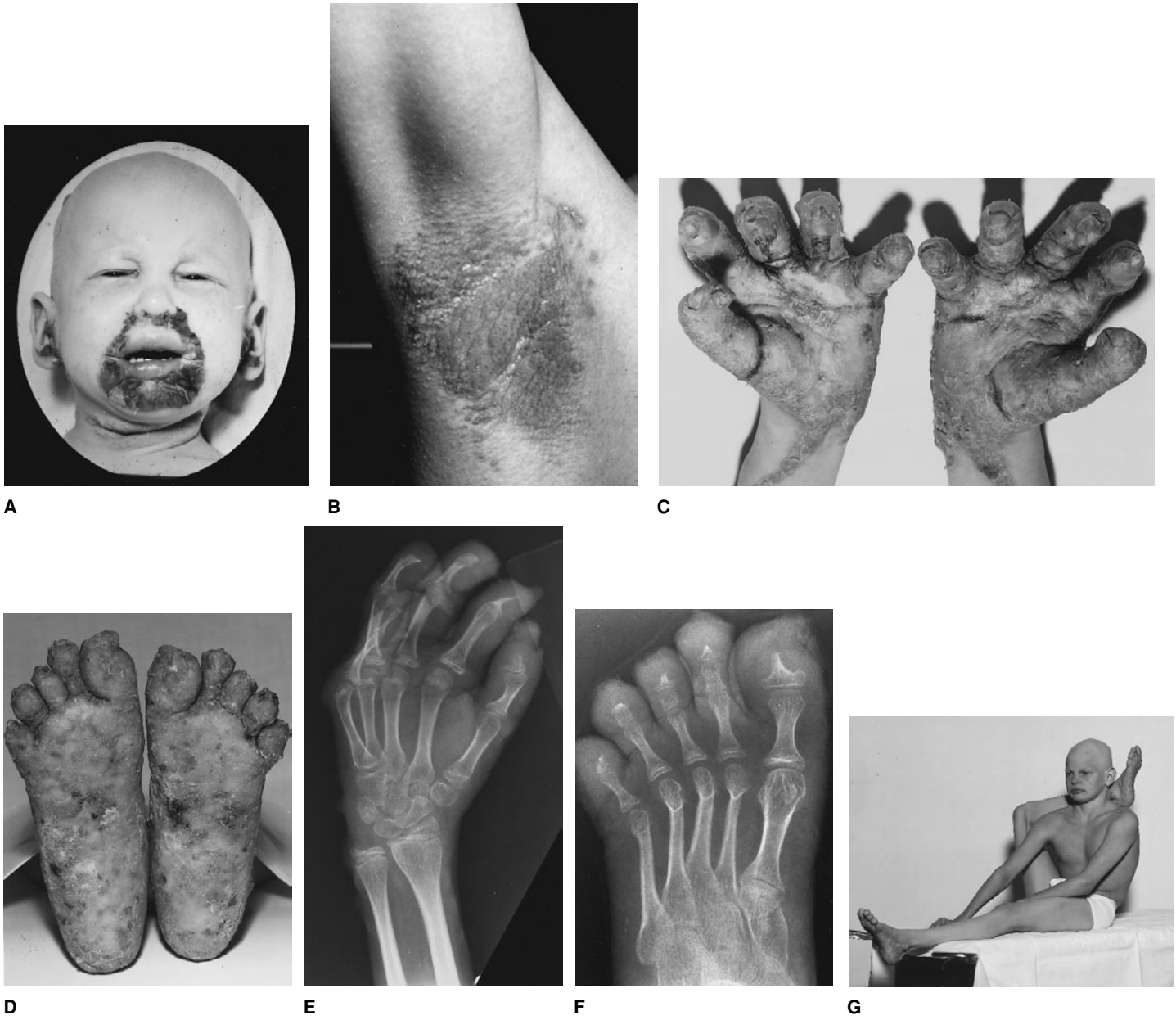

Fig. 29–31. *Mutilitating keratopachydermia, hypotrichosis, acrodermatitis enteropathica-like lesions, and sensorineural hearing loss (Olmsted syndrome).* (A) Acrodermatitis enteropathica-like changes around mouth, nose, ears at 2 years of age. (B–D) Involvement of hands, feet, and axilla at 21 years. Thick keratoderma with marked destruction of digits. Note sharp marginations at wrists with linear extension to forearms. (E,F) Severe osteoporosis with osteolysis of terminal phalanges and soft tissue swellings. (G) Large joints exhibit striking laxity. (C–G from Y Poulin et al, J Am Acad Dermatol 10:600, 1984.)

11. Kress DW et al: Olmsted syndrome. Case report and identification of a keratin abnormality. Arch Dermatol 132:797– 800, 1996.
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22. Wells BT, Winkelmann RK: Acrodermatosis enteropathica: Report of 6 cases. Arch Dermatol 84:40–52, 1961.

Congenital hypoparathyroidism, seizures, growth and mental retardation, and unusual facies

Richardson and Kirk (3), Sanjad et al (4), and Kalam and Hafeez (2) reported Saudi Arabian infants with congenital hypoparathyroidism, failure to thrive, growth and mental retardation, susceptibility to repeated

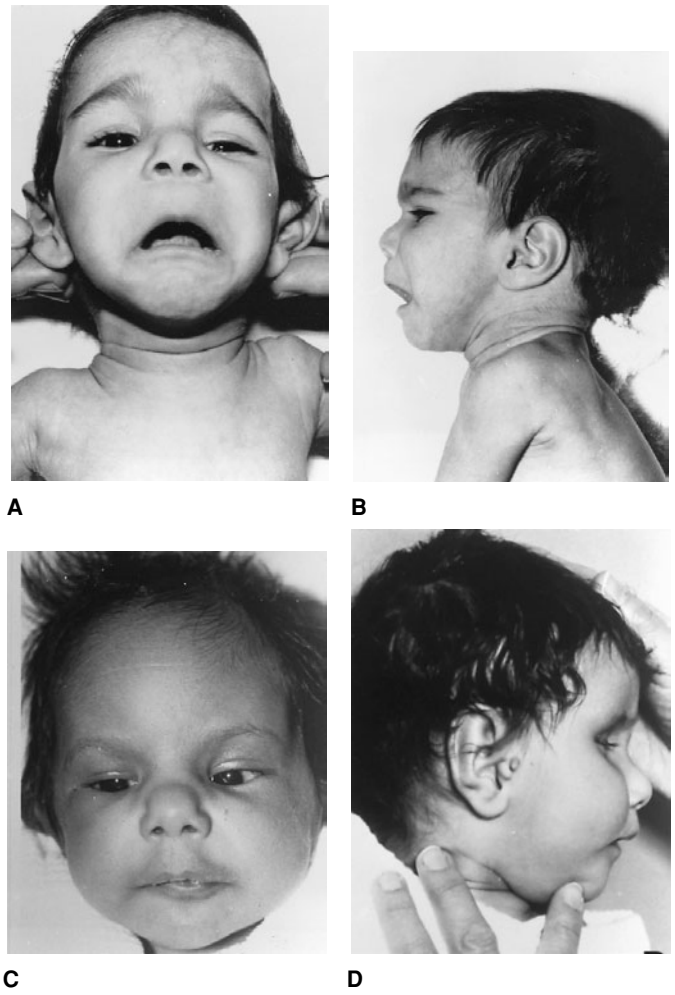


Fig. 29–32. *Congenital hypoparathyroidism, seizures, growth and mental retardation, and unusual facies*. (A–D) Frontal prominence, deep-set eyes, depressed nasal bridge, beaked nose, long philtrum with thin upper lip, large floppy pinnae, and micrognathia. (A,B from RJ Richardson and JM Kirk, Arch Dis Child 65:1113, 1990.)

life-threatening infections, and unusual facies. There were severe hypocalcemia, hyperphosphatemia, and normal response to vitamin D. An additional dozen cases were added by Hershkovitz et al (1).

The face was characterized by frontal prominence, deep-set eyes, depressed nasal bridge, beaked nose, long philtrum with thin upper lip, large floppy pinnae, bifid uvula, and micrognathia (Fig. 29–32). Low levels of insulinlike growth factor were noted by Hershkovitz et al (1).

Inheritance is autosomal recessive. Parental consanguinity has been noted in all three families.

One must exclude *DiGeorge sequence*, *del(10p) syndrome*, and *Kenny syndrome*.

References (Congenital hypoparathyroidism, seizures, growth and mental retardation, and unusual facies)

1. Hershkovitz E et al: The new syndrome of congenital hypoparathyroidism associated with dysmorphism, growth retardation, and developmental delay. Isr J Med Sci 31:293– 297, 1995.

2. Kalam MA, Hafeez W: Congenital hypoparathyroidism, seizure, extreme growth failure with developmental delay and dysmorphic features—another case of this new syndrome. Clin Genet 42:110–113, 1992.

3. Richardson RJ, Kirk JMW: Short stature, mental retardation and hypoparathyroidism: A new syndrome. Arch Dis Child 65:1113–1117, 1990.

4. Sanjad SA et al: A new syndrome of congenital hypoparathyroidism, seizures, growth failure, and dysmorphic features. Arch Dis Child 66:193–196, 1991.

Hypohidrotic ectodermal dysplasia-type Viljoen-Winship

Viljoen and Winship (1) reported a new tricho-onycho-hypohidrotic ectodermal dysplasia characterized by primary interdigital webbing and camptodactyly of fingers and toes, nasolacrimal duct atresia, sparse eyelashes, eyebrows, and scalp hair, brittle dysplastic nails, and hypohidrosis. Pili torti was demonstrated. Neither clefting nor dental anomalies were observed (Fig. 29–33).

In addition to the host of disorders excluded in their differential diagnosis, one must also exclude *Hay-Wells syndrome*.

Reference (Hypohidrotic ectodermal dysplasia-type Viljoen-Winship)

1. Viljoen DL, Winship WS: A new form of hypohidrotic ectodermal dysplasia. Am J Med Genet 31:25–32, 1988.

Hypotrichosis, syndactyly, and retinal degeneration

Albrectsen and Svendsen (1) noted male and female sibs with severe hypotrichosis, retinal degeneration, and strabismus. The female had syndactyly of fingers 3–4; the boy had syndactyly of fingers 4–5, ectrodactyly, and terminal aplasia of digits (Fig. 29–34).

The parents were consanguineous.

Reference (Hypotrichosis, syndactyly, and retinal degeneration)

1. Albrectsen B, Svendsen IB: Hypotrichosis, syndactyly, and retinal degeneration in two siblings. Acta Derm Venereol 36:96–101, 1956.

Macrosomia, obesity, macrocephaly, and ocular abnormalities (MOMO) syndrome

Moretti-Ferreira et al (1) described the occurrence of overgrowth (*M*acrosomia, *O*besity, *M*acrocephaly, and *O*cular abnormalities). Eye anomalies included retinal coloboma and nystagmus. Zannolli et al (2) reported another example.

Patients exhibited overgrowth but low birthweight, obesity, eye problems, and moderate psychomotor delay in childhood. Head circumference was above the 97th centile.

To be excluded are the *Simpson-Golabi-Behmel syndrome* and *macrosomia, microphthalmos, cleft palate, and early infant death*.

References [Macrosomia, obesity, macrocephaly, and ocular abnormalities (MOMO) syndrome)]

1. Moretti-Ferreira D et al: Macrosomia, obesity, macrocephaly, and ocular abnormalities (MOMO syndrome) in two unrelated patients: Delineation of a newly recognized overgrowth syndrome. Am J Med Genet 46:555–558, 1993.

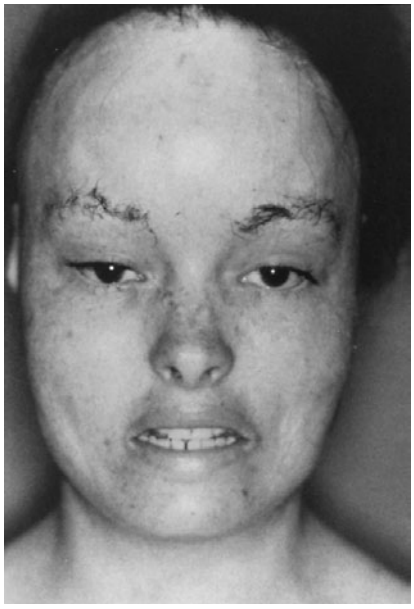
2. Zannolli R et al: MOMO syndrome: A possible third case. Clin Dysmorphol 9:281–284, 2000.

Oto-facio-osseous-gonadal syndrome

Da Silva (1), in 1997, described two male sibs and possibly a female sib, the product of a consanguineous union, with short stature, brachycephaly with prominent forehead, flat midface, downslanting palpebral fissures, low nasal root, hypoplastic alae and round nasal tip, prominent low-set pinnae, sensorineural hearing loss, narrow thorax, genua valga, inguinal hernia, and cryptorchidism (Fig. 29–35).

Radiographs showed Wormian bones, fusion of carpal bones, and delayed bone age.

There was some resemblance to *otopalatodigital syndrome*.



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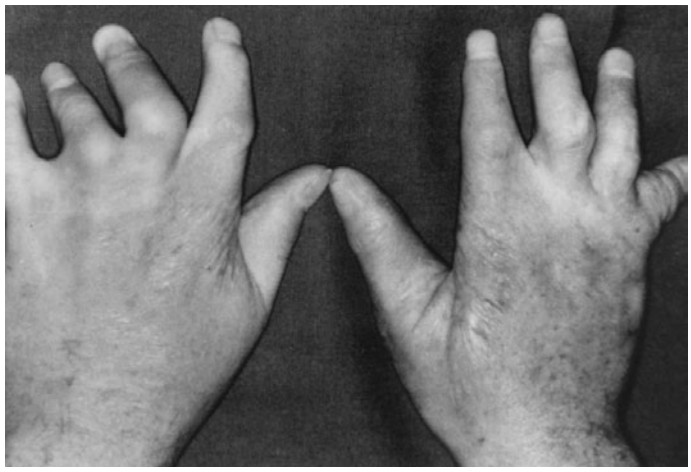

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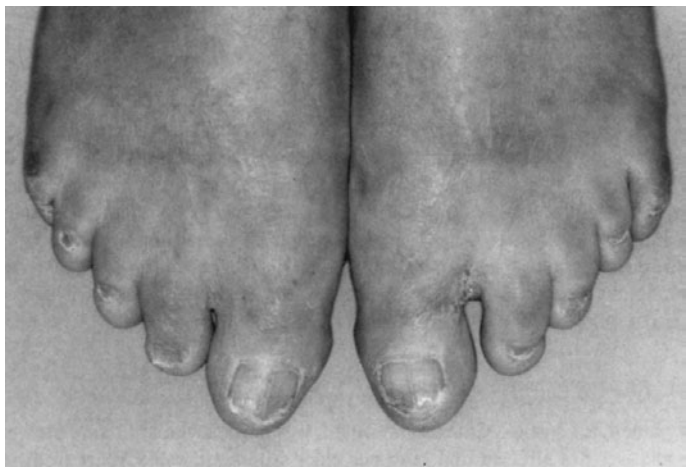


C

Fig. 29–33. *Hypohidrotic ectodermal dysplasia-type Viljoen-Winship*. (A) Sparse, wiry scalp and eyebrows, narrowed palpebral fissures, and mild microstomia. (B) Mild syndactyly and joint contractures. (C) Mild syndactyly and dysplasia of nails. (From DL Viljoen and WS Winship, Am J Med Genet 31:25, 1988.)

Reference (Oto-facio-osseous-gonadal syndrome)

1. da Silva EO et al: Oto-facio-osseous-gonadal syndrome: A new form of syndromic deafness. Clin Genet 52:51–55, 1997.

Mutchinick syndrome

Mutchinick (2), in 1972, described two sisters with microcephaly, high forehead, prominent nose and nasal bridge, large mouth, thin upper lip, dental malocclusion, protruding low-set, poorly differentiated pinnae, and prognathism. There was mental retardation and speech impairment. Three similarly affected brothers were reported by Doerfler et al (1). An isolated example is that of Tonoki et al (3).

While there was consanguinity in the first family, none was evident in the second. Inheritance is probably autosomal recessive.

References (Mutchinick syndrome)

1. Doerfler W et al: Three brothers with mental and physical retardation, hydrocephalus, microcephaly, internal malformations, speech disorder, and facial anomalies: Mutchinick syndrome. Am J Med Genet 73:210–216, 1997.
2. Mutchinick O: A syndrome of mental and physical retardation, speech disorders, and peculiar facies in two sisters. J Med Genet 9:60–63, 1972.
3. Tonoki H et al: Mutchinick syndrome in a Japanese girl. Am J Med Genet 83:96–99, 1999.

Odonto-tricho-ungual-digital-palmar syndrome

Mendoza and Valiente (1), in 1997, described autosomal dominant inheritance in a five-generation kindred involving 20 individuals. Findings included natal teeth, trichodystrophy, prominent interdigital folds, nail dystrophy, and transverse palmar creases. The patients also exhibited hypoplasia of the first metacarpal and metatarsal bones and distal phalanges of the toes (Fig. 29–36).

Reference (Odonto-tricho-ungual-digital-palmar syndrome)

1. Mendoza HR, Valiente MD: A newly recognized autosomal dominant ectodermal dysplasia syndrome: The odonto-tricho-ungual-digital-palmar syndrome. Am J Med Genet 71:144–149, 1997.

Hypertelorism, upper eyelid colobomas, mixed hearing loss, and hypospadias

Balci et al (1), in 1998, reported two brothers with hypertelorism, upper eyelid colobomas, saddle nose deformity, wide bulbous nose with dimpled tip, midfacial hypoplasia, mandibular prognathism, prominent eyes, mixed hearing loss, and hypospadias. Cranial sutures were found to be open at 17 years in one brother (Fig. 29–37).

The parents were first cousins. Autosomal recessive inheritance is surmised.

Possibly related is a syndrome of hypertelorism, unilateral upper eyelid coloboma, aberrant anterior hairline pattern, and anal anomalies described by Marles et al (2) in six Manitoba Indian children from four related families. One of the children had unilateral anophthalmia. Two had nasolacrimal duct obstruction, three a grooved nasal tip, and three anal stenosis and/or anteriorly displaced anus.

To be excluded are *cryptophthalmos, frontonasal malformation, oculo-auriculo-vertebral spectrum, cat eye syndrome,* and *Lenz microphthalmia*.

References (Hypertelorism, upper eyelid colobomas, mixed hearing loss, and hypospadias)

1. Balci S et al: Two brothers with hypospadias, hypertelorism, upper coloboma and mixed type hearing loss: A new syndrome. Clin Genet 54:440–442, 1998.
2. Marles SL et al: New familial syndrome of unilateral upper eyelid coloboma, aberrant anterior hairline pattern, and anal anomalies in Manitoba Indians. Am J Med Genet 42:793–799, 1992.

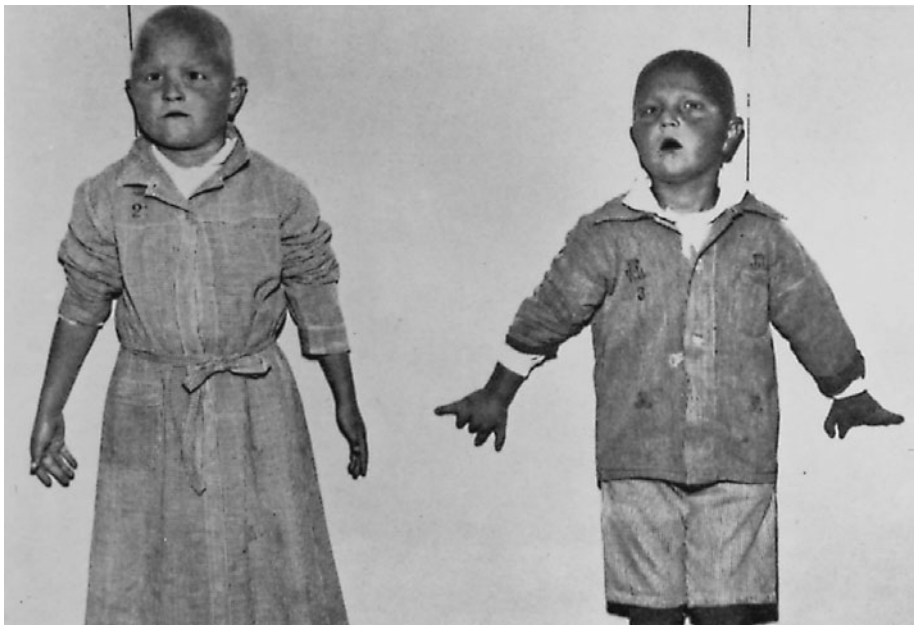
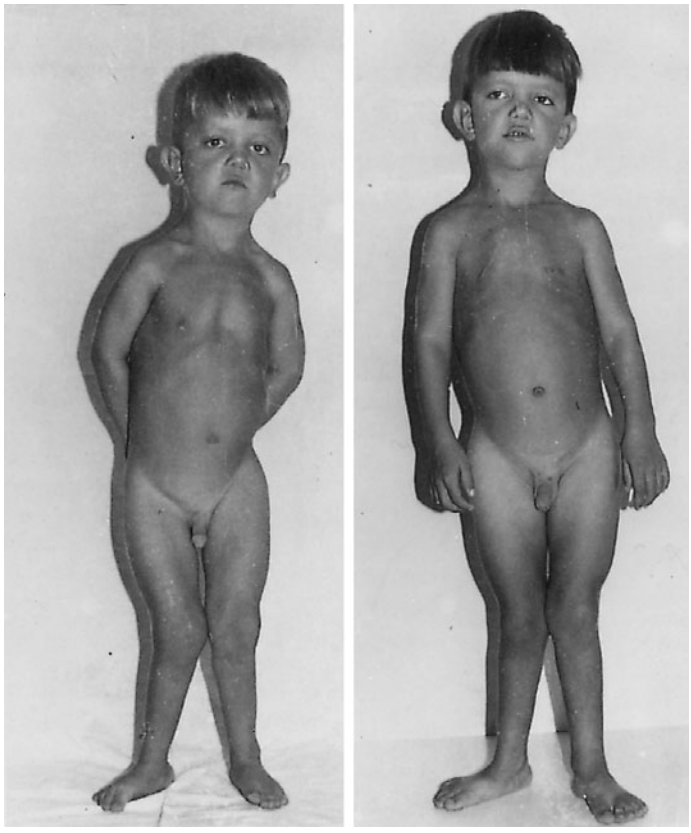


Fig. 29–34. *Hypotrichosis, syndactyly, retinal degeneration*. Male and female sibs with marked hypotrichosis, retinal degeneration, strabismus, syndactyly, and terminal aplasia of digits. The boy has unusual ectrodactyly and terminal aplasia of digits. (From B Albrechtsen and IB Svendsen, Acta Derm Venereol 36:96, 1956.)

Pseudotrisomy 13 (holoprosencephaly-polydactyly syndrome)

Cohen and Gorlin (5), in 1991, proposed the term *pseudotrisomy 13* to designate infants that resembled trisomy 13 but had normal karyotypes.

Fig. 29–35. *Oto-facio-osseous-gonadal syndrome*. (A,B) Brachycephaly, flat midface, downslanting palpebral fissures, low nasal root, round nasal tip, outstanding pinnae, narrow thorax, genu valgum, and pes planus. (From EO da Silva et al, Clin Genet 52:51, 1997.)



A B

Approximately 30 examples have been reported (1–7,9–25). A good summary is that of Ramos-Arroyo et al (21).

Inheritance is uncertain. Sibs have been reported (2,7,23) as has parental consanguinity (3,9,24). However, we find the dearth of affected sibs to be disconcerting for autosomal recessive inheritance. There is a 2.5M:1F predilection (21). Perhaps there is heterogeneity. All infants die within days of birth.

Central nervous system. All, by definition, have holoprosencephaly (alobar-55%, semilobar-25%, lobar-20%). Approximately 70% exhibit hydrocephalus, 15% have cerebellar hypoplasia, and 10% encephalocele.

Craniofacial findings. The face is that of holoprosencephaly with various degrees of hypotelorism (cyclopia-5%, cebocephaly-35%, premaxillary agenesis-60%). Microphthalmia is present in 55%, and the pinnae are dysplastic and/or low set in 40% (Fig. 29–38).

Musculoskeletal system. Postaxial polydactyly is present in over 80%, but the hands may be normal (21). Various foot deformities are seen in 20%. The limbs may be short (20%).

Genitourinary system. Micropenis or ambiguous genitalia is present in 65%, and cryptorchidism is noted in 10%. The uterus may be hypoplastic or duplicated or bicornuate. Renal agenesis is evident in 20%.

Other findings. Miscellaneous findings include lung malsegmentation (25%), adrenal hypoplasia (25%), anal atresia (15%), and gut malformation (10%).

Diagnosis. One must obviously exclude *trisomy 13*. There is similarity to *hydrolethalus syndrome* and *Dincsoy syndrome* (midline malformations, limb abnormalities such as midshaft tibial notch, camptodactyly and overlapping fingers, and hypopituitarism (8).

References [Pseudotrisomy 13 (holoprosencephaly-polydactyly syndrome)]

1. Amor DJ, Woods CG: Pseudotrisomy 13 syndrome in siblings. Clin Dysmorphol 9:115–118, 2000.

1a. André SA et al: Holoprosencéphalie, polydactylie, cardiopathie: Nouveau syndrome ou un nouveau cas d'hydrolethalus? J Genet Hum 36:463–468, 1988.

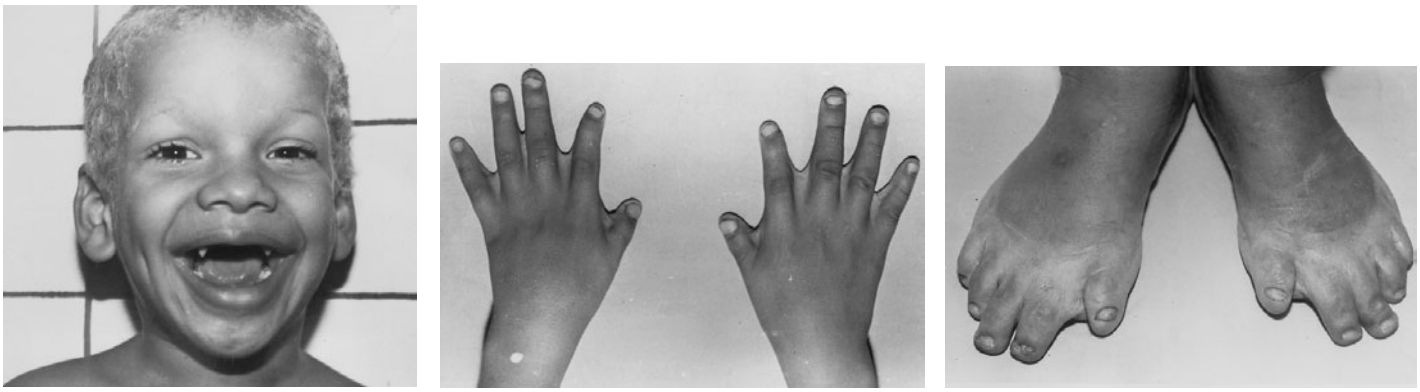


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Fig. 29–36. *Odonto-tricho-ungual-digital-palmar syndrome*. (A) Note strawlike discolored hair. Natal teeth were present in this 2 1/2 year old male but were lost. The lips are thick. (B) There is generalized brachydactyly and syndactyly. (C) A similar change was noted in the feet of the mothers. (From HR Mendoze, MD Valiente, Am J Med Genet 71:144, 1997.)

2. Atkin JF: A new syndrome with cyclopia and trisomy 13 features. Am J Hum Genet (Suppl) 43:A36, 1988.
3. Bachman H et al: Holoprosencephaly and polydactyly: A possible expression of the hydrolethalus syndrome. J Med Genet 27:50–52, 1990.
4. Boles RG et al: Pseudo-trisomy 13 syndrome with upper limb shortness and radial hypoplasia. Am J Med Genet 44:638–640, 1992.
5. Cohen MM, Gorlin RJ: Pseudo-trisomy 13 syndrome. Am J Med Genet 39:332–335, 1991.
6. Cohen MM, Gorlin RJ: Problems in the delineation of pseudotrisomy 13 syndrome: Reply to Drs. Norman, Donnai, Martínez-Frías, Urioste, Martin, and Frias. Am J Med Genet 43:636– 638, 1992.
7. De Lozier CD et al: Holoprosencephaly-polydactyly syndrome. Affected brother and sister with a spectrum of anomalies. Genet Couns 3:57–60, 1992.
8. Dincsoy MY et al: Multiple congenital malformations in two sibs reminiscent of hydrolethalus and pseudotrisomy 13 syndromes. Am J Med Genet 56:317–321, 1995.
9. Donnai D et al: Letter to the editor: Smith-Lemli-Opitz syndromes: Do they include the Pallister-Hall syndrome? Am J Med Genet 28:741–743, 1987.
10. Donnai D: Stillborn white male–30 weeks (MG 2746). Proc Greenwood Genet Ctr 7:64–65, 1988.
11. Hennekam RCM et al: Familial holoprosencephaly, heart defects and polydactyly. Am J Med Genet 41:258–262, 1991.
12. Hewitt BG et al: Holoprosencephaly, polydactyly and normal chromosomes: Pseudo-trisomy 13? Clin Genet 36:141–143, 1989.
13. Higgins JV, Minnick MA: Pseudo-trisomy 13 syndrome: Prenatal findings in a family with two affected siblings. Am J Hum Genet (Suppl) 51:A257, 1992.
14. Leichtman LG et al: Anophthalmia, cleft lip/palate, facial anomalies, and CNS anomalies, and hypothalamic disorder in a newborn: A midline developmental field defect. Am J Med Genet 50:39–41, 1994.
15. Lieber E et al: Multiple malformation syndrome suggestive of Smith-Lemli-Opitz syndrome with holoprosencephaly in a 46,XY still-born infant. Am J Hum Genet (Suppl) 39:A269, 1986.
16. Lurie IW, Wulfsberg EA: The "holoprosencephaly-polydactyly" (pseudotrisomy 13) syndrome: Expansion of the phenotypic spectrum. Am J Med Genet 47:405–409, 1993.
17. Meinecke P: Holoprosencephaly, polydactyly and lethal outcome. Proc Greenwood Genet Ctr 8:78–79, 1988.

Fig. 29–37. *Hypertelorism, upper eyelid colobomas, mixed hearing loss, and hypospadias*. Two brothers with upper eyelid colobomas, hypertelorism, saddle nose with bulbous dimpled tip. One brother has prominent eyes. (From S Balci et al, Clin Genet 54:440–442, 1998.)

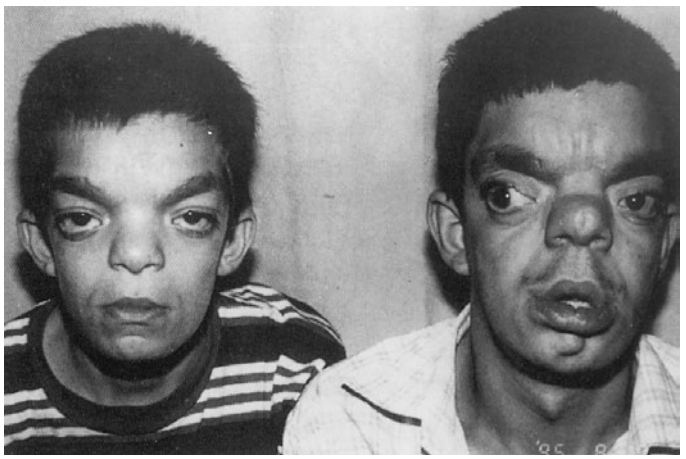
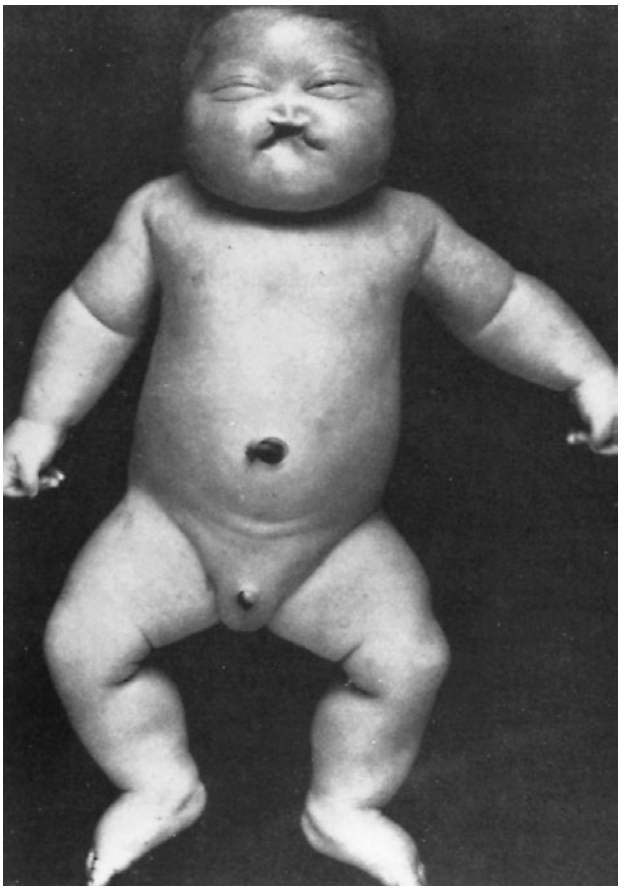


Fig. 29–38. *Pseudotrisomy 13 (holoprosencephaly-polydactyly syndrome)*. Infant with holoprosencephaly of premaxillary agenesis type and micropenis. (From U Rowlatt and S Pruzansky, Cleft Palate J 17:198, 1980.)



18. Moerman P, Fryns JP: Holoprosencephaly and postaxial polydactyly: Another observation. J Med Genet 25:501–504, 1988.
19. Norman AM, Donnai D: Letter to the editor: Response to Drs. Cohen and Gorlin. Am J Med Genet 38:336–337, 1991.
20. Ramaekers PR et al: Holoprosencephaly and postaxial polydactyly with normal chromosomes. Another observation of a new malformation syndrome; a case report. Eur J Obstet Gynecol Reprod Biol 36:161–165, 1990.
21. Ramos-Arroyo MA et al: Further delineation of pseudotrisomy 13 syndrome: A case without polydactyly. Am J Med Genet 50:177–179, 1994.
22. Rowlatt U, Pruzansky S: Premaxillary agenesis, ocular hypotelorism, holoprosencephaly, and extracranial anomalies in an infant with a normal karyogram. Cleft Palate J 17:197–204, 1980.
23. Seller MJ et al: Pseudotrisomy 13 and autosomal recessive holoprosencephaly. J Med Genet 30:970–971, 1993.
24. Verloes A et al: Holoprosencephaly-polydactyly ('pseudotrisomy 13') syndrome: A syndrome with features of hydrolethalus and Smith-Lemli-Opitz syndromes. A collaborative multicentric study. J Med Genet 28:297–303, 1991.
25. Young ID, Madders DJ: Unknown syndrome: holoprosencephaly, congenital heart defects and polydactyly. J Med Genet 24:714–716, 1987.

Rambam-Hasharon syndrome

Frydman et al (1) described two Arab males, the offspring of inbred families, with short stature, seizures, psychomotor retardation, cortical atrophy, hypotonia, recurrent infections with defective neutrophil chemotaxis, and Bombay phenotype.

In addition to microcephaly, there were low hairline, flat face and nasal bridge, hypertelorism, epicanthic folds, anteverted nostrils, large protruding tongue, and prominent mandible.

Reference (Rambam-Hasharon syndrome)

1. Frydman M et al: Ramban-Hasharon syndrome of psychomotor retardation, short stature, defective neutrophil motility and Bombay phenotype. Am J Med Genet 44:297–302, 1992.

Weaver-like syndrome

Teebi et al (1) noted two sibs of Bedouin origin with accelerated prenatal growth, psychomotor retardation, hypotonia, hernias, excess loose skin, and joint laxity. One had excess postnatal growth.

Craniofacial changes included thin hypopigmented scalp hair, frontal bossing, prominent metopic sutures, shallow orbits, hypertelorism, downslanting palpebral fissures, long grooved philtrum, large mouth, dysplastic teeth with serrated gingiva, dysmorphic pinnae, and short broad neck. Other findings were fetal finger pads, transverse palmar creases, short fifth fingers, joint laxity, talipes, pes planus, and long first toe.

Reference (Weaver-like syndrome)

1. Teebi AS et al: A new autosomal recessive disorder resembling Weaver syndrome. Am J Med Genet 33:479–482, 1989.

X-linked mental retardation, Prieto type

Prieto et al (2), in 1987, reported a large kindred with mental retardation with subcortical cerebral atrophy, febrile seizure, unusual facies, patellar luxation, clinodactyly, sacral dimple, and pale atrophied optic papillae.

Coxa valga was found in some of the affected.

Inheritance is clearly X-linked. The syndrome has been mapped to Xp11.22 (1,3).

The nose was prominent. A double row of lower incisors was reported but this may represent crowding or delayed shedding. The facies resembles that of *Rubinstein-Taybi syndrome*.

References (X-linked mental retardation, Prieto type)

1. Martinez F et al: Refined localization of the Prieto syndrome locus. Am J Med Genet 64:82, 1996.
2. Prieto F et al: X-linked dysmorphic syndrome with mental retardation. Clin Genet 32:326–334, 1987.
3. Watty A et al: Gene localization in a family with X-linked syndrome mental retardation (Prieto syndrome). Am J Med Genet 38:234–239, 1991.

Keppen-Lubinsky syndrome

L Keppen and M Lubinsky (personal communication, July, 2000) described a five-year-old child with severe developmental delay. Growth parameters were all above the 75th centile at birth, but fell to the 5th centile by 9 months. The facial appearance suggested severe lipodystrophy (Fig. 29–39). The skin was tightly adherent. The nose was small with no apparent subdural tissue. There was wrinkling of the forehead and chin, excess skin at the shoulders, and some laxness in the abdominal area.

Chromosomal analyses were normal. MRI of the brain was normal. There was no known parental consanguinity. *Beare-Stevenson syndrome* was excluded.

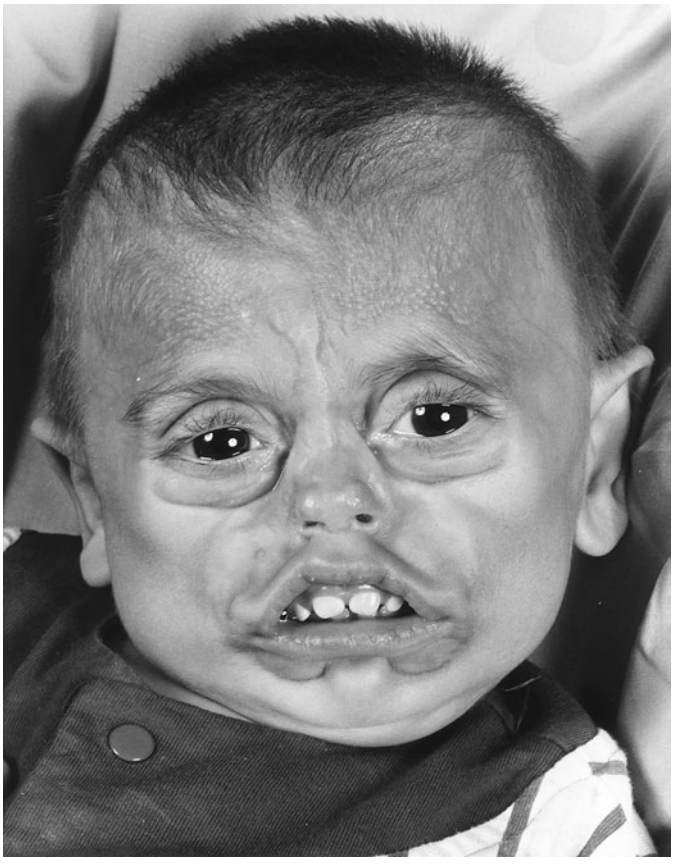
Hemangio-oculo-cardio-digital syndrome

Hall et al (1) reported three female infants with craniofacial defects (large anterior fontanel, eye colobomas, high nasal bridge, well-defined philtrum, multiple frenulae, micrognathia), congenital heart anomalies (truncus arteriosus, VSD), and digital anomalies (mild camptodactyly, missing nails of toes, digital hypoplasia). All had small, thick, low-set ears.

Two had hyperbilirubinemia and feeding and respiratory difficulties. All has extensive hemangiomas of the back.

Autosomal recessive inheritance with increased lethality has been posited.

Fig. 29–39. *Keppen-Lubinsky syndrome*. Five-year-old with severe developmental delay. Facial appearance suggests severe lipodystrophy. Skin tightly adherent, nose small with no apparent subdural tissue. Note wrinkling of forehead and chin. (Courtesy of L Keppen and M Lubinsky.)



Reference (Hemangio-oculo-cardio-digital syndrome)

1. Hall BD et al: Hemangio-oculo-cardio-digital syndrome: Three cases of a new syndrome with unusual back hemangioma. XXI David W. Smith Workshop on Malformations and Morphogenesis, La Jolla, California, August 2–5, 2000.

Hypoplastic/absent mandibular frenum, infantile hypertrophic pyloric stenosis, and Ehlers-Danlos syndromes

DeFelice et al (1,2) in a fascinating series of articles demonstrated that among 25 patients with hypertrophic pyloric stenosis, hypoplastic or absent mandibular frenum was noted in 92%, compared with 1.6% of 319 control infants. Further, they noted absence of both lingual and inferior labial frenum in Ehlers-Danlos syndromes I and III.

These observations need confirmation.

References (Hypoplastic/absent mandibular frenum, infantile hypertrophic pyloric stenosis, and Ehlers-Danlos syndromes)

1. DeFelice C et al: Hypoplastic or absent mandibular frenum: A new predictive sign of infantile hypertrophic pyloric stenosis. J Pediatr 136:408–410, 2000.
2. DeFelice C et al: Absence of the inferior labial and lingual frenula in Ehlers-Danlos syndrome. Lancet 357:1500–1502, 2001.

Chapter 30
Syndromes of the Eye

Rieger syndrome (hypodontia and primary mesodermal dysgenesis of the iris)

Hypodontia in combination with malformation of part of the anterior chamber of the eye was described as early as 1883 by Vossius (43). However, the condition was not recognized as a heritable syndrome until the report of Rieger (34), in 1935. The syndrome has been expanded to include absent maxillary incisor teeth, malformations of the anterior chamber of the eye (Rieger anomaly), and umbilical anomalies (11,22,38). Its frequency has been estimated as 1/200,000 population (2).

The syndrome has autosomal dominant inheritance (2,6,8,12,22) with almost complete penetrance and very variable expressivity (2). There is genetic heterogeneity (27). Two genes for Rieger syndrome have been mapped, a bicoid-related homeobox transcription factor gene, *RIEG1*, at 4q25–q26 (15,17,20,28,29,31,37,42) and another, *RIEG2*, at 13q14 (3,32,40). The former is near the epithelial growth factor gene (39). The two forms are called type 1 and type 2, respectively. Type 1 appears to be caused by haplotype insufficiency (36). There has been some difference in expression in monozygotic twins (18). Some evidence exists that mutations of *RIEG1* also cause Peters anomaly. Legius et al (27) demonstrated that the genetic defect in Rieger eye anomaly was different from that in Rieger syndrome. However, it is possible that this family had the 13q14 deletion. Dental and umbilical anomalies were not present. The type 2 gene in the mouse regulates lung asymmetry, cardiac positioning, and pituitary and tooth morphogenesis (28a,28b).

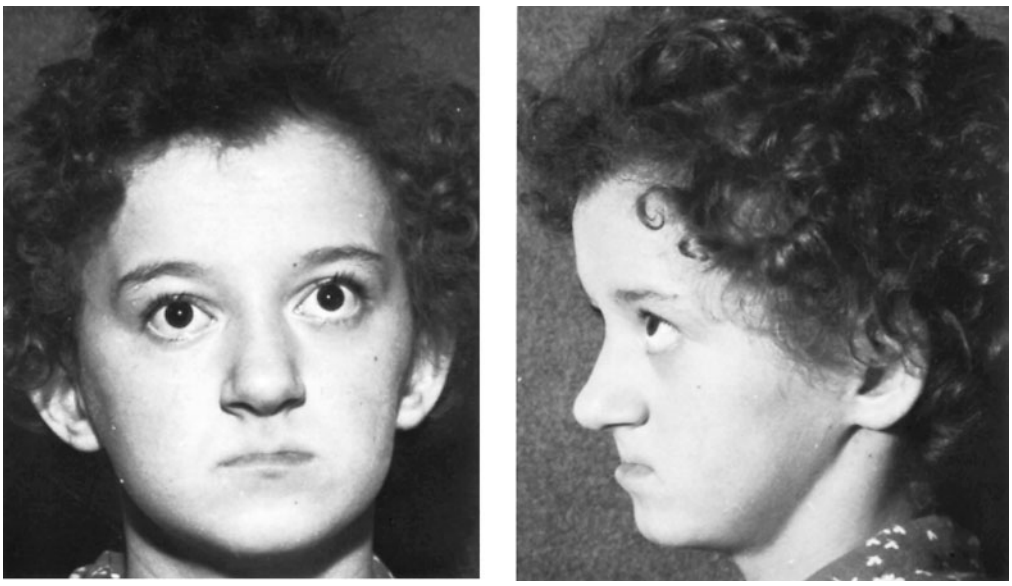
Facies. Some patients have broad flat nasal root, prominent supraorbital ridges, and relative prognathism due to underdevelopment of the maxilla and/or to loss of vertical height because of hypodontia (7,11,23,38) (Fig. 30–1).

Eyes. Iridogoniodysgenesis, that is, abnormal development of the anterior chamber of the eye (Axenfeld–Rieger or Reiger anomaly), is characteristic. Anterior displacement and thickening of the Schwalbe line (posterior embryotoxon) with attached strands of iris and stromal hypoplasia are hallmarks (8,11).

Pupils may be normal but are frequently displaced and nonspherical (dyscoria) or even slitlike. Polycoria is common and may be progressive, occasionally leading to secondary aniridia. Iris strands to the Schwalbe line are present in 90%. Absence of the anterior iris layer in the presence of a prominent Schwalbe line is diagnostic (Fig. 30–2). Anterior segment dysgenesis results from faulty migration of the third wave of neural crest cells to this region (9,45). Corneal leukomas may occur peripherally. Waring et al (44) noted onset of increased intraocular pressure in 50% by age 20. An additional 10%–15% per decade develop increased intraocular pressure thereafter. Shields et al (38) also found glaucoma in about half the patients. The glaucoma is difficult to control and may lead to significant damage to the optic nerve head and to blindness (8,11,38). Microcornea, megalocornea, corneal opacity, aniridia, and strabismus may occur (38).

Umbilical abnormalities. The only other frequent anomaly is failure of the periumbilical skin to involute (8,12,16,38,41) (Fig. 30–3). Reddihough et al (33) found exomphalos in two patients. *RIEG2* gene mutations do not appear to affect the umbilicus.

Fig. 30–1. *Rieger syndrome*. (A,B) Note midfacial hypoplasia with relative mandibular prognathism. [From E Frandsen, Acta Ophthalmol (Kbh) 41:757, 1963.]



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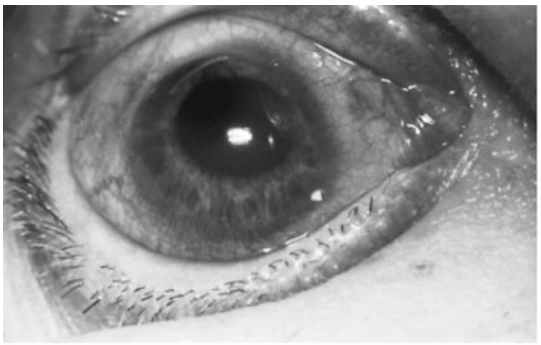

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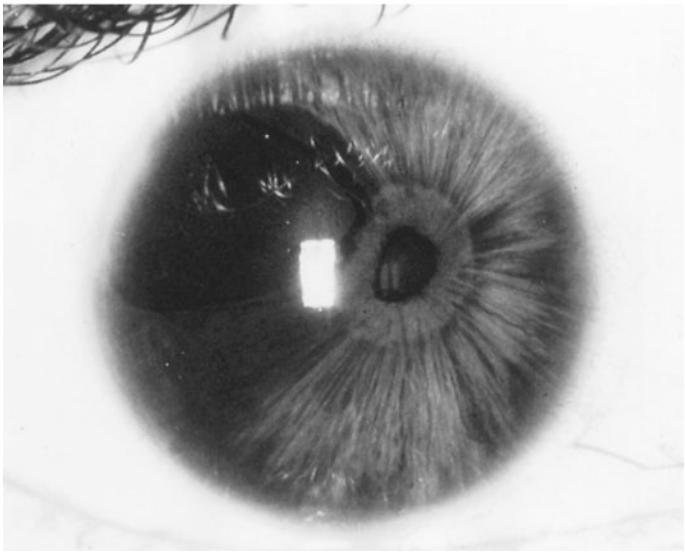
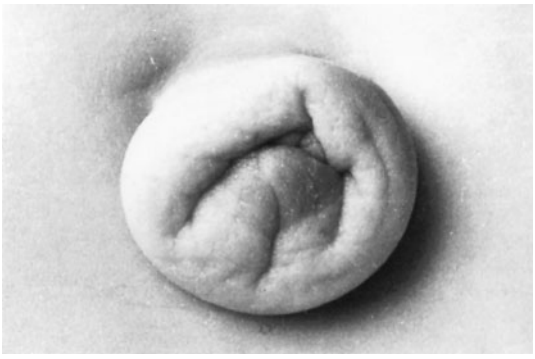


B

Fig. 30–2. *Rieger syndrome*. (A) Vertical slit pupil and polycoria are evident. (B) Congenital hypoplasia of anterior iris layer. The patient had prominence of the Schwalbe line and the dental and umbilical changes of Rieger syndrome. (A from W Lemmingson, Klin Monatsbl Augenheilkd 138:96, 1961. B courtesy of IH Maumenee, Baltimore, Maryland.)

Other abnormalities. Hypospadias (8,22,23), inguinal hernia (2,8,12), anal stenosis (4,10,13), and Meckel's diverticulum (26,33) have been found. Empty sella syndrome has been documented (24,38). A wide spectrum of other abnormalities has been tabulated by Alkemade (2), Fitch and Kaback (13), and Brooks et al (5), but they are inconsistent and some are certainly aleatory. Psychomotor retardation has been described

Fig. 30–3. *Rieger syndrome*. Umbilical defect with characteristic projection of periumbilical skin. (From DS Reddihough et al, Aust Paediatr J 18:130, 1982.)



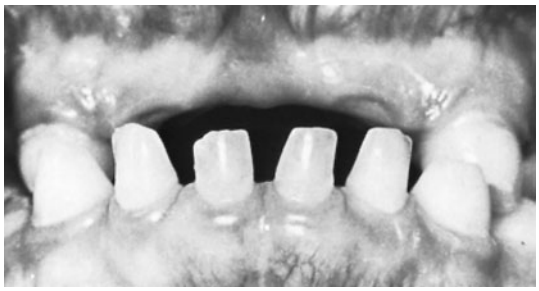


Fig. 30–4. *Rieger syndrome*. Absence of maxillary incisors and peg-shaped crowns of lower incisors and canines. (From M Feingold et al, Pediatrics 44:564, 1969.)

(2,13,23). Koshino et al (25) reported prominent posterior clinoid process, pseudoepiphyses of fifth metacarpals and metatarsals, and irregular ossification of femoral heads and distal femoral and distal tibial epiphyses.

Oral manifestations. The premaxillary area is relatively underdeveloped (2,6,28), and a reduced number of teeth is frequent, more often in the upper jaw (6,7,12,14,22). The maxillary deciduous and permanent incisors and second premolars are most commonly missing (22,23). Conical crown form of anterior teeth has been recorded by several authors (12,22,28,43) (Fig. 30–4). Cleft palate has been described by Fitch and Kaback (13). Hyperplastic frenula are occasionally noted (11,12).

Differential diagnosis. Congenital absence of teeth and teeth with conical crowns are seen in *hypohidrotic ectodermal dysplasia, Ellis-van Creveld syndrome, incontinentia pigmenti, hypodontia, and nail dysgenesis*, and *acrodental dysostosis*. Autosomal dominant glaucoma iridogoniodysgenesis, an overlapping condition, maps to 6p25 (21).

Goniodysgenesis has been found in binary combination with anal atresia, arachnodactyly, hearing loss, glaucoma, and myopathy (22). *SHORT syndrome* consists of goniodysgenesis, severe growth retardation, inguinal hernia, joint hypermobility, deep-set eyes, and delayed teething. The disorder has autosomal recessive inheritance. A similar disorder was reported by Sadeghi-Nejad and Senior (35) and Aarskog et al (1), but inheritance was autosomal dominant.

Mesodermal dysgenesis of the iris (Rieger anomaly) has been reported in association with orbital hypertelorism, psychomotor retardation, moderate sensorineural hearing loss, dilatation of the cerebral ventricles, generalized hypotonia, and pelvic anomalies (*DeHauwere syndrome*). No dental abnormalities were found. Inheritance was autosomal dominant. The patient described by Brooks et al (5) did not correspond to any of the above mentioned associations with Rieger anomaly. She had a wide nasal bridge, choanal atresia, kyphoscoliosis, and short stature. Moog et al (30) reported female sibs with Rieger anomaly, sensorineural hearing loss, hydrocephalus, and leptomeningeal calcifications as a new autosomal recessive syndrome.

Dysgenesis of the anterior chamber angle is also found with Peters anomaly, and congenital hypoplasia of iris stroma (faulty migration of neural crest cells), *rubella embryopathy*, Norrie syndrome, *Marfan syndrome*, and in some chromosomal aberrations.

References [Rieger syndrome (hypodontia and primary mesodermal dysgenesis of the iris)]

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DeHauwere (iris dysplasia, hypertelorism, and mental retardation) syndrome

In 1973, DeHauwere et al (3) described a syndrome of mesodermal dysgenesis of the iris, hypertelorism, telecanthus, sensorineural hearing loss, mild psychomotor retardation, and hypotonia in a mother and her three children. Possible cases were reported by Von Noorden and Baller (9). Chitty et al (1) described a three-generation family with absence of eye muscles, anterior chamber defects, strabismus, proptosis, and minor skeletal changes. However, no developmental delay was present. Three unpublished familial cases are known to RC DeHauwere (personal communication 1995), and another familial case and a single case are known to RCM Hennekam.

Craniofacial findings. Head circumfence was below the third centile in one of the original patients, but in all other patients there was macrocephaly. Ossification of the calvaria can be delayed. The face tends to be flat, especially the midface. There is hypertelorism, mild proptosis, and a relatively large chin (Fig. 30–5A–C).

Eyes. Hypoplasia of the iris stroma, abnormally prominent line of Schwalbe, adhesions between the iris and the posterior surface of the cornea, and pear-shaped pupils (Rieger anomaly) have been constant features. Strabismus is marked. The medial and lateral rectus muscles were found to be absent in two patients (1), the other eye muscles being hypertrophied and abnormally inserted (Fig. 30–5D).

Hearing. Mild sensorineural hearing loss was noted by DeHauwere et al (3). It was non-progressive in an adult female at 60 years (RCM Hennekam, unpublished).

Musculoskeletal system. Hypotonia and hyperlaxity of joints with dislocation of the hips was reported by DeHauwere et al (3). One unpublished patient had hallux valgus. Height is generally below the 3rd centile. Chitty et al (1) reported tall lumbar vertebrae, mild metaphyseal flare with unusually flat epiphyses at the hips, and delayed ossification at radiological investigations.

Central nervous system. Ventricular dilatation has been found in all patients. In one adult female intracerebral vascular spasms occurred, causing mild hemiplegia. Corpus callosum may have been absent in one patient (3).

Differential diagnosis. One must exclude *Peters plus syndrome*, and *Rieger syndrome*, in which hypodontia and umbilical anomalies

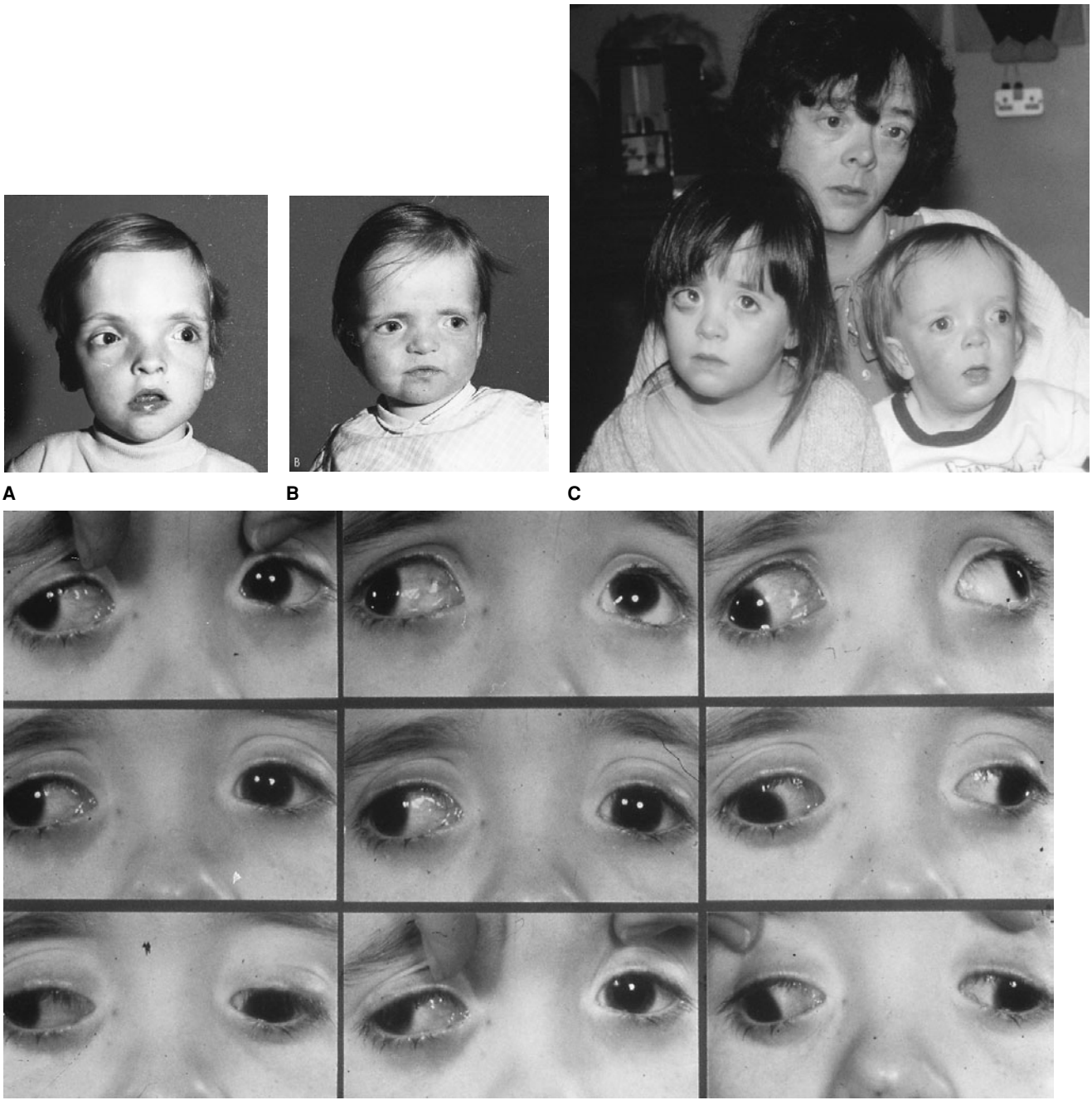

Fig. 30–5. *DeHauwere (iris dysplasia, hypertelorism, and mental retardation) syndrome*. (A,B) Note irregular pupils and orbital hypertelorism in two children. A similarly affected sib had died. Mother was also involved. *Absent eye muscles, unusual facies, hydrocephaly, and skeletal anomalies*. (C) Mother and two affected children with macrocephaly, proptosis, maxillary hypoplasia. (D) Limited eye movement in 5-year-old girl. (A,B from RC De Hauwere et al, J Pediatr 82:679, 1973. C,D from LS Chitty et al, Am J Med Genet 40:417, 1991.)

are common (4). Congenital absence of eye muscles has been reported together with anterior chamber anomalies in an isolated case without other symptoms (6). Sommer et al (7) reported two sibs from unrelated parents with partial aniridia, glaucoma, agenesis of the medial rectal muscle, hypertelorism, psychomotor retardation, dilated cerebral ventricles, and short stature, and, in another case, they also had hip dysplasia and sensorineural hearing loss. This may still represent DeHauwere syndrome, although no microsymptoms were present in the parents (A Sommer, personal communication 1992). Absent eye muscles have occasionally been noted in *Crouzon syndrome* and *Apert syndrome* (2,5).

References [DeHauwere (iris dysplasia, hypertelorism, and mental retardation) syndrome]

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Absent eye muscles, unusual facies, hydrocephaly, and skeletal anomalies

Chitty et al (1) described a grandmother, mother and her daughter and son with absent eye muscles, anterior chamber defects (prominent Schwalbe ring, hypoplasia of anterior iris stroma, and iris processes), strabismus, downslanting palpebral fissures, proptosis, hydrocephalus, hypertelorism, maxillary hypoplasia, and skeletal changes including tall lumbar vertebrae, flat capital femoral epiphyses, and delayed appearance of carpal bones.

DeHauwere syndrome had some overlap. Absent eye muscles are very unusual. This condition has been described in association with *Crouzon syndrome* and with *Apert syndrome* (2,3).

References (Absent eye muscles, unusual facies, hydrocephaly, and skeletal anomalies)

1. Chitty LS et al: Dominantly inherited syndrome comprising partially absent eye muscles, hydrocephaly, skeletal anomalies, and a distinctive facial phenotype. Am J Med Genet 40:417–420, 1991.
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Ophthalmo-mandibulo-melic (Pillay) dysplasia

A father and his son and daughter were described by Pillay (1) in 1964, with dense corneal opacities, macrocorneae, possibly glaucoma, temporomandibular fusion with agenesis of the coronoid processes and obtuse mandibular angle, mesomelic shortening of the upper limbs, aplastic lateral humeral condyle and caput radii, radiohumeral and proximal radioulnar dislocations, agenesis of the lower third of the ulna, bowed radii, ulnar deviated club hands, diminished mobility of the third, fourth, and (especially) fifth fingers, coxa valga, and mild genua valga. There were no internal anomalies, and development was normal (Fig. 30–6).

Pattern of inheritance is likely autosomal dominant.

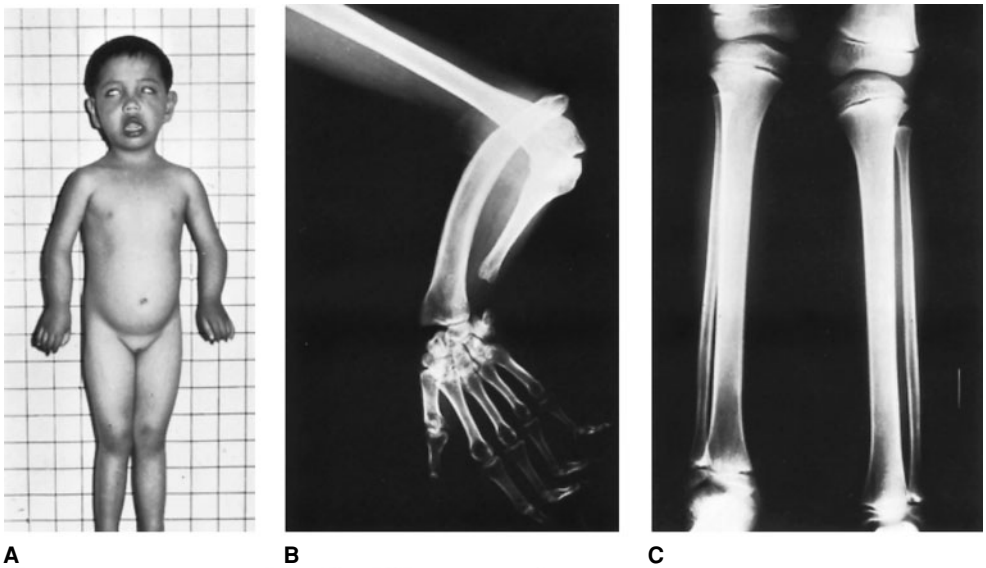

Fig. 30–6. *Ophthalmo-mandibulo-melic dysplasia*. (A) Seven-year-old girl with bilateral complete corneal opacities, shortened forearms. Father and brother similarly affected. (B) Aplastic lateral humeral condyle, abnormal trochlea, and olecranon. Coronoid processes absent, as are radial heads. Both radial shaft heads end in points that are located posterolateral to lower end of humerus. Radius bowed and short, ulna short with distal third absent. Articulation of radius only with lunate. Distal interphalangeal fusion. (C) Lateral malleolus higher than medial malleolus. Fibula shorter than tibia. (D) Temporomandibular joint ankylosis, lack of mandibular angle, and absence of coronoid process. (From VK Pillay, J Bone Joint Surg Am 46: 858, 1964.)

Reference [Ophthalmomandibulomelic (Pillay) dysplasia]

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Anophthalmia-syndactyly (ophthalmo-acromelic) syndrome

A syndrome described in two families by Waardenburg (12), in 1935, consisted of anophthalmia and syndactyly. Two sisters had unilateral anophthalmia, four toes, and proximal synostosis of metatarsals 4–5. Bilateral anophthalmia, short fingers, four toes, and cutaneous syndactyly were seen in sibs in the other family. Richieri-Costa et al (7) reported five children from two families. Four had bilateral and one had unilateral anophthalmia. All had similar limb anomalies. Traboulsi et al (11) noted male and female sibs and a cousin with the syndrome. Turkish brothers were described by Sayli et al (8). They exhibited bilateral anophthalmia, soft tissue syndactyly of toes 2–5, and partial synostosis of metatarsals 4–5. A Turkish girl was reported by Cogulu et al (2) and a Turkish boy by Tekin et al (10).

Al-Gazali et al (1) reported a male infant of Syrian consanguineous parents with microphthalmia and distal limb abnormalities. Quarrel (6) reported a male child of nonconsanguineous parents. The infant had anophthalmia and postaxial polydactyly of the feet. Suyugül et al (9) reported two inbred Turkish families. There were two affected in the first family and one in the second family. All had bilateral anophthalmia and mental retardation. There were also fused metacarpals 4–5 and a reduced number of metatarsals and corresponding toes (Fig. 30–7). Pallotta and Dallapiccola (5) also found mental retardation. Le Merrer et al (3) noted three sibs and suggested the term *ophthalmo-acromelic syndrome*. Mégarbané et al (4) reported a Lebanese boy with split hand and polydactyly.

Inheritance is clearly autosomal recessive.

References [Anophthalmia-syndactyly (ophthalmo-acromelic) syndrome]

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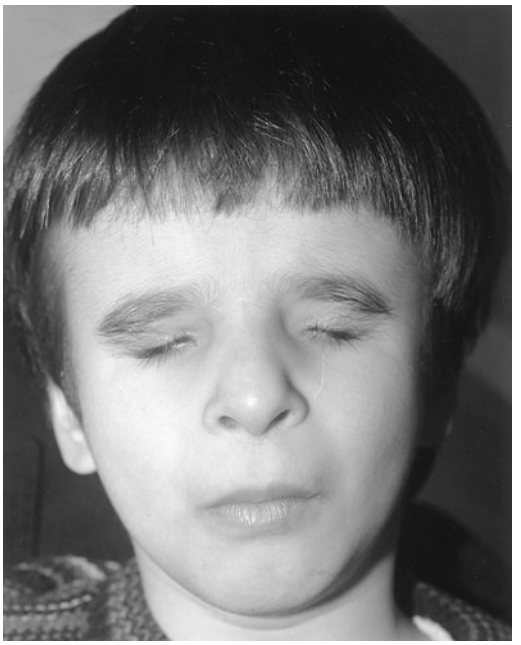
Bardet-Biedl syndrome

A syndrome characterized by mental retardation, hypogenitalism, retinopathy and ataxia was first described in four sibs by Laurence and Moon (53) in 1866. All four later developed spastic paraplegia. Independently, Bardet (3), in 1920, and Biedl (8), in 1922, described another disorder with similar features, but without ataxia and spasticity, and with obesity and polydactyly. Shortly afterward, both entities were subsumed under one heading: Laurence-Moon-Bardet-Biedl or



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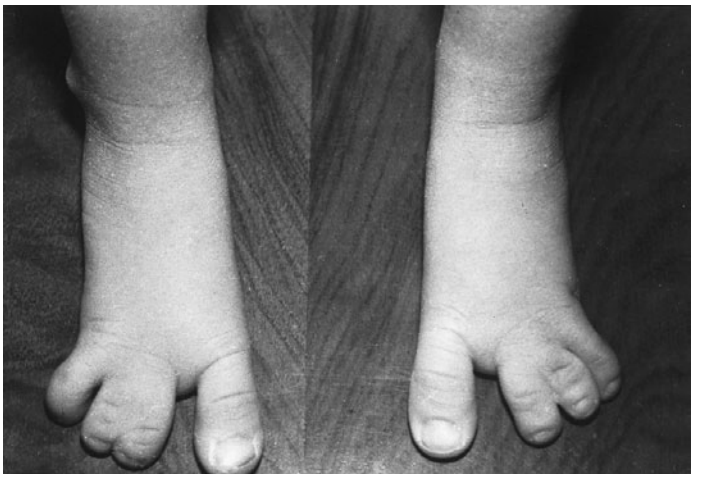


B

Fig. 30–7. *Anophthalmia-syndactyly (ophthalmo-acromelic) syndrome*. (A) Female with bilateral anophthalmia, bushy eyebrows, downslanting palpebral fissures, long philtrum. (B) Oligodactyly, wide gap between halluces and rest of toes, syndactyly of toes 2–3. (From Z Suyugül et al, Am J Med Genet 62:391, 1996.)

Laurence-Moon-Biedl syndrome (10,19,22,29,32,39,43,45,51,57–59, 61,63,64,66,67,69,71–74,79–81). However, especially through the work of Ammann (1) it became clear that Laurence-Moon syndrome and Bardet-Biedl syndrome are different disorders, and we and others concur (77,81). Bauman and Hogan (4) were the first to add renal anomalies as a cardinal sign of the entity.

There are about 850 cases of Bardet-Biedl syndrome described in the literature. Epidemiologic estimates vary: Klein and Amman estimated the prevalence in Switzerland to be 1 in 160,000 (49), in Norway prevalence was 1 in 128,000 (57), in Denmark 1 in 59,000 (41), in the United Kingdom 1 in 125,000 (5), and in Kuwait 1 in 65,000 (33). Unusual high frequencies were reported by Green et al (39) in Newfoundland of 1 in 17,500, and by Farag and Teebi (34) among the Bedouins of 1 in 13,500. In some countries, clustering of the geographic distribution was found (34), but in others, this was not present (39,49,81).

Inheritance is clearly autosomal recessive. Both sexes are equally affected; some reports have mentioned an excess of affected males (1,6,7),

leading some authors to suggest that the entity follows a polygenic inheritance (7), but others found an excess of females (39,81). Concordant monozygotic twins have been reported (59). Parental consanguinity of various series has ranged from 20% (6,9) to 35% (39), to 50% (1), to 100% (34). Heterozygous relatives have been described to have polydactyly (77), retinitis pigmentosa (29,47,61), hypospadias (70), developmental delay (29), diabetes (24,29,49), obesity (24,25,49), renal disease (25,76), and hypertension (25), but probably only renal diseases and hypertension, and possibly obesity, are truly more common in relatives compared to the population frequency. Beales et al (5) did not find a difference in weight in the parents of their study group.

The entity was linked first to chromosome 16q21 (52) in a large inbred Bedouin family, followed by linkage to chromosome 11q13 studying 28 families from Northern European descent and three Hispanic families (54), to chromosome 3p12–13 in an isolated Bedouin tribe and a large family from Newfoundland (78,85), and again in a highly inbred Bedouin family to chromosome 15q22–23 (18). Hence, nonallelic heterogeneity exists, and locus distribution is likely to be subject to regional variation. Bruford et al (13) studied 29 families from predominantly European ethnic origin and confirmed linkage to 11q13 in 36%–56%, to 15q22–23 in 32%–35%, to 16q21 in 24%–27%, and to an unknown other locus in 8%; no linkage to 3p12–13 was found. They found no major clinical differences between the families linked to the different loci. Carmi et al (17) suggested that affected members of families linked to chromosome 3p12–13 were clinically different in having polydactyly of all four limbs, but this was not confirmed by Young et al (85). Beales et al (5), studying 14 families of Northern European descent and 4 from the Middle East, confirmed linkage to 11q13 in 44%, to 15q22 in 6%, to 16q21 in 17%, and no linkage to 3p12–13; in 28% no linkage to any known locus was found. Linkage to the McKusick-Kaufman gene at 20p12 was found in 10% (78a,b). The gene is a chaperonin. Patients born in families linked to 11q13 were found to be somewhat taller compared to their parents and had atopic asthma more often (5).

Absence of linkage to the known loci indicate that at least one other locus for Bardet-Biedl syndrome exists. Chromosome anomalies that have been described are sex chromosome mosaicisms (10,12,40,65) and an apparently balanced translocation between chromosome 2p and 17p (26). Linkage to the 2p and 17p loci was excluded (13). A patient reported to have Oliver-McFarlane syndrome (27) with a partial trisomy of chromosome 13q may have had Bardet-Biedl syndrome. A high resolution cytogenetic study in 28 patients failed to show anomalies (32). There is evidence that one form of Bardet-Biedl syndrome is allelic to McKusick-Kaufman syndrome (47a,78b).

Ammann (1), and Klein and Ammann (41), Bell (6), Green et al (39), and Stiggelbout (81) surveyed the disorder.

Central nervous system. In early reports development was often reported to be severely impaired, but this has probably been due to the diminished vision and accordant deprivation (1,6). Green et al (39) reported an IQ below 70 in 41%, 9% being severely retarded, and Beales et al (5) found 36% to have a developmental delay. Speech defects, that is, poor articulation, slurring, and dropping of consonants, were common in one investigation (5). Dyslexia was reported (49). Although no formal behavioral studies have been reported, inappropriate mannerisms and shallow affect has been noted (39,49). Several authors reported normal findings in neuroradiologic studies, but rarely hypothalamic hamartoma and other hypophyseal or suprasellar tumors were found (28). Brain autopsy findings were limited and have included small gyri, especially of the frontal lobes, gliosis, fibrosis of blood vessels, and moderate internal hydrocephaly (58). Convulsions occur, especially in early childhood, but only rarely (49,81). Nyska et al (66) described a patient who developed spastic quadriparesis at 36 years because of cervical myelopathy due to cervical canal stenosis. Rizzo et al (74) described a case with ataxia and cerebellar vermis hypoplasia, but this patient probably had Laurence-Moon syndrome.

Growth. Although obesity may already be present at birth, it usually develops in infancy. It is not accompanied by an increased appetite similar to that in Prader-Willi syndrome, although hyperphagia during childhood was noted by parents in 64% (5). The localization is of the 'Frohlich' type, that is, along the trunk and proximal parts of the limbs. The obesity becomes more prominent through the usually somewhat diminished height (Fig. 30–8). Green et al (39) reported 88% of patients to be obese and 64% to have a stature below the 50th centile. Beales et al (5) found a mean height of offspring to be 3 cm below that of the parents. On the contrary, when dissected for linkage to the different loci of Bardet-Biedl syndrome, males and females showing linkage to chromosome 11q13 locus were taller (mean, 6 cm and 11 cm) than their fathers and mothers, respectively (5). Body mass was higher in all offspring compared to their parents (5). A patient weighing more than 200 kg has been reported (49). After renal failure, myocardial infarction has been the major cause of death in Bardet-Biedl syndrome (72). Type II diabetes mellitus occurs (31,39,47), but the frequency has varied widely from 0% (5) to 45% (39). Fatal diabetic coma was reported (31). Hypopituitarism with growth hormone deficiency has been described (70) as well as sibs with hypopituitarism without growth hormone deficiency (83).

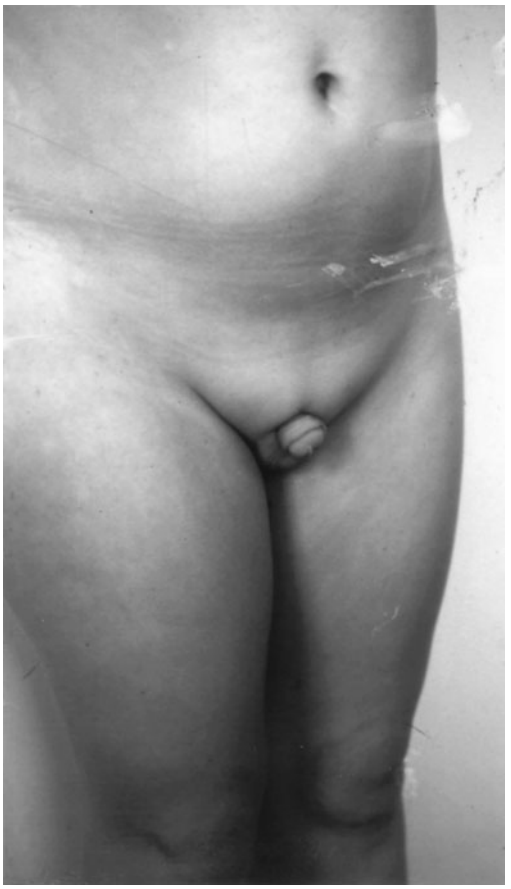


Fig. 30–8. *Bardet-Biedl syndrome*. Obesity and hypogenitalism.

Eye findings. The retinal disorder is primarily a degeneration of the photoreceptors (76) and affects both rods and cones, causing both central and more peripheral functions to be affected (36). The macula is involved early (39,67). Retinal dystrophy is found in 85%–100% of reported series (1,6,39,48,81) (Fig. 30–9). The entity constitutes 5% of all cases with retinitis pigmentosa (41). Onset of the visual impairment is in the first and, especially, the second decade (36,71), and leads to legal blindness in 85% of cases by the age of 30 years (49), or, in another study, a visual acuity less than adequate to count fingers in 73% of cases older than 30 years (39). This is more rapid than in isolated retinitis pigmentosa. Light perception is retained. Eye symptoms rarely debut after 18 years of age (41). In individual cases the progression of visual impairments is variable and unpredictable (36,55). The fundoscopic appearance can be that of typical retinitis pigmentosa but more often is atypical with sparse

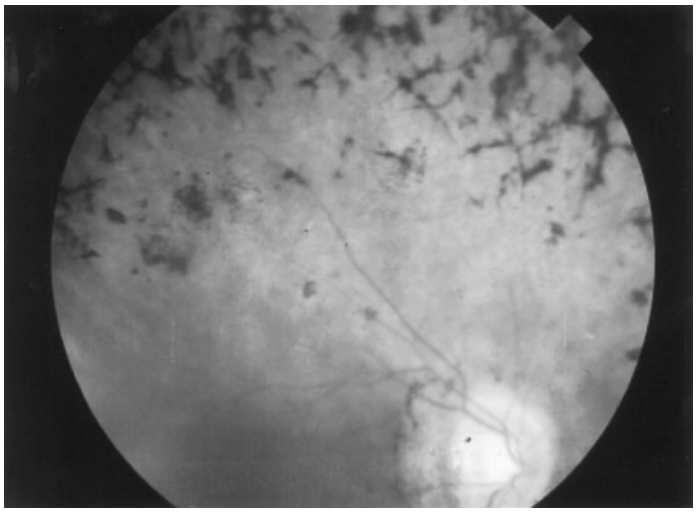


Fig. 30–9. *Bardet-Biedl syndrome*. Fundus showing retinal pigmentation.

pigmentation, central and peripheral atrophy, and especially attenuated vessels and pale optic disks (39).

Electroretinographic abnormalities precede retinal anomalies and can already be present in infancy or early childhood (29,58). Other eye symptoms have been cataract (8,14,29,39,47,51,69,71,77), myopia (39,47,48,71,79), nystagmus (39,47,71), glaucoma (39), and microphthalmia (4).

Renal system. The renal symptoms in the entity are well reviewed by Harnett et al (43). In an unbiased series they found structural or functional renal abnormalities in all 20 studied adults. The characteristic radiologic changes are symmetrical and irregular parenchymal reduction, fetal type lobulation, noncommunicating cysts and diverticula, and blunting and clubbing of the calyces (23,56), all suggesting a defect in renal maturation. Other reported structural renal anomalies have included hypoplasia, hydronephrosis, and focal scarring (2,23,43,56,58). Ultrastructural findings were mesangial proliferation and sclerosis, increase in mesangial matrix, and glomerular basement membrane abnormalities (19).

Sonography of the kidneys prenatally or in the neonatal period may show findings identical to those of autosomal recessive polycystic kidneys (37,38,73). Confusion with the latter entity can become even stronger because of the occurrence of congenital hepatic fibrosis in Bardet–Biedl syndrome (64,68,75). Biliary cirrhosis (24), cholecystitis (80), and portal hypertension (75) have been reported.

Functional renal problems are hypertension, partial defects in urine concentration, incomplete or complete renal tubular acidosis, and end stage renal disease (43,45). Nephrolithiasis has been mentioned repeatedly (51,80). Functional problems may become apparent in infancy, but usually in the first two decades (45), and do not show a strong correlation with the structural defects (23,43). First symptoms can be polyuria, polydipsia, proteinuria (2), and pyelonephritis (14). Remission of proteinuria may be established with steroids, but residual proteinuria and recurrence have been described (20). Severe, progressive renal disease occurs in 15% of cases (43). Renal transplantations have mostly been successful, without recurrence of the renal problems, but follow-up was usually only very short (56,75). Increased obesity as a complication of the transplantation has been noted (22,82). End stage renal disease is the major cause of death in Bardet-Biedl syndrome (72). The average age of death of 43 years mentioned by Riise (72) is too low because of biased ascertainment. Autopsies of nine patients who died because of uremia showed chronic glomerulonephritis, cystic tubulo- interstitial disease, and advanced sclerosis (20).

Urogenital system. Hypogenitalism is almost universal in male patients. It is primary, and not secondary to hypopituitarism (39) (see Fig. 30–8). Cryptorchidism was found in 25% (5). Testicular biopsies showed fibrosis (68) and degenerative lesions of the seminiferous tubules (83). Hypospadias was reported (81). Pubertal development is normal, with normal hair distribution and other secondary sexual characteristics. No fully affected male is known to have fathered a child, but one male with a "forme fruste" had three sons (81).

Stoler et al (82) have summarized the genital anomalies in females. Vaginal atresia (23,39,49,80,82), ovarian cysts (77), uterus duplex with vaginal septum (49,58), hypoplastic uterus and ovaries (14,58), hydrometrocolpos (60,82), hematocolpos (23,49), female hypospadias (opening of urethra into upper vaginal wall) (23), and persistent urogenital sinus (63,82) are found. One patient was virilized because of ovarian dysfunction due to stromal hyperplasia with focal hyperthecosis (42). Most females have normal menarche and menses, and normal secondary sexual characteristics (14,39), although primary amenorrhea and absence of breast occur (13). Hypogonadotrophic hypogonadism may occur but is not a common symptom in females (39). At least seven females have given birth to healthy children (5,6,9,39,81).

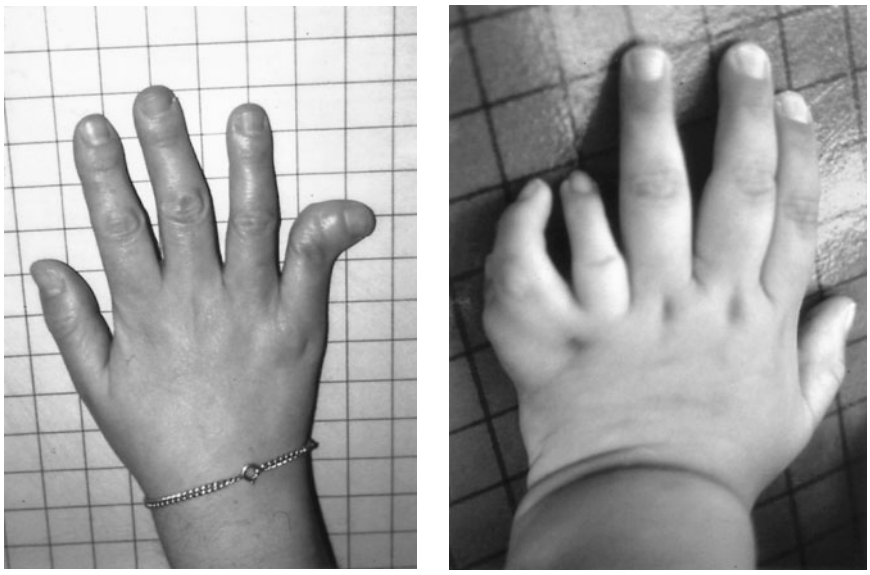
Skeletal system. Polysyndactyly is extremely common, occurring in 93% (39) to 98% (5) (Fig. 30–10). Polydactyly, almost exclusively on the ulnar side, can be postaxial and paraaxial, unilateral or on all four limbs, and usually asymmetrical. Some reports did not find a difference between hands and feet (5); others found the feet to be more commonly affected (39,49). Hexadactyly up to octodactyly occurs. Syndactyly is usually subtle, between the second and third toes, and between the polydactylous fingers or toes. If no polydactyly is present, hands and feet are usually broad. Brachydactyly is proven with metacarpophalangeal pattern profiles in 93% (39). Intrafamilial variability is extremely large.

Other symptoms include hip dislocations (29,61,81), genua valga (49,79,81), tibia vara (62), club feet (49,68,81), camptodactyly (35), and kyphoscoliosis (12,49,81). The skeleton may be osteoporotic (12).

Oral manifestations. Kobrin et al (50) noted oligodontia and microdontia in two sibs. One of the authors (RCMH) has seen these brothers and their nephew who may have an X-linked disorder. A Norwegian study showed hypodontia, short roots, tendency to taurodontia, obliterated pulp chambers, and sclerotic areas in the jaws (57). This was confirmed in another Scandinavian study (11), which also found that the saliva showed a higher buffering capacity than normal.

Other findings. Conductive hearing deficits due to chronic middle ear effusions were reported in 35% (5). Cardiac anomalies have included dilated cardiomyopathy (30), bicuspid aortic valves (20,30,55), aortic (20) and tricuspid (30) regurgitation, pulmonic valve stenosis (30,55,58), atrial septal defect (30,35,81), ventricular septal defects (58), transposition of the great vessels (58,81), and hypertrophy of the intraventricular septum (30) or left ventricle (30,58). Other reported anomalies have been sparse hair (13), skin depigmentations (14), supernumerary nipples (68), basal cell carcinoma of the skin of the nose (69), choanal stenosis (4), anal atresia (8,79,81), and Hirschsprung disease (46,70).

Differential diagnosis. There is marked overlap with McKusick-Kaufman syndrome (hydrometrocolpos, poataxial polydactyly, and congenital heart anomalies) (60,78a). This should not be surprising as the disorders are allelic. Many components of the syndrome can occur as isolated findings or as features of other syndromes, making a firm diagnosis in the isolated, young patient, that is, without symptoms yet of retinal dystrophy, difficult. Entities to be considered are *Meckel syndrome* (38), *Pallister-Hall syndrome* (28), mitochondrial disorders (76), and *Smith-Lemli-Opitz syndrome*. Several authors have discussed the difference with other multiple congenital anomalies syndromes that show retinitis pigmentosa such as Alstrom syndrome, Biemond syndrome, *Cohen syndrome*, Laurence-Moon syndrome, and several case reports (9,15,77). Pigmented retina without retinitis pigmentosa occurs in *Cohen syndrome*. About 30 cases of Laurence-Moon syndrome have been described (33,74,77). Besides the absence of polydactyly and the presence of ataxia and spastic paraplegia in this entity, the retinal dystrophy also differs from Bardet-Biedl syndrome, resembling more



A B

Fig. 30–10. *Bardet-Biedl syndrome*. (A,B) Polydactyly ranges from postminimum digit to postaxial extra digits with variable digital distortion.

choroideremia (77). Nephronophthisis, congenital hepatic fibrosis, and retinal degeneration can occur as separate entities (16). The sibs reported by McLoughlin et al (58) had *Carpenter syndrome*. Case 58 of Klein and Ammann (49) obviously had *Rubinstein-Taybi syndrome*, and Farag et al (35) and Hauser et al (44) may have described Alström syndrome. The case reported by Whitaker et al (84) as having Kearns-Sayre syndrome is likely to have had the entity, and a case with Oliver-McFarlane syndrome may also have had Bardet-Biedl syndrome (27).

Laboratory findings. In familial cases linkage studies are helpful. Prenatal diagnosis using the hand anomalies and renal cysts as clues have been accomplished (32,33,72).

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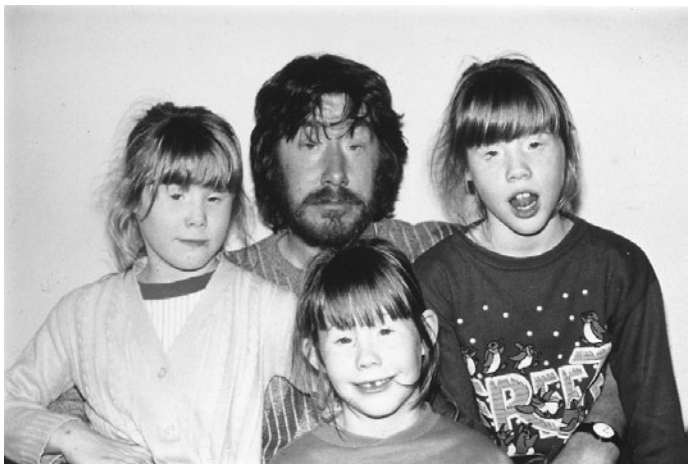
Blepharophimosis-ptosis-epicanthus inversus (BPES)

Initial description of blepharophimosis, ptosis, and inverse epicanthus was probably that of Vignes (23) in 1889. An earlier example has been suggested by Harrar et al (9). At least 180 families have been described (15).

Inheritance is autosomal dominant (16,20,21). Several patients with chromosome deletions or rearrangements led to the gene being mapped to 3q22–6q23 (1,2,8,9). Crisponi et al (2a) found the forkhead transcription factor *FOXL2* to be mutated. Both type 1 and type 2 (vide infra) map to this region (2). There is evidence that this may represent a contiguous gene deletion (6–8,19). There is current debate regarding the *SOX14* gene (8a,24). However, there appears to be genetic heterogeneity with other families mapping to 7p13–p21 (14,24). The facies is different in the 7p13 type. A maternal age effect for new mutations has been demonstrated (4). Occasionally, nonpenetrance can cause a counseling problem (21).

The facies is distinct (3). It appears flattened and expressionless due to taut facial skin. In addition to the narrow palpebral fissures [18–22 mm versus 25–33 mm (normal range)], there are telecanthus and ptosis of the upper eyelids. The supraorbital ridges are flattened. The head is often held tilted backward and the brow is furrowed to compensate. Eyebrows are highly arched and elevated (Fig. 30–11). The margin of the upper eyelid may have a mild S-shaped curve. Due to drooping of the lateral canthus, there may be some ectropion of the lower lids. Trichiasis has been reported. Lateral displacement of the lacrimal puncta is common. The superior rectus, less often the lateral rectus, is hypoplastic and fibrotic. Epicanthal folds run upward and inward from the lower lid rather than downward. The lid folds are usually absent with smooth overlying skin. The normal depression at the inner canthus is missing. The caruncle and plica semilunaris are hypoplastic and secluded beneath the epicanthic fold. The nasal bridge is rather low (11,13,15,16). The nostrils may be obliquely shaped.

Affected females have amenorrhea, irregular menses, infertility and/or elevated gonadotropin levels due to primary ovarian failure (5,17,19,22).



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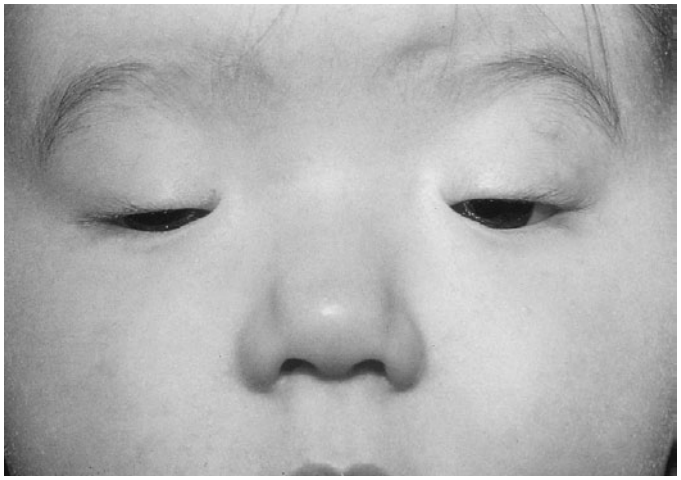

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Fig. 30–11. *Blepharophimosis-ptosis-epicanthus inversus (BPES)*. (A) Note ptosis, narrow palpebral fissures, highly arched eyebrows in several members of a family. (B) Observe telecanthus, smooth skin of eyelids, inverse epicanthus, flat nasal bridge. (A courtesy of MA Patton, London, England. B from C Oley and M Baraitser, J Med Genet 25:47, 1988.)

Endometrial carcinoma has been noted (13a). Breast development is normal, but axillary and pubic hair is scant. Zlotogora et al (26) suggested that there were two forms: one with infertile females (type 1), the other without (type 2).

Occasionally, microcephaly and/or hypoplasia of the cerebellar vermis have been described. Such examples have been attributed to contiguous gene deletion (8,10–12). Mental retardation has been common in those with obvious deletions (8).

Hypoplasia of superior rectus muscle and occasionally the lateral rectus muscle occurs.

Differential diagnosis would include autosomal dominant congenital ptosis (18) and a host of syndromes with blepharophimosis and/or ptosis. One must exclude *Schwartz-Jampel syndrome, Marden-Walker syndrome, Dubowitz syndrome, Ohdo syndrome*, and *Michels syndrome*.

References [Blepharophimosis-ptosis-epicanthus inversus (BPES)]

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Blepharophimosis-ptosis, mental retardation, and hearing loss (Ohdo syndrome)

Ohdo et al (11), in 1986, reported a syndrome of blepharophimosis, blepharoptosis, hypoplastic teeth, mental retardation, and hearing loss in two sibs and their first cousin. About 15 examples have been subsequently documented (1,3,7,8,11–13).

Inheritance is unknown. Nearly all examples have been sporadic except for the affected sibs reported by Ohdo et al (11). Mhanni et al (10) reported a mother and son but raised the possibility of mitochondrial inheritance.

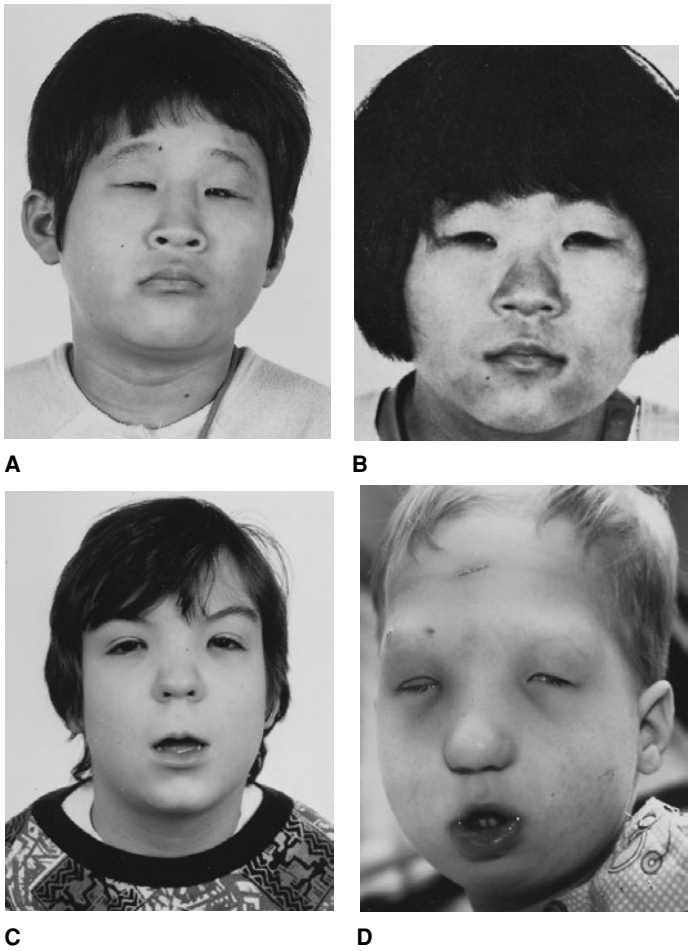

Fig. 30–12. *Blepharophimosis-ptosis, mental retardation, and hearing loss (Ohdo syndrome)*. (A,B) Two sibs with blepharophimosis, blepharoptosis, wide and depressed nasal bridge, and microstomia. (C,D) Similarly affected children. (A,B from S Ohdo et al, J Med Genet 23:242, 1986. C courtesy of A Chudley, Calgary, Alberta, Canada. D courtesy of L Biesecker, Bethesda, Maryland.)

The facies is characterized by blepharophimosis, blepharoptosis, epicanthus, amblyopia, wide and depressed nasal bridge, short upturned nose, long flat philtrum, thin vermilion, microstomia, hypoplastic teeth, and small mandible (Fig. 30–12). Auricular stenosis (1,11) and small pinnae (4,6,11,13) were documented. Hearing loss was noted in 50% but was not a well-documented feature (1,3,7,9,11,12).

Mental retardation is a constant feature, with IQs ranging from 37 to 56. Hypotonia is present in 70% (1,3,7,12,13).

Cryptorchidism has been a constant feature in males (1,7,12,13).

Variable features have included congenital heart anomalies (3,11–13), cleft palate (6), hyperextensible joints and clinodactyly of fifth fingers (1,7,13), café-au-lait spots (1,7), bladder diverticula (6), and proteinuria (11,13).

Differential diagnosis would include *dup(10q), trisomy 18, dup(20p), Dubowitz syndrome, Michels syndrome, COFS syndrome, craniocarpotarsal dysplasia, Schwartz-Jampel syndrome, Marden-Walker syndrome*, Tsukahara syndrome, and *alcohol embryopathy* (3). Buntinx and Majewski (2) reported a patient with blepharophimosis, iris coloboma, postaxial polydactyly, agenesis of corpus callosum, hydroureter, developmental delay, and hearing loss. Biesecker (1) has elegantly discussed differential diagnosis. Also to be considered in diagnosis is *blepharophimosis-ptosis epicanthus inversus syndrome* (BPES) for which the gene has been mapped to 3q22 (5). The ROCA-Wiedemann syndrome (growth and developmental retardation, ocular ptosis, cardiac anomalies, and anal atresia) must be excluded.

References [Blepharophimosis-ptosis, mental retardation, and hearing loss (Ohdo syndrome)]

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Microcephaly, blepharophimosis, esophageal/duodenal atresia, and digital anomalies [oculodigitoesophageal duodenal (Feingold) syndrome, MODED]

Feingold (5,6) briefly described two families with microcephaly, normal intelligence, blepharophimosis, and hand and foot anomalies (clinodactyly of V, syndactyly of toes 2–3), and duodenal atresia. Fourteen additional families involving 50 persons have expanded the syndrome more fully (1,4,7–13). Other less certain examples have been cited (4,9).

Inheritance is clearly autosomal dominant (9). The gene maps to 2p23–p24 (3).

About 80% had microcephaly with short palpebral fissures. Intelligence in most patients has been normal, but learning disabilities have been noted in 30% (8).

All had absent or hypoplastic middle phalanges of I and II bilaterally (brachydactyly A4). Syndactyly of toes 2–3 and/or 4–5 was noted in 60%–85%. The middle phalanges of the last four toes is often absent.

Intestinal atresia or obstruction (esophageal atresia, TE fistula, duodenal atresia or duodenal obstruction) was documented in about 25%. Imperforate anus was noted by Büttiker et al (2).

Miscellaneous findings have included congenital heart anomalies (1) and vertebral abnormalities (13).

References (Microcephaly, blepharophimosis, esophageal/duodenal atresia, and digital anomalies [oculodigitoesophageal duodenal (Feingold) syndrome, MODED])

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Blepharophimosis, ptosis, syndactyly, and mental retardation

Cohen et al (1) described a single male mentally retarded case with blepharophimosis, ptosis, deficient lashes of the lower eyelids, maxillary hypoplasia, a grooved nasal tip, and small protruding ears. There was complete cutaneous syndactyly of the third and fourth finger, kyphoscoliosis, mild hypospadias, and diminished movements in fingers, elbows, and toes. It was reported that the mother took phenobarbital during pregnancy.

Reference (Blepharophimosis, ptosis, syndactyly, and mental retardation)

1. Cohen MM Jr et al: Case report 26. Syndrome Ident 3:1–2, 1975.

Blepharophimosis, atrial and ventricular septal defects, and anal and radial anomalies

Houston et al (1) reported male and female sibs with atrioventricular septal defect, blepharophimosis, and anal and radial anomalies. In addition to blepharophimosis, there were upslanting palpebral fissures, and convergent squint. Other anomalies included growth retardation, anteriorly placed anus, aplastic radius, clinodactyly V, and atrioventricular septal defect.

VACTERL association and *Ohdo syndrome* were considered.

Reference (Blepharophimosis, atrial and ventricular septal defects, and anal and radial anomalies)

1. Houston RS et al: Association of atrial-ventricular septal defect, blepharophimosis and radial defects in sibs: A new syndrome? Genet Couns 5:93–96, 1994.

Blepharophimosis, hypotelorism, pseudopapilledema, and anomalies of the hands (acro-oto-ocular syndrome)

Paes-Alves et al (2), in 1991, reported three individuals in a Brazilian inbred family. Bertola et al (1) described another isolated case.

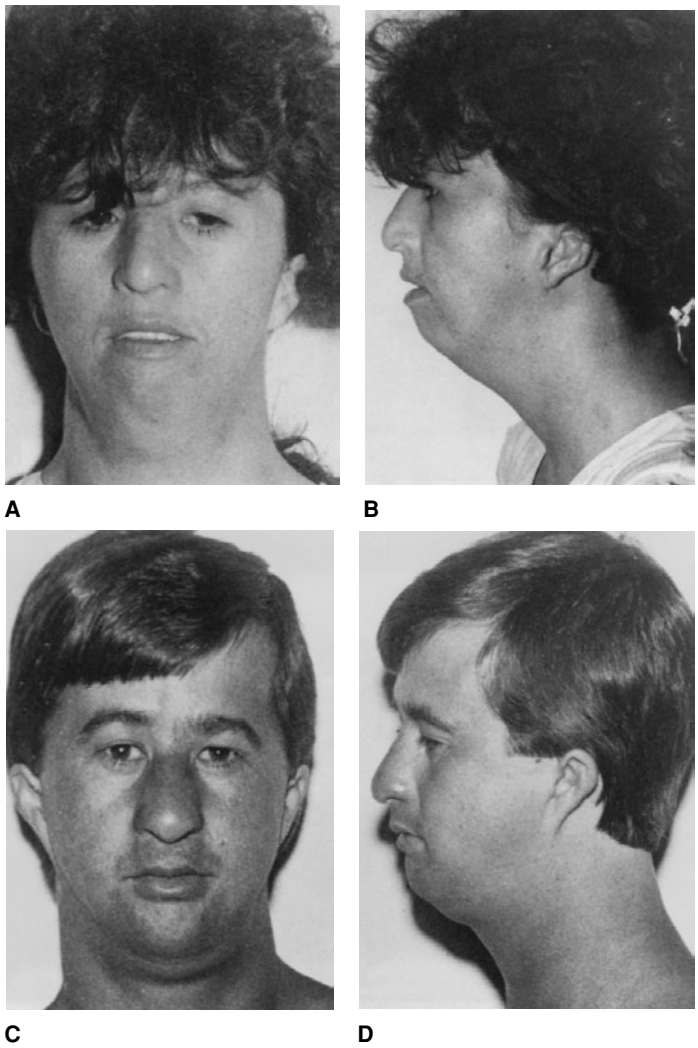

Fig. 30–13. *Blepharophimosis, hypotelorism, pseudopapilledema, and anomalies of the hands (acro-oto-ocular syndrome).* (A–D) Brother and sister with ocular hypotelorism, blepharophimosis, deep base of nose, and downslanting palpebral fissures. Note malformed, low-set pinnae. (From AF Paes-Alves et al, Am J Med Genet 41:141, 1991.)

The affected were small at birth and subsequently had small stature. In addition to blepharophimosis, the patients exhibited hypotelorism and epicanthic folds (Fig. 30–13).

Pseudopapilledema and mixed hearing loss were documented.

The nasal base was broad. The pinnae were small and low-set with narrow canals. Teeth were late in eruption. Intelligence was normal.

The thenar, hypothenar, and interdigital areas of the hands were flattened, and a wide space was evident between the hallux and the second toe. The calcaneus protruded.

Inheritance is probably autosomal recessive.

References [Blepharophimosis, hypotelorism, pseudopapilledema, and anomalies of the hands (acro-oto-ocular syndrome)]

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2. Paes-Alves AF et al: Autosomal recessive malformation syndrome with minor manifestation in heterozygotes: A preliminary report of a possible new syndrome. Am J Med Genet 41:141–152, 1991.

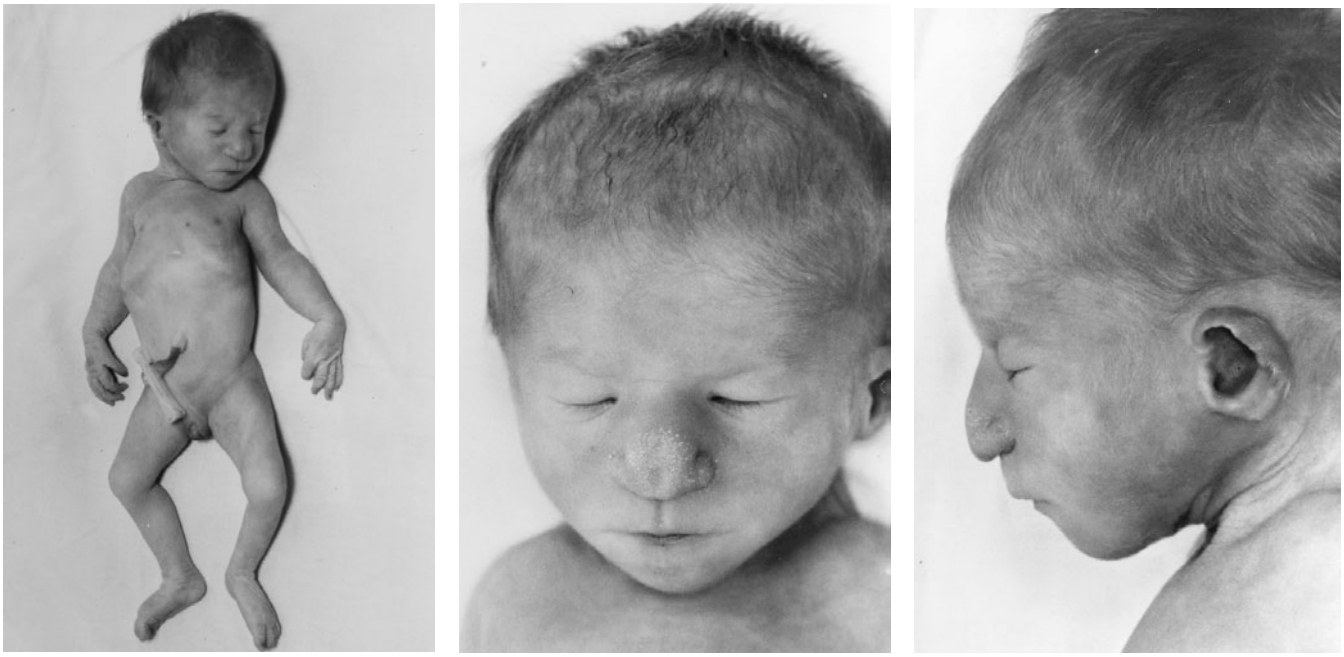

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Fig. 30–14. *Blepharophimosis, large cylindrical nose, and severe intrauterine growth retardation*. (A–C) Female infant with blepharophimosis, hypotelorism, large nose with broad nasal bridge and midline groove, flexed posturing of hands. (From CEM de Die-Smulders et al, J Med Genet 30: 525, 1993.)

Blepharophimosis, large cylindrical nose, and severe intrauterine growth retardation

De Die-Smulders et al (1) described a female child of nonconsanguineous parents with blepharophimosis, hypertelorism, micrognathia, large nose with broad nasal bridge and midline groove, flexed posturing of the hands, severe growth retardation, and early death (Fig. 30–14).

Reference (Blepharophimosis, large cylindrical nose, and severe intrauterine growth retardation)

1. De Die-Smulders CEM et al: Severe intrauterine growth retardation, blepharophimosis, and cylindrical nose with midline groove: A new syndrome? J Med Genet 30:525, 1993.

Blepharophimosis, ptosis, syndactyly, and short stature

Frydman et al (1) reported several sets of Yemenite Jewish sibs from a highly inbred family with blepharophimosis, ptosis, and weakness of extraocular and frontal muscles. V-esotropia and upper gaze paralysis were demonstrated. Synophrys of thick eyebrows and mandibular prognathism contributed to the unusual facies. Short stature and syndactyly of toes 2–3 were also noted.

The autosomal recessive inheritance pattern makes this a very distinct entity among the many blepharophimosis-ptosis syndromes. One must exclude the autosomal recessive *Mutchinick syndrome* (2).

References (Blepharophimosis, ptosis, syndactyly, and short stature)

1. Frydman M et al: Autosomal recessive blepharophimosis, ptosis, V-esotropia, syndactyly, and short stature. Clin Genet 41:57–61, 1992.

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Blepharophimosis, telecanthus, microstomia, and unusual facies (Simosa syndrome)

Simosa et al (1) described a mother and son with elongated and somewhat flattened face, short palpebral fissures, long nose with hypoplastic alae, chin dimples, and unusually formed pinnae. Suri et al (2) reported a male infant with a similar facies and camptodactyly of the fingers (Fig. 30–15).

References [Blepharophimosis, telecanthus, microstomia, and unusual facies (Simosa syndrome)]

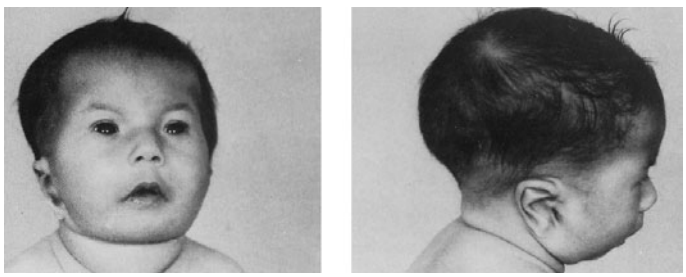
1. Simosa V et al: A new syndrome with distinct facial and auricular malformations and dominant inheritance. Am J Med Genet 32:184–186, 1989.

2. Suri M et al: Blepharophimosis, telecanthus, microstomia, and unusual ear anomaly (Simosa syndrome) in an infant. Am J Med Genet 51:222–223, 1994.

Blepharophimosis, ptosis, polythelia, and brachydactyly

Wittebol-Post and Hennekam (1) reported a father and two sons who all three had blepharophimosis, ptosis, and brachydactyly type A3. Father

Fig. 30–15. *Blepharophimosis, telecanthus, microstomia, and unusual facies (Simosa syndrome)*. Note blepharophimosis, small mouth, and unusual ear malformations. (From M Suri et al, Am J Med Genet 51:222, 1994.)



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and one son had polythelia, the other son had a congenital hyperpigmentation above one of his nipples. The sons had protruding ears, but otherwise no other anomalies were present. Development was normal. Inheritance is probably autosomal dominant.

Reference (Blepharophimosis, ptosis, polythelia, and brachydactyly)

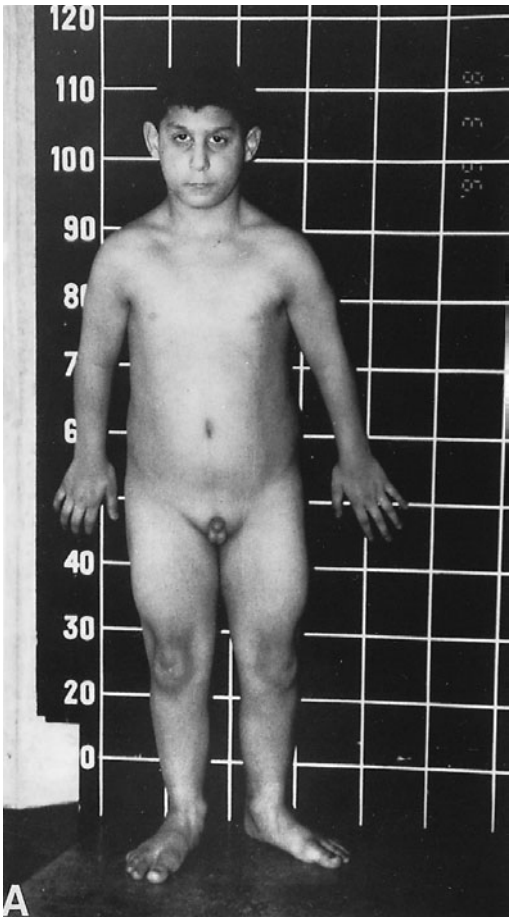
1. Wittebol-Post D, Hennekam RCM: Blepharophimosis, ptosis, polythelia and brachydactyly (BPPB): A new autosomal dominant syndrome? Clin Dysmorphol 2:346–350, 1993.

Cataracts, microcephaly, rhizomelia, and micropenis

Verloes et al (3) described a single case with severe microcephaly, borderline intelligence, cataracts detected in early childhood, rhizomelic shortness, especially of the lower limbs, giving rise to a muscular build, advanced bone age, and micropenis. Facial features included hypotelorism, long nose with anteversion of the nares in infancy, flat malae, highly arched palate, crowded teeth, and micrognathia (Fig. 30–16). The extension of elbows was limited, the second and third toes showed a Y-shaped cutaneous syndactyly. The case resembled *Smith-Lemli-Opitz syndrome* to a great extent, but cholesterol metabolism was reported to be normal. Parents were consanguineous.

The case reports by Harrod et al (1) and Pavone et al (2) need to be excluded.

Fig. 30–16. *Cataracts, microcephaly, rhizomelia, and micropenis*. Seven-year-old male with juvenile cataract, muscular build, rhizomelic shortness of limbs, advanced bone age, and micropenis. (From A Verloes et al, Am J Med Genet 68:455, 1997.)



References (Cataracts, microcephaly, rhizomelia, and micropenis)

1. Harrod MJ et al: A syndrome of craniofacial, digital, and genital anomalies. Birth Defects 13(3B):11–115, 1977.
2. Pavone L et al: Syndactyly type I with cataracts and mental retardation. Clin Dysmorphol 2:257–259, 1993.
3. Verloes A et al: Microcephaly, muscular build, rhizomelia, and cataracts: Description of a possible recessive syndrome and some comments on the use of electronic databases in syndromology. Am J Med Genet 68:455–460, 1997.

Cataracts, enamel hypoplasia, and aqueductal stenosis

Seow et al (1) reported a single female case who was found to have anterior and posterior subcapsular cataracts with radial spoke opacities in the cortex in childhood, generalized enamel defects of the hypomaturation-hypocalcification type in primary and permanent teeth, anterior overbite, and aqueductal stenosis at brain imaging. There were no other anomalies, and intelligence was normal.

Reference (Cataracts, enamel hypoplasia, and aqueductal stenosis)

1. Seow WK et al: Enamel hypoplasia, bilateral cataracts, and aqueductal stenosis: A new syndrome? Am J Med Genet 58:371–373, 1995.

Cataracts, multiple oral frenula, and growth retardation

Wellesley et al (1) described a mother and two children with posterior polar cataracts in early childhood, multiple oral frenula, growth retardation, microcephaly, and borderline intelligence. One child had unilateral ptosis. Facial features were epicanthal folds, small nose with upturned tip, somewhat prominent premaxilla, and posteriorly angulated ears. Inguinal and umbilical hernias occurred. Inheritance appears to be autosomal dominant.

Reference (Cataracts, multiple oral frenula, and growth retardation)

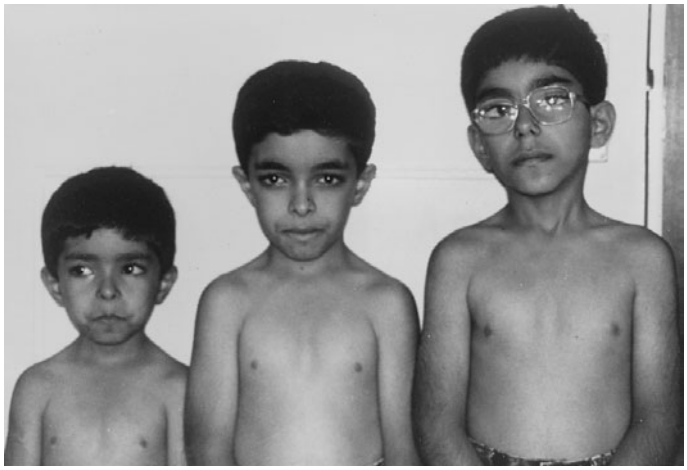
1. Wellesley D et al: Cataracts, abberant oral frenula, and growth retardation: A new autosomal dominant syndrome. Am J Med Genet 40:341–342, 1991.

Cataracts, hearing loss, hypertrichosis, short stature, and mental retardation

Schaap et al (3), in 1995, reported three brothers with congenital lamellar cataracts, sensorineural hearing loss that became apparent in early childhood, moderate to severe growth retardation, and mild mental retardation, especially involving speech. All had generalized hypertrichosis and a somewhat triangular-shaped face and full eyebrows (Fig. 30–17). Two sibs had blue sclerae and mild gingival hyperplasia. Pubertal development was delayed in all three. Radiologically, there were a partial fusion of the second and third cervical vertebrae and a moderately delayed bone age in two. As the parents were consanguineous, autosomal recessive inheritance was suggested, although X-linked recessive inheritance was also possible. The authors provide a useful differential diagnosis, which included mainly *Martsolf syndrome* (2) and the entity described by Begeer et al (1).

References (Cataracts, hearing loss, hypertrichosis, short stature, and mental retardation)

1. Begeer JH et al: Two sisters with mental retardation, cataract, ataxia, progressive hearing loss, and polyneuropathy. J Med Genet 28:884–885, 1991.
2. Hennekam RCM et al: Martsolf syndrome in a brother and sister: Clinical features and pattern of inheritance. Eur J Pediatr 147:539–543, 1988.



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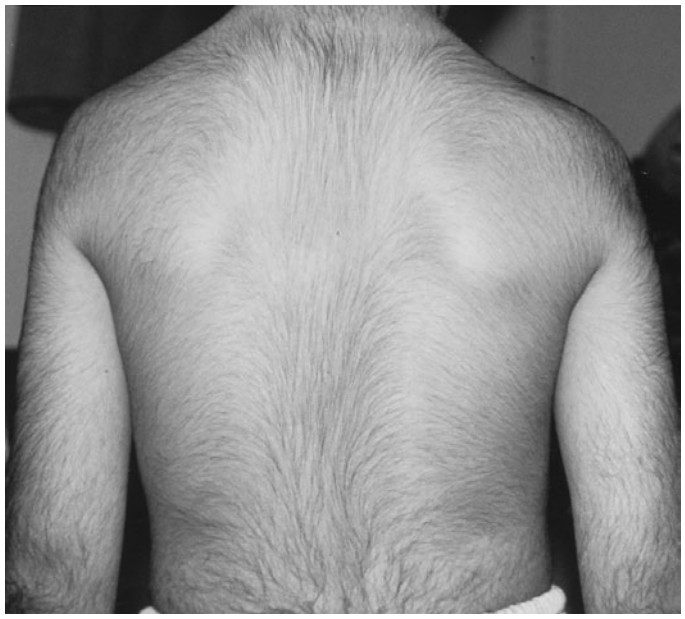

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Fig. 30–17. *Cataracts, hearing loss, hypertrichosis, short stature, and mental retardation*. (A) Three sibs at ages 10, 12, and 13 years. Note triangular face, full eyebrows. (B) Marked hypertrichosis. (From C Schaap et al, Clin Dysmorphol 4:283, 1995.)

3. Schaap C et al: Three mildly retarded siblings with congenital cataracts, sensorineural deafness, hypogonadism, hypertrichosis and short stature: A new syndrome? Clin Dysmorphol 4:283–288, 1995.

CHIME (neurectodermal dysplasia) syndrome

In 1983, Zunich and Kaye (4) described a child with migratory ichthyosiform erythroderma, retinal colobomas, ectodermal anomalies, and neurologic involvement. Five other patients have been described (1–3,5,7). Autosomal recessive inheritance has been suggested because of recurrence in one family (7), although none of the parents were consanguineous. CHIME is an acronym for *C*olobomas of the eyes, *H*eart defects, *I*chthyosiform dermatosis, *M*ental retardation, and *E*ar defects (2).

Features have included high birthweight and normal growth. All patients have been moderately to severely mentally retarded and may show episodes of violent behavior, sometimes correlating with exacerbation of the skin rash (2). Seizures are common and often therapy resistant. Neuroradiology may show cerebral atrophy (1,3–5).

Craniofacial findings. Brachycephaly, retinal colobomas,and sometimes cloudy corneas (5) or ptosis (3,4), epicanthal folds, hypertelorism, conductive hearing loss, overfolded helices, broad nasal tip and root, short philtrum (3–5), wide mouth with full lips, widely spaced teeth, bifid or additioal incisors (4,5) and cleft uvula or soft palate (3–5) have been described.

Cardiovascular system. Cardiac anomalies that were reported were Fallot's tetralogy (5), transposition of the great arteries (6), peripheral pulmonic stenosis (7), and a ventricular septal defect (2,3).

Skin. The skin showed a migratory ichthyosiform rash in all patients, present at birth or shortly afterward, and sometimes difficult to manage. Palms and soles can be thickened without scaling. Ultrastructural characteristics were nonspecific, and included disturbed keratinization with incomplete cornified cells in the lower horny layer, perinuclear edema of granular cells surrounded by a shell of keratin filaments and small keratinhyalin granules, inflammatory cells in the epidermis, and disorganization of myelin sheaths (2,6). Hair was sparse and fine. In one patient trichorrhexis nodosa was described (3). Sweating was normal. Nails may be dystrophic (3).

Skeletal system. Symptoms have been a broad second toe, brachydactyly (1,2,4,5), hypoplasia of the terminal phalanges (3), clubfoot (3,5), deviated fingers (5) or toes (3), and hypermobile joints (1). Radiological changes in one patient were short clavicles, brachydactyly of fingers and toes, pseudoepiphyses of the second and third metacarpal bones, and hypoplasia of terminal phalanges of toes (3). Bone age was normal. Their gait was often described as wide based.

Neoplasms. Three patients had a skin lipoma (3,4,6), and the patient described by Schnur et al (2) developed fatal leukemia at 5 years of age.

Other findings. Clavicles may be short (3) and nipples small and low set (1,2,4–6); one patient had a supernumerary nipple (1). Patients have been described with a duplicated renal collecting system, partially ectopic renal pelvis (3), and a ureteropelvic junction obstruction (2).

Differential diagnosis. Rud syndrome, *infantile Refsum syndrome*, Sjögren-Larsson syndrome, Netherton syndrome, *KID syndrome, IBIDS syndrome*, and *trichothiodystrophy* should be considered (2).

References [CHIME (neurectodermal dysplasia) syndrome]

1. Schnur RE et al: Acute lymphoblastic leukemia in a child with the CHIME neurectodermal dysplasia syndrome. Am J Med Genet 72:24–29, 1997.
2. Shashi V et al: Neurectodermal (CHIME) syndrome: An additional case with long term follow-up of all reported cases. J Med Genet 32:465–469, 1995.
3. Tinschert S et al: Zunich neuroectodermal syndrome: Migratory ichthyosiform dermatosis, colobomas, and other abnormalities. Pediatr Dermatol 13:363–371, 1996.
4. Zunich J, Kaye CI: New syndrome of congenital ichthyosis with neurologic abnormalities. Am J Med Genet 15:331–333, 1983.
5. Zunich J, Kaye CI: Additional case report of a new neuroectodermal syndrome. Am J Med Genet 17:707–710, 1984.
6. Zunich J et al: Congenital migratory ichthyosiform dermatosis with neurologic and ophthalmologic abnormalities. Arch Dermatol 121:1149–1156, 1985.
7. Zunich J et al: Autosomal recessive transmission of neuroectodermal syndrome. Arch Dermatol 124:1188–1189, 1988.

Coloboma of eyelid, abnormal anterior hairline, and anal anomalies

Marles et al (1) reported six Manitoba Indian cases from four related families with asymmetrical facial anomalies consisting of upper lid colobomata, in one accompanied with anophthalmia, and in others with palpebral synechiae and nasolacrimal duct obstruction, and hypertelorism. Three had mild groove of the nasal tip. The anterior hairline extended

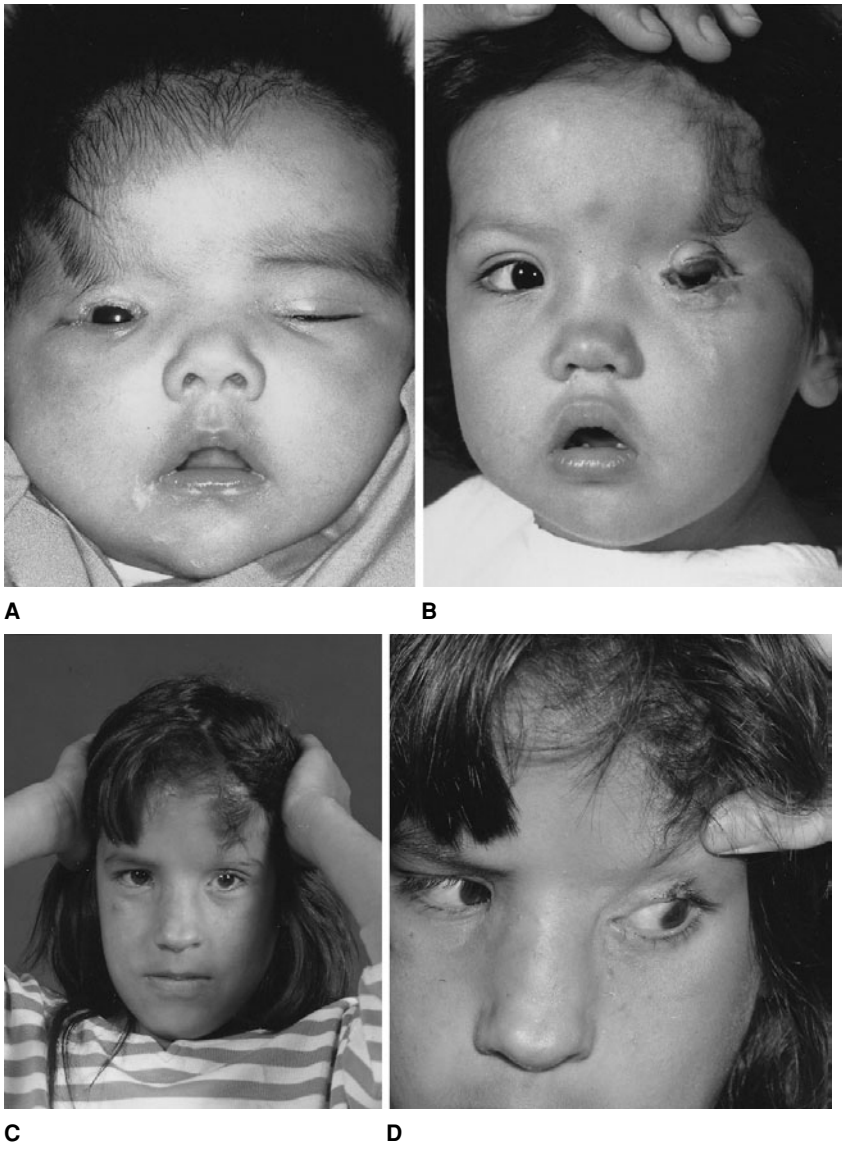


Fig. 30–18. *Coloboma of eyelid, abnormal anterior hairline, and anal anomalies*. (A–D) Compare children of various ages. Note coloboma of upper eyelids, aberrant wedge of scalp hair, absent eyelashes, slight groove of nasal tip. (A,B from SL Marles et al, Am J Med Genet 42:793, 1992. C,D from AE Chudley, Winnipeg, Manitoba, Canada.)

onto the forehead down to the affected eye (Fig. 30–18). Macrocephaly was present in two. Anal anomalies consisted of stenosis or anterior displacement. No syndactyly was found. Growth and development was normal. Inheritance is probably autosomal recessive.

The symptoms resemble *cryptophthalmos syndrome* and *cat eye syndrome*.

Reference (Coloboma of eyelid, abnormal anterior hairline, and anal anomalies)

1. Marles SL et al: New familial syndrome of unilateral upper eyelid coloboma, aberrant anterior hairline pattern, and anal anomalies in Manitoba Indians. Am J Med Genet 42:793–799, 1992.

Coloboma of lens and nasal alae

In 1983, Magli et al (1) reported a monozygotic twin with either unilateral or bilateral coloboma of the lens and unilateral coloboma of the nasal alar cartilage. There was also a disorganized vitreous and a chorioretinal myopic dystrophy, but these were also present in otherwise unaffected family members. Bone age was retarded. Both had an open first sacral neural arch, but otherwise no anomalies were present and development was normal.

In differential diagnosis, coloboma of the nasal alae with pseudohypertelorism (2) and arhinia with hypertelorism and Peters anomaly (3) should be considered.

References (Coloboma of lens and nasal alae)

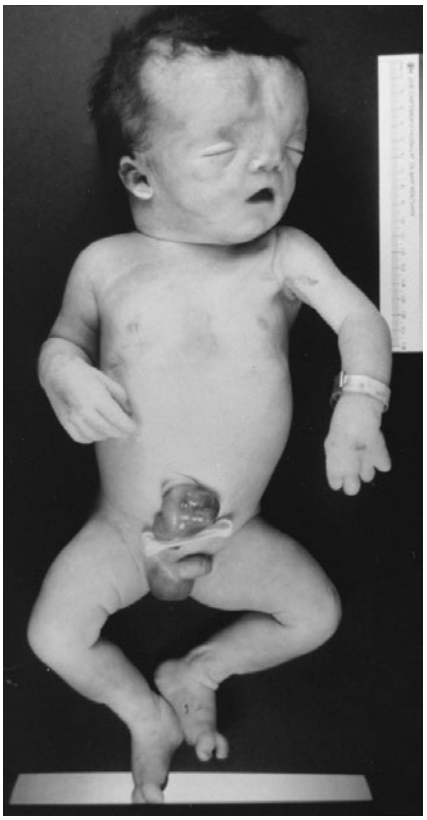
1. Magli A et al: Coloboma of the lens associated with coloboma of the alar nasal cartilages in a pair of female monozygotic twins: A new syndrome? Ophthalmic Paediatr Genet 2:83–87, 1983.

2. Rimoin DL: Hypoplasia and coloboma of the alar-nasal cartilages with pseudohypertelorism in sibs. Birth Defects 5:224–225, 1969.

3. Ruprecht KW, Majewski F: Familiare Arhinie mit Petersscher Anomalie und Kiefermisbildungen, ein neues Fehlbildungssyndrom? Klin Monatsbl Augenheilkd 172:708–715, 1978.

Diaphragmatic hernia-exomphalos-hypertelorism (Donnai-Barrow, FOAR, Holmes-Schepens) syndrome

Donnai and Barrow (2), in 1993, described three unrelated sets of sibs with hypertelorism, severe myopia, diaphragmatic hernia, omphalocele and/or malrotation of the bowel, and sensorineural hearing loss. Gripp et al (4) confirmed the syndrome and added two examples. Schowalter et al (10) noted that it is the same as facio-oculo-acoustico-renal (FOAR,



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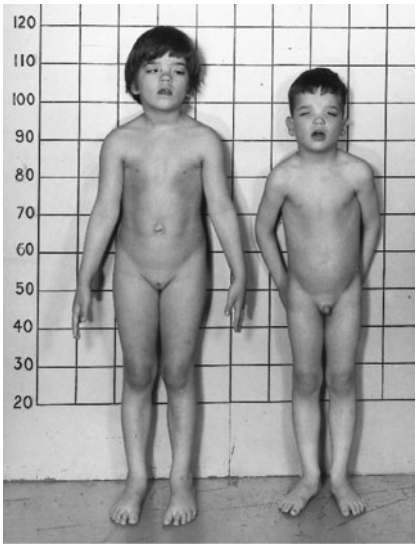

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Fig. 30–19. *Diaphragmatic hernia-exomphalos-hypertelorism (Donnai-Barrow, FOAR, Holmes-Schepens) syndrome*. (A) Open metopic suture, frontal bossing, hypertelorism, omphalocele. (B) Sibs with severe congenital hearing loss, hypertelorism, ptosis, flat nasal bridge. [A from K Gripp et al, Am J Med Genet 68:441, 1997. B from FL Özer, Birth Defects 10(4):168, 1974.]

Holmes–Schepens) syndrome (6–10), which was confirmed by Devriendt et al (1).

The disorder appears to be autosomal recessive. The parents were normal. There were affected sibs and parental consanguinity (2,4,7,10). Mutations in the *PAX2* gene have been suggested as a possible cause (10).

Birthweight was at the 97th centile for two of the children (2). Macrocephaly has been noted repeatedly (1,2,4,5,10).

Craniofacial findings. The face exhibited wide anterior fontanel, marked hypertelorism, downslanting palpebral fissures, prominent eyes, and short nose with broad, indented lip (Figs. 30–19 and 30–20). The myopia is exceptionally severe. Bilateral inferior iris coloboma has been present (1,4,10). The ears were low and posteriorly rotated. Sensorineural hearing loss was marked (1,2,4,5,7,9,10).

Other findings. Developmental delay varied from mild to severe. On ultrasound scan, agenesis of the corpus callosum was found (2,4). Diaphragmatic hernia, exomphalos, and/or intestinal malrotation were present in almost all cases. VSD was also found (4). Proteinuria has been reported (1,4,7,10), usually without structural anomalies.

Differential diagnosis. The facies is similar to that of *DeHauwere syndrome*, but that disorder has autosomal dominant inheritance and is not associated with diaphragmatic hernia or exomphalos. Diaphragmatic hernia and omphalocele has been reported to occur together with bilateral radioulnar synostosis, hepatic cyst, unilateral absent thumb and contralateral triphalangeal thumb (3).

References [Diaphragmatic hernia-exomphalos-hypertelorism (Donnai-Barrow, FOAR, Holmes-Schepens) syndrome]

1. Devriendt K et al: Proteinuria in a patient with the diaphragmatic hernia-hypertelorism-myopia-deafness syndrome: Further evidence that the facio-oculo-acoustico-renal syndrome represents the same entity. J Med Genet 35:70–71, 1998.

2. Donnai D, Barrow M: Diaphragmatic hernia, exomphalos, absent corpus callosum, hypertelorism, myopia and sensorineural deafness—a newly recognized autosomal recessive disorder? Am J Med Genet 47:679–682, 1993.

3. Gershoni-Baruch R et al: Unknown syndrome: Radial ray defects, omphalocele, diaphragmatic hernia, and hepatic cyst. J Med Genet 27:403–404, 1990.

4. Gripp KW et al: Diaphragmatic hernia-exomphalos-hypertelorism syndrome: A new case and further evidence of autosomal recessive inheritance. Am J Med Genet 68:441–444, 1997.

5. Holmes LB, Schepens CL: Syndromes of ocular and facial anomalies, telecanthus and deafness. J Pediatr 81:552–555, 1972.

6. Murdoch JL, Mengel MC: An unusual eye-ear syndrome with renal abnormality. Birth Defects 7(4):136, 1971.

7. Ohlsson L: Congenital renal disease, deafness and myopia in one family. Acta Med Scand 63:77–84, 1968.

8. Özer FL: A possible 'new' syndrome with eye and renal abnormalities. Birth Defects 10(4):168, 1974.

9. Regenbogen LS, Coscas CJ: Oculo-Auditory Syndromes. Masson, New York, 1985, pp 104–105.

10. Schowalter DB et al: Facio-oculo-acoustico-renal (FOAR) syndrome: Case report and review. Am J Med Genet 69:45–49, 1997.

Gum/jaw fusion (syngnathia), colobomata, and developmental delay

Dobrow (1) reported a 6-month-old female with bony fusion of the maxillary and mandibular bones except for the incisor region, bilateral iris coloboma giving rise to microphthalmia on one side, and global developmental delay. There was in addition microcephaly, thin blond scalp hair, a small fontanel, unilateral choanal atresia, cleft palate, hypoplasia of the tongue, and pursed lips. Growth was delayed. Radiographs showed the bony fusion of mandible and maxilla, and hemivertebrae at the first, second, and third thoracic level. A brain CT scan gave normal results.

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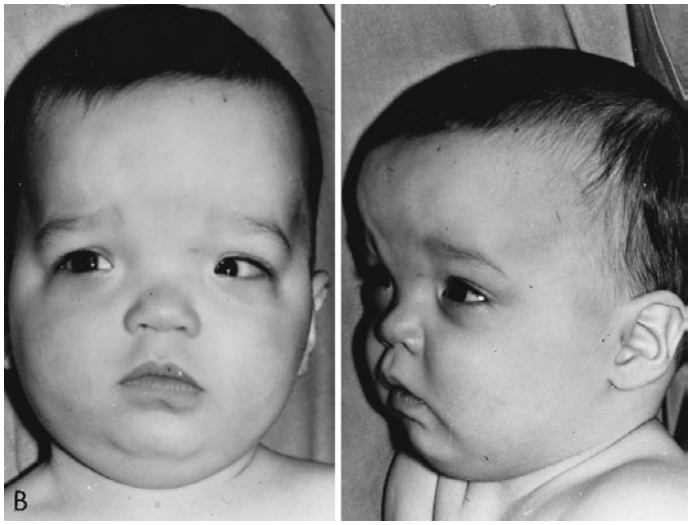

B

Fig. 30–20. *Diaphragmatic hernia-exomphalos-hypertelorism (Donnai-Barrow, FOAR, Holmes-Schepens) syndrome*. (A) Note hypertelorism, downslanting palpebral fissures, low-set posteriorly rotated ears, and mild mandibular prognathism. (B) Male sib at 7 months of age. Note large head circumference, prominent frontal bone, and ocular hypertelorism. (A from D Donnai and M Barrow, Am J Med Genet 47:679, 1993. B from LB Holmes and CL Schepens, J Pediatr 81:552, 1972.)

Grosse and Wiedemann (3) and Sternberg et al (5) reported cases with gum/jaw fusion and colobomata of the lower eyelids. Good literature reviews (2–4) are available.

References [Gum/jaw fusion (syngnathia), colobomata, and developmental delay]

1. Dobrow B: Syngnathia and multiple defects. J Clin Dysmorphol 1(2):5–7, 1983.

2. Gartlan FR et al: Congenital oral synecchiae. Ann Otol Rhinol Laryngol 102:186–197, 1993.

3. Grosse FR, Wiedemann H: Syndromes with reduction and surplus anomalies of the hand. Birth Defects 13(1):301–318, 1977.

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Iris coloboma, macrocephaly, agenesis of the corpus callosum, brachydactyly, and mental retardation

Temtamy et al (1) reported three sibs with colobomata of the iris, retina, and choroid, upward dislocated lenses and myopia, macrocephaly, dolichocephaly, hypertelorism, beaked nose, long philtrum, thin upper vermilion border, micrognathia, and prominent, simple ears. The published figures also show sparsely implanted curly hair, and full lower lip. The teeth were crowded and hypoplastic. In one case the closure of the fontanels was delayed. Cardiovascular examination showed moderate dilatation of the aorta and aortic regurgitation in two. One of them died at 22 years of sudden heart failure. Bulbous thumbs and brachydactyly of the second to fifth finger were present in all three. One case had talipes equinovarus, and developed contractures and hip dislocations at 10 years of age. Radiologically there were striking digital markings of the skull and complete agenesis of the callosal body. Development was mildly delayed. Parents had no anomalies and were first cousins, suggesting autosomal recessive inheritance.

The authors provide a useful differential diagnosis of entities accompanied by iris coloboma. The facial features resemble those of *trichorhinophalangeal syndrome* to some extent. The lens dislocations, aortic dilatation, and joint problems may point to a connective tissue disorder.

Reference (Iris coloboma, macrocephaly, agenesis of the corpus callosum, brachydactyly, and mental retardation)

1. Temtamy SA et al: New autosomal recessive multiple congenital anomalies/mental retardation syndrome with craniofacial dysmorphism, absent corpus callosum,iris colobomas and connective tissue dysplasia. Clin Dysmorphol 5:231–240, 1996.

Iris coloboma, ptosis, hypertelorism, and mental retardation (Baraitser-Winter syndrome)

Baraitser and Winter (2) reported the occurrence of coloboma of the iris, ptosis, hypertelorism, broad flat nasal bridge, and growth retardation in patients with mental retardation. Seventeen other patients were described (1,3–11), although some authors were of the opinion that their cases had a similar but still different entity (4), or Noonan syndrome (3). Inheritance may be autosomal recessive (2,4), but as two cases had an apparently balanced pericentric inversion of chromosome 2 (breakpoints p12 and q14)(1,6,7), a submicroscopic deletion or duplication can not be discarded. Ramer et al (9) drew attention to the localization of the *PAX8* gene at chromosome 2q12–14.

Postnatal growth is retarded in all patients. Ramer et al (9) and Megarbane et al (4) provide useful reviews.

Craniofacial findings. Usually there is microcephaly, but normal head circumference is also described. There is trigonocephaly or metopic ridging, epicanthal folds, hypertelorism, ptosis with virtual absence of folding of the eyelids, downslanting of the palpebral fissures, broad and flat nasal bridge, short nose with a broad and sometimes upturned tip, long and hypoplastic philtrum, and thin upper vermilion border. The mouth is large, and the palate may be highly arched (Fig. 30–21). Most but not all (1,4) patients have colobomas of the iris, sometimes unilateral (2). Also chorioretinal colobomas may be present. The colobomas can cause microphthalmia and microcornea. The ears may be short and low set with overfolded helices. Several patients had sensorineural hearing loss (8,9,11). In one patient the synostosis of the metopic ridge was of sufficient severity to warrant surgery (8).

Cardiac manifestations. Ventricular septal defects (8), pulmonary stenosis (3,8), tricuspid insufficiency (11), and bicuspid aortic valve (9) are described.

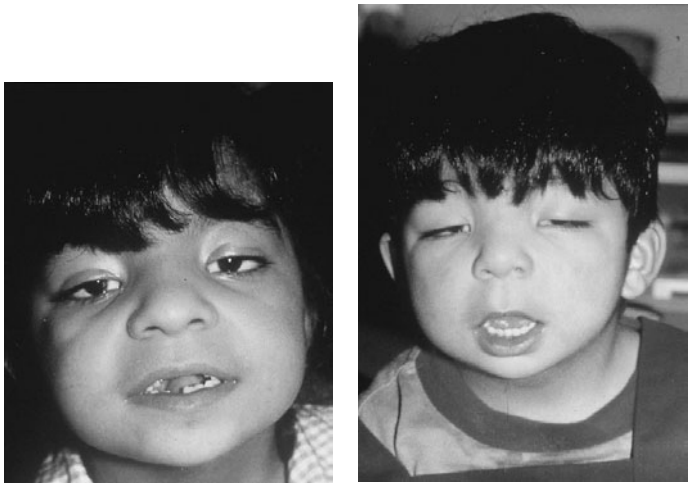

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Fig. 30–21. *Iris coloboma, ptosis, hypertelorism, and mental retardation (Baraitser-Winter syndrome)*. (A) Seven-year-old girl with bilateral ptosis, hypertelorism, epicanthic folds, broad and flat nasal bridge. (B) Sib with similar features. (A,B from M Baraitser and RM Winter, J Med Genet 25:41, 1988.)

Central nervous system. Most patients are moderately to severely mentally retarded. Reported structural brain anomalies are lissencephaly (type I) (9), focal pachygyria (2,8), lobar holoprosencephaly (9), generalized bilateral cerebral atrophy (4), thin corpus callosum (4), and occipital and temporal ischemic lesions (8).

Other findings. Most had a short and webbed neck, with low posterior hairline. The chest has been descibed as broad (9) with pectus excavatum (3,11), short sternum (9), and hypoplastic nipples (4,9). One case had multiple hemivertebrae and apparently unilateral absent lung (9), another had an omphalocele and accessory spleen (5), and yet another, a horseshoe kidney (11). Clinodactyly of the fifth finger (8), and cryptorchidism and hypoplasia of the external genitalia were mentioned.

Differential diagnosis. A host of other syndromes combining coloboma-ptosis-hypertelorism have been reviewed by Verloes (11), but all manifest additional findings. There is superficial resemblance to *Noonan syndrome*, but we concur that the facial features in *Baraitser-Winter syndrome* are different (2).

References [Iris coloboma, ptosis, hypertelorism, and mental retardation (Baraitser-Winter syndrome)]

1. Aymé S et al: Abnormal childhood phenotypes associated with the same balanced chromosome rearrangements as in parents. Hum Genet 48:7–12, 1979.
2. Baraitser M, Winter RM: Iris coloboma, ptosis, hypertelorism, and mental retardation: A new syndrome. J Med Genet 25:41–43, 1988.
3. Hall BD: Iris coloboma, ptosis, hypertelorism and mental retardation. J Med Genet 26:69, 1989.
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5. Le Marec B et al: A new syndrome with ptosis, coloboma and mental retardation. Genet Couns 3:119–120, 1992.
6. Pallotta R: Una nuova sindrome a probabile localizzazione sul cr 2. Riv Ital Pediatr 13:207, 1987.
7. Pallotta R: Iris coloboma, ptosis, hypertelorism, and mental retardation: A new syndrome possibly localised on chromosome 2. J Med Genet 28:342–344, 1991.
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Kaufman (oculo-cerebro-facial) syndrome

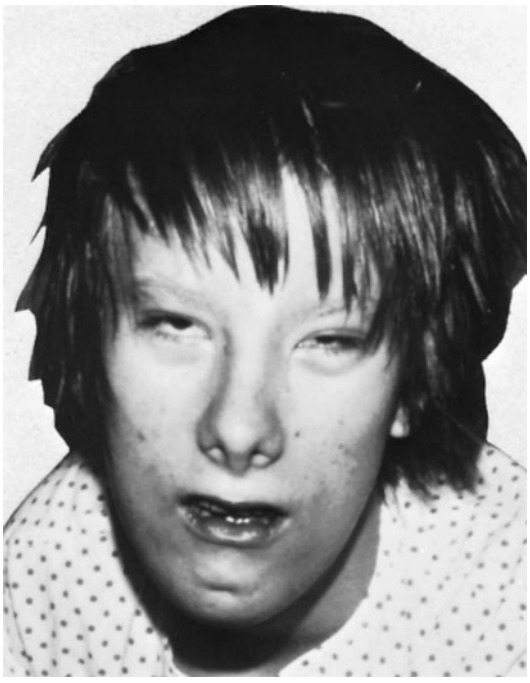
In 1971, Kaufman et al (5) documented four of seven sibs with mental retardation, microcephaly, long narrow face, and ocular and skeletal anomalies. Five other cases were reported (1–4), although the diagnosis in case B described by Figuera et al (2) seems doubtful to us. Autosomal inheritance seems likely (1).

Height is at or just below the third centile, although the original patients had normal height (5). Developmental delay is severe. In three cases, pubertal development was reported to be normal (1,5). Briscioli et al (1) provide a useful review.

Craniofacial findings. Almost all patients had microcephaly, brachycephaly, and a long and narrow face (Fig. 30–22). There are upward slanted palpebral fissures, sparse eyebrows that are laterally broadening, mild blepharophimosis, and epicanthi or telecanthi. Eye symptoms include myopia, microcornea, and pale optic discs. Several patients had nystagmus and strabismus. One case had a subluxated lens (1). The columella is especially low in part due to a hypoplasia of the alae, the tip of the nose is rounded. The philtrum is poorly defined, the vermilion border thin, but the total upper lip is protruding. The mouth is usually large, the teeth small, the palate high and narrow, and the chin small. One patient had increased dental caries (1,5); another had a single upper central incisor (2). The ears are small, and posteriorly rotated. Most cases had preauricular tags. In one case thin blond hair was noted (5).

Musculoskeletal findings. Almost all cases had a diminished muscle tone. A moderately increased kyphosis or lordosis may be present. Hands and feet are reported to be thin and long. There may be pes

Fig. 30–22. *Kaufman (oculo-cerebro-facial) syndrome*. Note microcornea and unusual nasal configuration. [From RL Kaufman et al, Birth Defects 7(1):135, 1971.]



varus (3). Radiographs have showed turricephaly and hypoplastic medial and distal phalanges (1).

Other findings. Respiratory problems in the neonatal period are very common. One case had pyloric stenosis (4), another had hypsarrhythmia (1), and yet another prolonged neonatal jaundice (5). Mitral valve prolapse (3) and enlarged clitoris (2,4) have been described.

Differential diagnosis. Heart-hand syndrome type IV, *oculodentoosseous dysplasia*, and *Hallermann-Streiff syndrome* should be considered (1).

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Knobloch syndrome (myopia, retinal detachment, and encephalocele)

In 1971, Knobloch and Layer (4) reported a syndrome in four sibs characterized by high myopia, vitreoretinal degeneration which eventuated in detachment, and encephalocele. Most encephaloceles are occipital, but anterior examples have been noted (9). Several other authors have confirmed the syndrome (2,3,5,6,10).

The myopia is severe, greater than 20 diopters. Vitreous syneresis leads to retinal detachment. There is no lattice degeneration. Nystagmus, macular abnormality, early cataract formation, and young age of onset of retinal detachment (from 2–10 years of age) are seen (1).

CT scan or MRI often shows a cranial bone defect (5), most often occipital, or an extracranial nodular lesion covered by skin. Congenital occipital scalp defects with heterotopic neuronal tissue is the least expression of the encephalocele (Fig. 30–23).

Miscellaneous findings include duplicated collecting system and bifid ureter (2), mild hyperextensibility (6), scimitar syndrome (4), patent ductus arteriosus (10), single umbilical artery (10), and pyloric stenosis (10).

Inheritance is clearly autosomal recessive, there being multiple affected sibs (1–6,9,10) and parental consanguinity (5). The gene has been mapped to 21q22.3 (7). Type 18A1 collagen gene has been suggested as a possible candidate (8).

Two other autosomal recessive disorders with scalp defects and retinal dysplasia are *Walker-Warburg syndrome* and *Meckel syndrome*.

References [Knobloch syndrome (myopia, retinal detachment, and encephalocele)]

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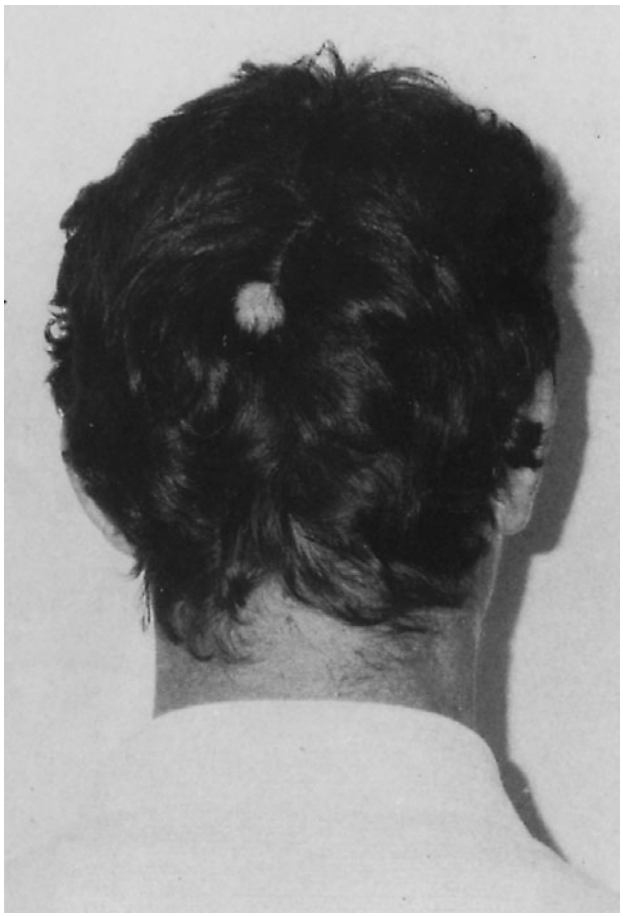

Fig. 30–23. *Knobloch syndrome (myopia, retinal detachment, and encephalocele)*. Congenital occipital scalp defect with heterotopic neuronal tissue. (From MR Passos-Bueno et al, Am J Med Genet 52:170, 1994.)

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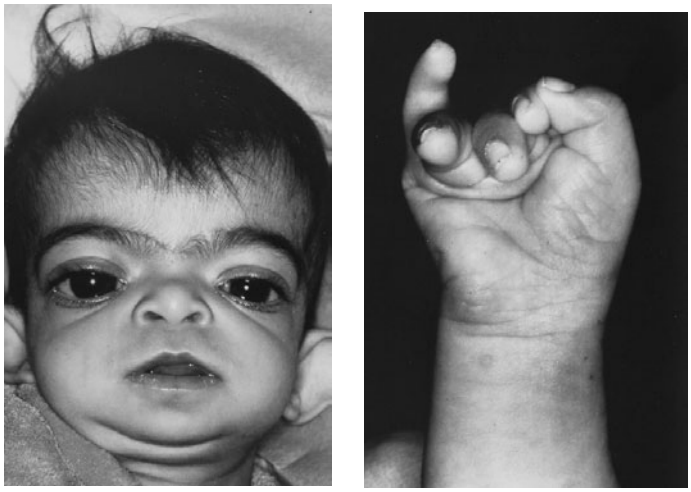
Megalocornea and mental retardation

Although at least two dozen examples of this combination have been described, there is pronounced heterogeneity which encompasses at least four syndromes. A thoughtful analysis is that of Verloes et al (17), although this has been criticized (2). Barisic et al (2) provide a useful tabulation of the total group of disorders.

Megalocornea is a congenital symmetrical nonprogressive enlargement of the cornea (13 mm or above) with normal intraocular pressure. It may be (a) an isolated finding, (b) in combination with iris hypoplasia or iridocorneal dysgenesis, probably due to abnormal migration of neural crest cells, or (c) in syndromal combination. X-linked inheritance is common in the isolated form, the gene having been mapped to Xq21–q22 (4).

At least four types of megalocornea-mental retardation syndrome can be delineated (17):

1. Neuhäuser syndrome—megalocornea, iris hypoplasia, mild telecanthus, epicanthal folds, broad nasal base, long philtrum, mental retardation,



A B

Fig. 30–24. *Megalocornea and mental retardation (Frank-ter Haar type).* (A,B) Megalocornea, frontal bossing, hypertelorism, downslanting palpebral fissures, bushy eyebrows, outstanding pinnae, short nose with anteverted nostrils, prominent lips and ears, finger contractures. (From T Billette de Villemeur et al, Eur J Pediatr 151:146, 1992.)

hypotonia, seizures, and autosomal recessive inheritance [1,2,5(Case 1), 11,13(Cases 1–3),15].

2. Frank–ter Haar syndrome—megalocornea, frontal bossing, flat occiput, hypertelorism, downslanting palpebral fissures, bushy eyebrows, short saddle nose with broad nasal tip, anteverted nostrils, large ears, prominent lips, carp-shaped mouth, gingival enlargement, micrognathia, normal intelligence, delayed closure of anterior fontanel, short extremities, camptodactyly, scoliosis, talipes, growth retardation, prominent coccyx with skin fold, and autosomal recessive inheritance (2,3,8,10,12,16) (Fig. 30–24). Some of the cases cited, however, have congenital glaucoma (12).

3. Verloes syndrome—megalocornea, mental retardation, short saddle nose, large ears, short stature, talipes, delayed closure of fontanels, hypertelorism, micrognathia, prominent coccyx with skin fold, frontal bossing, broad prominent nasal root, downslanting palpebral fissures, malar hypoplasia, long thorax, thin fingers [5(Case 2),9,17(Cases 1 and 4)].

4. Frydman form—megalocornea, mental retardation, downslanting palpebral fissures, macrocephaly, fleshy ears, obesity, long fingers, joint hypermobility, and unknown inheritance [5(Case 2),8].

Several other syndromes associated with megalocornea have to be taken into account in the differential diagnosis (14,17).

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Michels syndrome (craniosynostosis and lid anomalies)

In 1978, Michels et al (5) reported four siblings with anomalies of the anterior chamber of the eye, the triad blepharophimosis, ptosis, and epicanthus inversus, clefting, craniosynostosis, and mild developmental delay. The same sibship was updated by de La Paz et al (3), and two other patients were described (2,4). Affected sibs born to unaffected parents (3,5), and consanguinity (4) suggest autosomal recessive inheritance.

Postnatal growth deficiency and in one case postnatal overgrowth occurs. A useful tabulation of the symptoms is available (4).

Craniofacial findings. Two cases were microcephalic, one had a large head (2). Craniosynostosis of the lambdoid (5) and coronal sutures (2,4) is common. The skull may be markedly asymmetrical, especially in infancy. The anterior fontanel can be large. Supraorbital ridges were found hypoplastic (2,4). Cleft lip and palate was present in three cases. As a consequence, teeth were sometimes crowded. Conductive hearing loss has been found (3,4).

Eye symptoms were increased arching of the eyebrows, hypertelorism, blepharophimosis, ptosis, epicanthus inversus, and anterior chamber anomalies: opacities of the corneal stroma, conjunctival telangiectasia, and iridocorneal adhesions (3). One patient developed glaucoma (3), another had astigmatism.

Other findings. A periumbilical depression and short fifth finger are common other findings. Rare symptoms are accessory nipple (5), small omphalocele (5), hydronephrosis (5), limited pronation-supination in the elbows (4,5), short and broad feet (4), sacral dimple (4,5), and seizures associated with fever (2).

Differential diagnosis. There are similarities with *Peters plus syndrome, Ohdo syndrome, Saethre-Chotzen syndrome*, and the family described by Paes-Alves et al (6). The condition reported by Al-Gazali et al (1) may be related.

References [Michels (craniosynostosis and lid anomalies) syndrome]

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Midline craniofacial anomalies and morning glory disc anomaly

The morning glory disc anomaly is a large scleral defect with an elevated funnel-shaped optic disc. The center of the funnel is usually filled with white glial tissue, while the disc is surrounded by a raised chorioretinal pigmentary border. Ocular, craniofacial, and renal anomalies are frequently associated. Nucci et al (11) described a girl with unilateral morning glory anomaly and a 4q12–qter duplication. Morioka et al (10) reviewed the literature.

Craniofacial anomalies. Marked hypertelorism, basal encephalocele and cleft lip/palate are the most common findings. The cleft is usually midline, separating the two nostrils (1–10,12,13), resulting in a frontonasal malformation appearance (Fig. 30–25).

The most common ocular complication is retinal detachment (35%). However, other findings include decreased visual acuity, strabismus, cataract, anterior segment dysgenesis, and persistent hyaloid remnants (Fig. 30–26A). The morning glory defect is usually unilateral (10), but bilateral defects have been documented (6,8,13).

Brain malformations include basal encephalocele, porencephaly, and agenesis of the corpus callosum (3) (Fig. 5– 26B). Pituitary dwarfism can complicate the picture (3,7).

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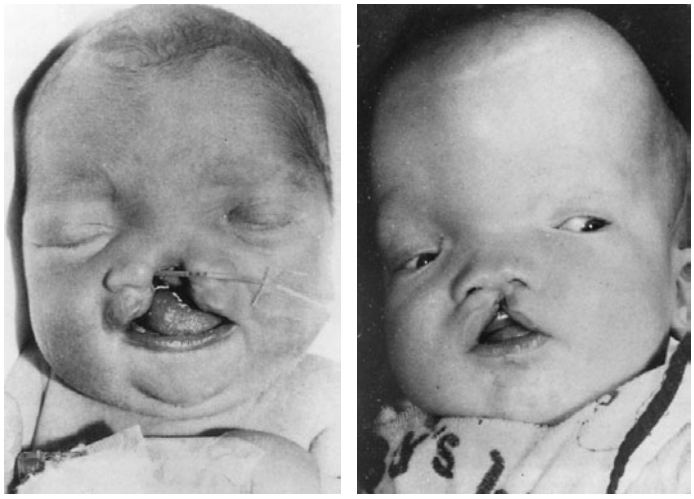
Fig. 30–25. *Midline craniofacial anomalies and morning glory disc anomaly*. (A,B) Marked hypertelorism and midline cleft separating the two nostrils. In B, note exotropia. Both have basal encephalocele. (A from RJ Lestch and RM Winter, Acta Ophthalmol Scand 74:16, 1996. B from M Hope-Ross and SS Johnston, Ophthalmic Paediatr Genet 11:147, 1990.)



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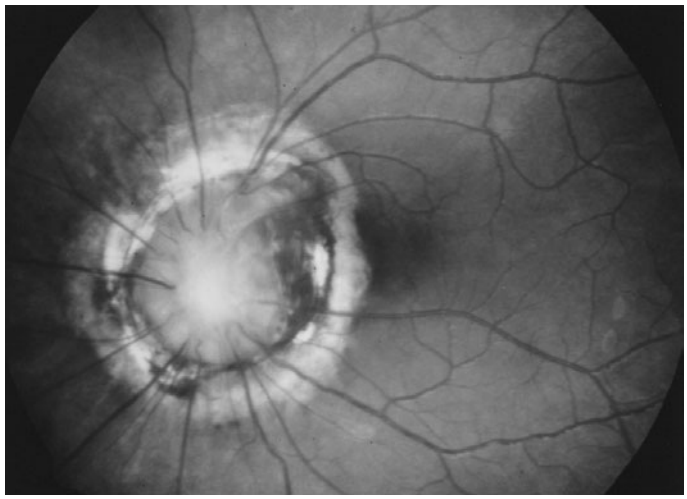

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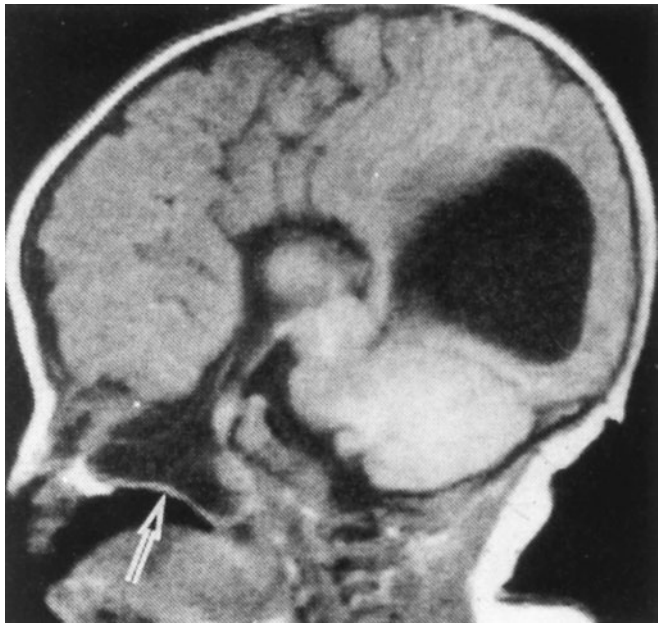

B

Fig. 30–26. *Midline craniofacial anomalies and morning glory disc anomaly*. (A) Retina showing morning glory disc anomaly. (B) Mass extending into retropharyngeal region and posterior oral cavity (arrow) and agenesis of corpus callosum. (A courtesy of CG Summers, Minneapolis, Minnesota. B from T Itakura et al, J Neurosurg 77:949, 1992.)

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Myopia, cataracts, saddle nose, and sensorineural hearing loss (Marshall syndrome)

Seven members in four generations of a family studied by Marshall (5), in 1958, had short stature, hypoplastic nasal bones, congenital and juvenile cataracts, myopia with vitreoretinal degeneration, and sensorineural hearing loss. Other kindreds have been reported (4,6,7,9–12,14,15). There has been considerable debate concerning the identity of this disorder with Stickler syndrome, a condition that has considerable overlap (3,8,11a,14,16). Aymé and Preus (2) suggested that they are separate conditions. Griffith et al (3) demonstrated a splicing defect at the COL11A1 locus at 1p21. This would raise the question of identity with type 2 Stickler syndrome. Shanske et al (11) have questioned the diagnosis of Griffith et al (3). COL11A1 gene is a good candidate for Marshall syndrome (13).

The disorder, occurring in several generations, is clearly dominant. However, since there have been no examples of male-to-male transmission, X-linkage cannot yet be excluded.

The facies, produced by the markedly small nose with sunken nasal bridge, anteverted nostrils, and hypoplastic or flattened midface, is striking (Fig. 30–27).

Failing vision usually occurs in the second decade of life, but in one patient of Ruppert et al (9) and in another of Marshall (5), it occurred within the first 6 months. Posterior polar cortical and subcapsular opacities that were spontaneously resorbed were noted in the second, third, and fourth decades by Ruppert et al (9). Although the mother reported by Zellweger et al (15) had cataracts since 15 years of age, her children had not yet developed cataracts at 7–11 years of age. Severe myopia (10 diopters or more) was also evident from birth, as was fluid vitreous. Retinal detachment occurred in one patient of Marshall (5) and in the father of the Ruppert et al (9) proband at 14 years of age.

In the kindred studied by Marshall (5), affected family members reported some hearing loss in childhood. This loss progressed and eventually hearing aids were required. Audiometric tests were reported as showing about 50 dB mixed or mostly sensorineural hearing loss in several members. Ruppert et al (9) found severe hearing loss as early as 9 months of age in one child; at 6 years it did not appear to be progressive. A moderate high-tone sensorineural loss was noted in the father, and there were normal vestibular findings.

Radiographic changes include hypoplastic nasal bones, hypoplastic maxilla, absent frontal sinuses, and thickening of the outer table of the skull. O'Donnell et al (7) noted intracranial calcifications, beaked or bullet-shaped vertebrae in children, markedly concave vertebral margins in adults, small irregular pelvis with delayed closure of pubic and ischial bones, coxa valga, mild bowing of radius and ulna, and somewhat irregular epiphyses of extremities.

Saddle-nose defect may be seen in congenital syphilis, *acrodysostosis, chondrodysplasia punctata, coumarin embryopathy*, and *OSMED*. Myopia may occur as an isolated finding, as an autosomal dominant or recessive trait, or as a component of numerous syndromes such as X-linked myopia and external ophthalmoplegia, *spondyloepiphyseal dysplasia congenita, Stickler syndrome*, and *Wagner syndrome*.

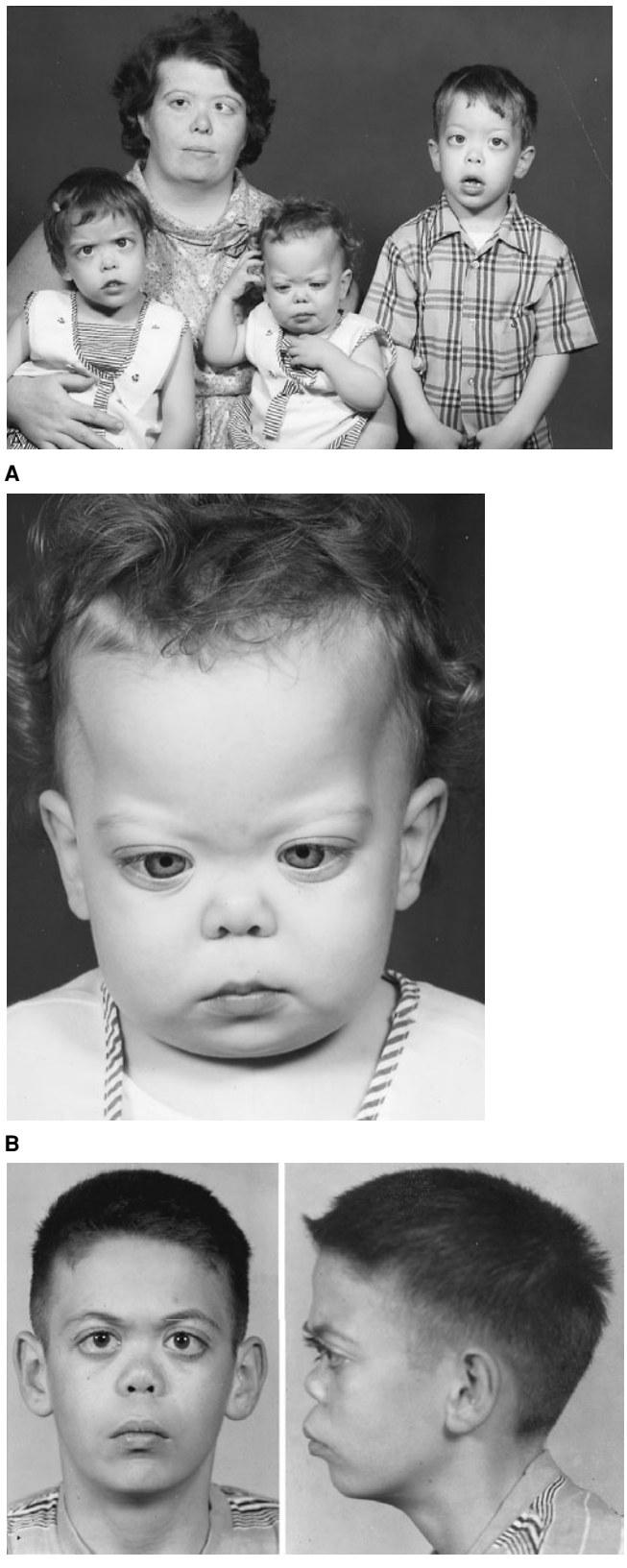

Fig. 30–27. *Myopia, cataracts, saddle nose, and sensorineural hearing loss (Marshall syndrome)*. (A) Similar facies in a mother and three of her affected children. (B) Facies of child seen in A. (C) Facies shows small nose, depressed nasal bridge, and anteverted nostrils. Note that both eyes may be seen from the side. (A,B from H Zellweger et al, J Pediatr 84:868, 1975. C from D Marshall, Am J Ophthalmol 45:143, 1958.)

References [Myopia, cataracts, saddle nose, and sensorineural hearing loss (Marshall syndrome)]

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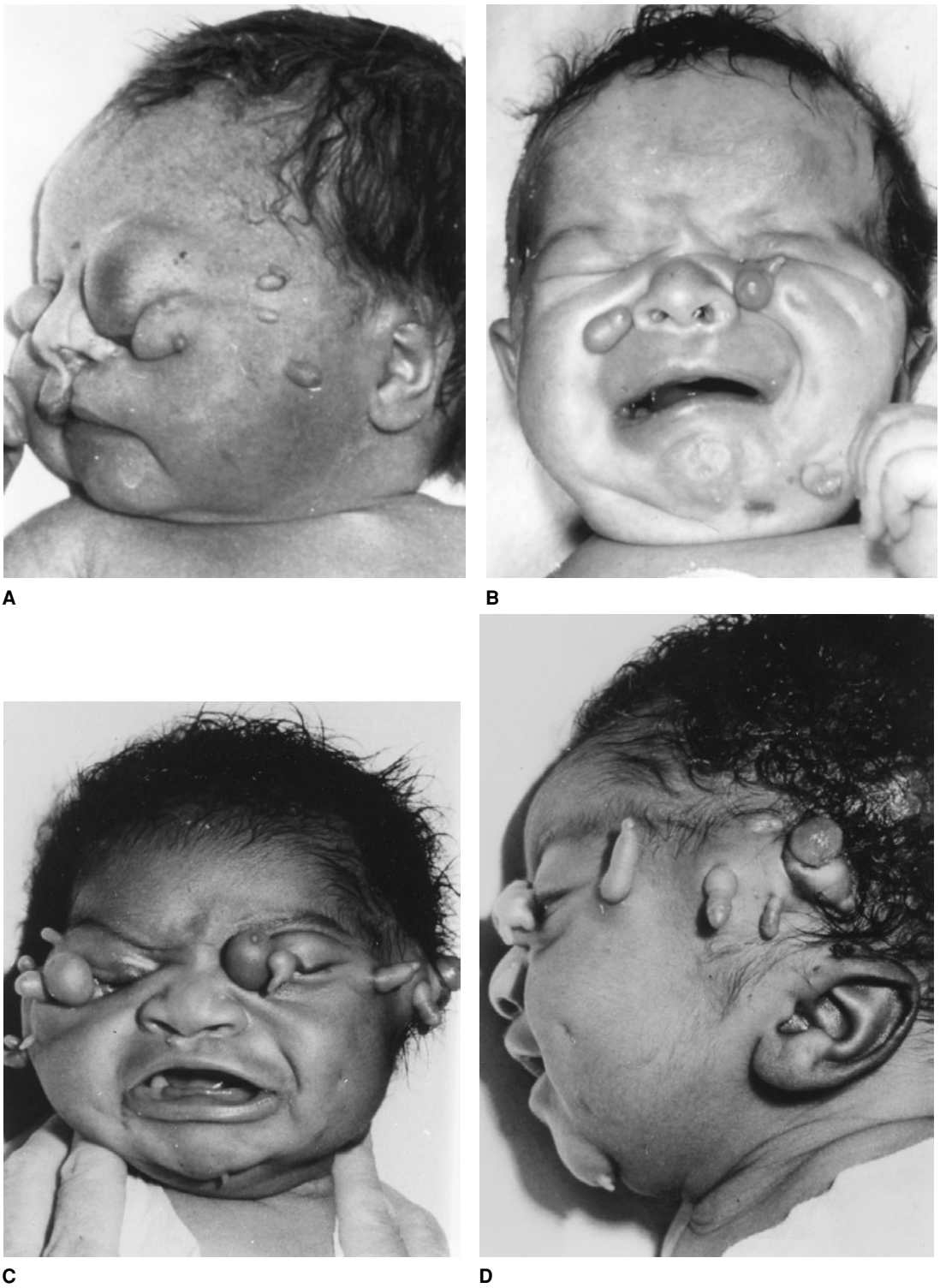

Fig. 30–28. *Oculocerebrocutaneous syndrome*. (A) Note orbital cysts in addition to cleft lip. (B) Note multiple skin tags, depressions in skin of chin and left cheek. (C,D) Another child showing skin tags as well as low-set posteriorly rotated pinna. (A from JW Delleman et al, Clin Genet 25:470, 1984. B courtesy of I Schafer, Cleveland, Ohio.)

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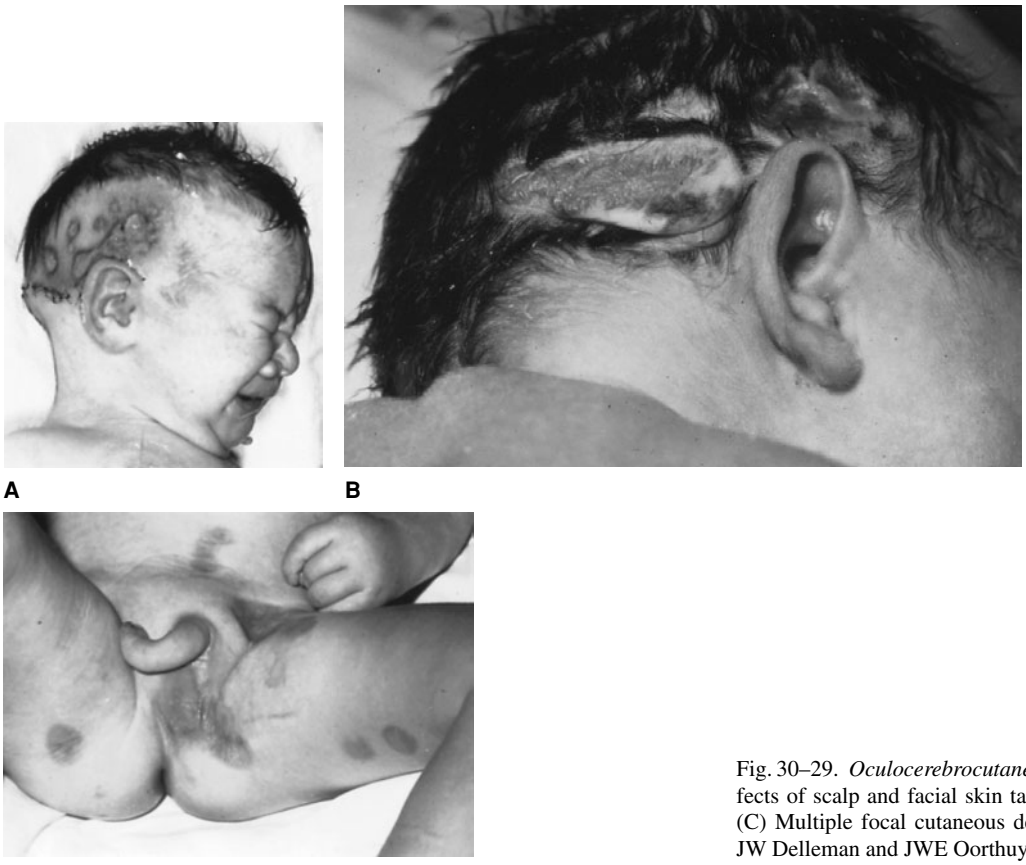

Fig. 30–29. *Oculocerebrocutaneous syndrome*. (A) Numerous cutaneous defects of scalp and facial skin tags. (B) Characteristic retroauricular defect. (C) Multiple focal cutaneous defects and underdeveloped scrotum. (From JW Delleman and JWE Oorthuys, Clin Genet 19:191, 1981.)

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Oculocerebrocutaneous syndrome (Delleman syndrome)

Delleman et al (7,8) first delineated the syndrome of orbital cysts, cerebral malformations, accessory skin tags, and focal cutaneous hypoplasia (aplasia cutis congenita). About 35 other cases have been published (1,3,4,6,9–17,19–27). All have been isolated examples. Happle (12) suggested the disorder is due to an autosomal dominant lethal somatic mutation that survives by mosaicism. The male:female ratio is 3:2. Disruption of the anterior neuroectodermal plate has been posited (19,20). We believe that this disorder has been underreported, since many examples of cystic eye represent incomplete forms. Some cases have been labeled as examples of rhabdomyomatous mesenchymal hamartomas (24).

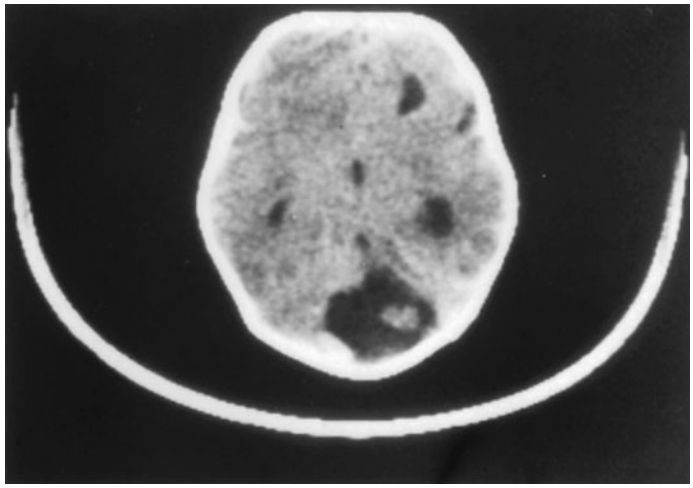
Facies. The face is asymmetric in 60%. Other findings include unilateral or bilateral orbital cysts (65% with microphthalmia), upper or lower eyelid coloboma (50%), and iris coloboma. In the contralateral eye, persistent hyaloid artery hamartomas or opacified cornea have been reported (Fig. 30–28). Cleft lip/palate has been noted in 15% (19,20).

Skeletal findings. Skeletal defects include underdeveloped orbits, zygomas, and the sphenoid part of the lateral orbital wall on the side of the involved eye (60%) as well as scoliosis and rib malformation (40%) (1,7,9,11). Some patients have exhibited body asymmetry, and several have manifested hip dislocations (1,7,11,19).

Skin. Cutaneous appendages (85%) have largely been periorbital but crescentric postauricular, malar, and even labial examples have been noted (1–4,7,8,10,16) (Fig. 30–29). Rarely, tags are present on the trunk. Focal skin lesions have been of three types: aplasia, hypoplasia, and/or punchlike defects (75%) (Fig. 30–29C). The postauricular crescent-shaped hypoplastic skin lesion is pathognomonic (20). A few patients have involvement of the trunk. Multiple trichofolliculomas have been reported (10,19).

Central nervous system. Most patients have exhibited severe psychomotor retardation (75%) and seizures (75%) , but some have been only mildly retarded. CAT scans have revealed agenesis of the corpus callosum (50%) and multiple fluid-filled spaces in the cortex (75%) (Fig. 30–30).

Fig. 30–30. *Oculocerebrocutaneous syndrome*. Fluid-filled spaces in cortex.



Occipital meningoencephalocele, hypoplasia of cerebellum (20%), Dandy–Walker malformation (10) polymicrogyria and heterotopias, and spastic tetraplegia have also been reported (1,6,7,19,27).

Differentiation for *encephalocraniocutaneous lipomatosis* must be made (13,18,19,20). We are uncertain regarding the diagnosis in the cases of Brodsky et al (5) and Angle and Hersch (2).

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Peters plus (Krause-Kivlin) syndrome

The term Peters plus syndrome was first coined in 1984 by Van Schooneveld et al (43) in describing 11 patients with defects in the anterior chamber of the eye, typical face, clefting, short limb dwarfism, and developmental delay. Kivlin et al (26) later pointed out that Krause et al (28) had already described a single case in 1969, and others (20,41) mentioned the 1961 report of Haney and Falls (18) regarding two cases. Because of the mnemonic value of the term Peters plus, this is most commonly used in literature. In total almost 50 cases have been described (2,8,9,13,14,18–20,24,26,28,29,35,37,38,40–45). Other reports (17,23) might have also described the entity, but lack sufficient data for us to be sure about the diagnosis.

Table 30–1. Peters plus (Krause-Kivlin) syndrome

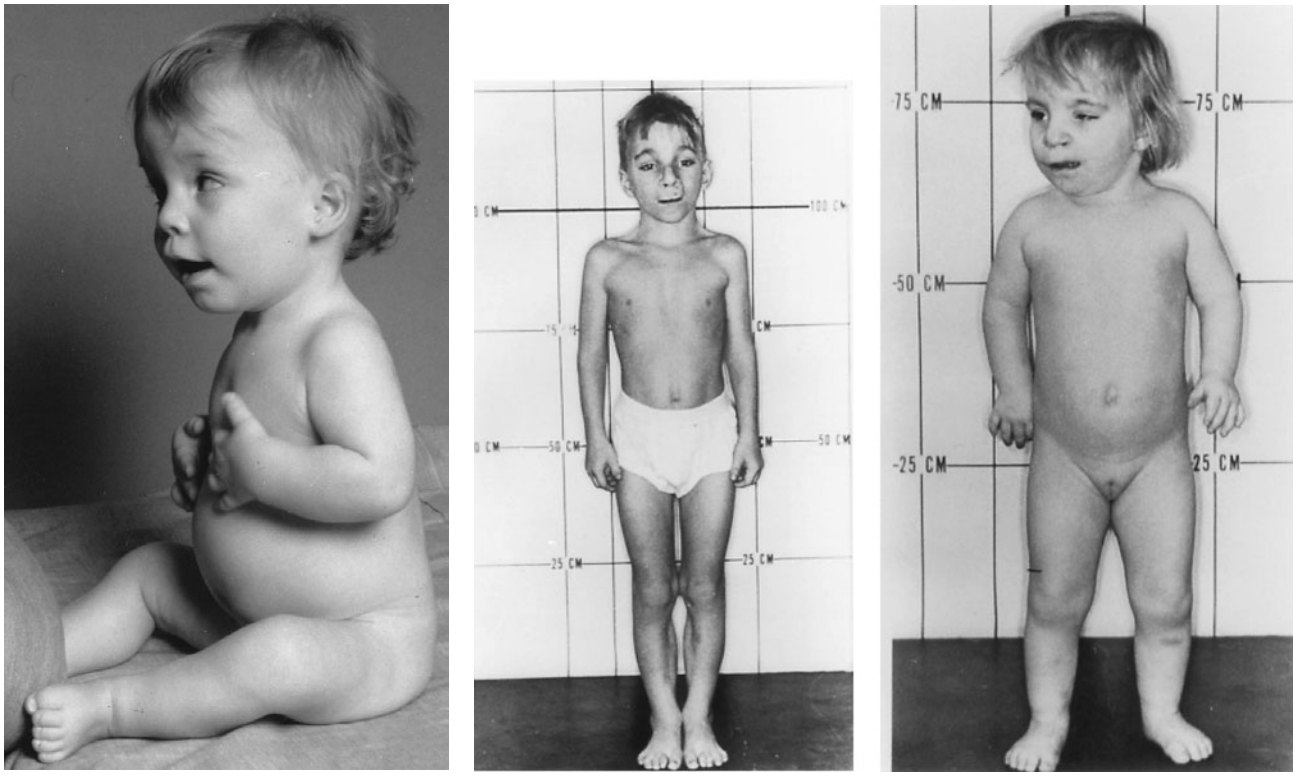
Major symptoms	Percent ($n = 49$)
Growth	
Birthweight at/below 3rd centile	87
Birth length at/below 3rd centile	63
Postnatal height below 3rd centile	92
Developmental delay	83
Eye	
Peters anomaly	73
Any anterior chamber defect	98
Any congenital eye malformation	100
Face	
Microcephaly	22
Macrocephaly	8
Prominent forehead	70
Hypertelorism	76
Narrow palpebral fissures	79
Upslanted palpebral fissures	32
Long philtrum	91
Cupid bow upper lip	98
Cleft lip/palate	45/33
Micrognathia	44
Small ears	42
Preauricular pits	37
Broad neck	73
Extremities	
Short limbs	95
Short, broad hands	100
Clinodactyly 5th finger	91
Congenital heart malformations	31
Congenital renal anomalies	19

Inheritance is clearly autosomal recessive, consanguinity being present in about one-third of the families. Hennekam et al (20) pointed out that the increased rate in miscarriages and fetal losses may well indicate that the entity causes intrauterine death in some cases. In one case a familial and probably coincidental balanced translocation between chromosome 2q21 and 15q26.1 was found (26). In another example, a mutation in the *RIEG1* gene was found (11a). The reader should also see the discussion in Differential diagnosis. Hanson et al (18a) found a point mutation in the *PAX6* gene, located at 11p13.

Extensive reviews are available (13,20,41). The major clinical symptoms are summarized in Table 30–1.

Growth and development. Most cases have prenatal growth retardation, and virtually all cases are disproportionally short postnatally. Arms and legs are equally shortened, and, although formal studies are lacking, published pictures usually show rhizomelic shortening. Adult height varies from 1.28 m to 1.51 m in females and 1.41 m and 1.55 m in males.

Mental delay is present in 83% of cases, and varies from mild (34%), to moderate (20%) and severe (26%). There is no correlation between physical findings and mental development. Specific behavioral studies have not been performed, but Young et al (45) and Hennekam et al (20) mentioned a strikingly friendly and amiable personality in several patients;



A B C

Fig. 30–31. *Peters plus (Krause-Kivlin) syndrome*. (A) Rhizomelic shortened limbs and relatively large head. (B,C) Mentally retarded brother and sister with cleft lip-palate, short stature, mild neck webbing, small hands and feet. (A from RCM Hennekam et al, Clin Dysmorphol 2:283, 1993. B,C courtesy of ID Young et al, J Med Genet 19:332, 1982.)

Thompson et al (41) reported outbursts of anger and difficult behavior in another case.

Craniofacial features. The most specific facial features are a round face in infancy, prominent forehead, hypertelorism, short palpebral fissures, long philtrum, and cupid bow shape of the upper lip with a thin vermilion border (Fig. 30–31). The latter is difficult to determine in the presence of a cleft lip, but after surgical repair the typical lip configuration becomes evident. A cleft lip is present in 45% of cases and can be accompanied by a cleft palate. Sometimes only the vermilion border is irregular, as an incomplete form of cleft lip (20). Other signs are small and mildly dysmorphic ears, preauricular pits, narrow auditory canals (26), unilateral or bilateral ptosis, mild malar hypoplasia, micrognathia, and a broad and sometimes webbed (45) neck. The lingual frenulum is frequently short. Absent (20) or abnormally pointed (41,42) lateral upper incisors, facial hirsutism (41), and prominent ears (41) have been described.

Eyes. The Peters anomaly is characterized by central corneal opacity (leukoma), thinning of the posterior cornea, and iridocorneal adhesions (33). It has formerly been called anterior chamber cleavage defect, but as early as 1969 Alkemade (1) explained that the anterior chamber does not arise by cleavage. Posterior embryotoxon (also indicated as thickening of Schwalbe's line) is the least severe expression of abnormal anterior chamber development, more severe expressions being keratoconus posterior (or keratoconus posticus circumscriptus), Axenfeld anomaly, Rieger anomaly, and iridogoniodysgenesis. In Peters plus syndrome, bilateral Peters anomaly is most often found, but it can also occur unilaterally or as another form of anterior chamber defect. Some patients do not have any anterior chamber anomaly and are recognized only because of the family history (20). In several cases, corneal opacities have gradually diminished in density in infancy (20,38,41,45). Cataract and glaucoma are common complications that can also occur at a later age. Unusual eye symptoms are severe myopia (20,41), iris coloboma (20,26), retina coloboma (2,20,45), optic atrophy (2), and microphthalmia (14,40).

Skeletal system. Short limbs and brachydactyly are invariably present. The hands and feet can be very broad, which may give considerable problems in wearing shoes. Clinodactyly of the fifth finger can be very marked. The elbows often show diminished mobility; the other joints can be hyperextensible. Pectus excavatum (18,20), broad (14) or narrow (20) thorax, hyperkyphosis (20), scoliosis (45), and pes cavus (20,45) occur, as do mild cutaneous syndactylies (8,14,20,41) and proximally placed thumbs (35). Ossification of the skull can be unusual: often the fontanel is large at birth, extending to the forehead, but within the first months rapid ossification closes the fontanels before 1 year of age (20). No genuine craniosynostosis has been reported. Cabral de Almeida et al (8) and Hennekam et al (20) mentioned prominent metopic ridges. Both microcephaly and macrocephaly can be present.

Specific radiographic findings are uncommon but can include early arthritic changes of the upper cervical (20) or lumbar (41) spine, thoracic hemivertebrae (20), multiple vertebral segmentation defects (45), square pelvis with flat iliac crests (41), and underdevelopment of the proximal radii (35). Hand and foot radiographs show general shortening of metacarpals, metatarsals, and (especially proximal and middle) phalanges. In one case, a regular bony defect of the proximal part of the first phalanx of the thumbs was found (29), and in another case there were cone-shaped epiphyses (45).

Other findings. Hearing loss (20), recurrent cystitis (13,20,26,28, 29,38,45), intractable diarrhea (20), fat malabsorption (35), seizures (2,13,20), stereotypic movements (20), and high-pitched voice or dysphonia (20,38) have been noted. Almost all cases have feeding problems in infancy. Other reported congenital anomalies have included heart defects such as atrial septal defect (13,20), ventricular septal defect (29,35,37), subvalvular aortic stenosis (14), pulmonary stenosis (8,20,29), and recurrent endocarditis (41). Genitourinary problems have included

hydronephrosis (2,13,20,38), renal or uretral duplication (2,20,35,41,45), renal hypoplasia with oligomeganephronia (29), hypospadias (13,20), incomplete foreskin (13), cryptorchidism (13,20,26,45), hypoplastic clitoris (37), hypoplastic labia majora (20,37), rudimentary vagina and uterus (38,41), ureteral orifice opening in the vagina. Anal stenosis (20), double gall bladder (41), hypoplastic adrenals at autopsy (13), soft skin (20), widely spaced nipples (8,14,35), diastasis recti (40), and umbilical and inguinal herniae (8,20,45) have been reported.

Central nervous system. Anomalies have commonly included enlarged ventricles, sometimes necessitating shunting, and mild spastic diplegia, and rarely agenesis of the corpus callosum (8), porencephaly (6), parietotemporal (13) or general (24) brain atrophy.

Differential diagnosis. The Peters anomaly is in general a sporadic, nongenetic condition (1). Genetically determined forms are usually autosomal recessive (7), but autosomal dominant forms are also known (22). The Peters anomaly has been described in several chromosome anomalies: terminal *deletion of chromosome 4p* (30), *mosaic trisomy 9* (30), deletion of 11q14 or q22 (5), *trisomy 13* (30), *terminal deletion of 18q* (15), and *ring 21* (10). Anterior chamber defects of the eye are also found in *Rieger syndrome*, *SHORT syndrome, Abruzzo-Erickson syndrome, alcohol embryopathy*, GMS syndrome, *Weill-Marchesani syndrome, Michels syndrome*, and *Walker-Warburg syndrome*. The entity has been confused with *de Lange syndrome* (20,35,44) and compared with *Robinow syndrome* (37,40,42). Jung et al (25) reported on a similar disorder, but the facial features were different, and the affected sibs had also cerebellar hypoplasia, tracheostenosis, and hypothyroidism. Moog et al (31) mentioned two sibs with anterior chamber defects, mild mental retardation, diminished growth, hydrocephaly, and intracranial calcifications. Inheritance was probably autosomal recessive. Peters anomaly with brachymesomelia, but with different facial features, no brachydactyly, bowed radii, long thumbs, and normal intelligence was published by Kivlin et al (27). Appelmans et al (3) described a case with microcephaly, growth delay, and mental retardation, but without other abnormalities, and a case with mental retardation, large anterior fontanel, and intestinal atresia. A family with three brothers with anterior chamber anomalies, mental retardation, microcephaly, growth delay, slender build, long face, multiple lentigines, and situs inversus was reported by Elmer et al (12). The father had anterior chamber anomalies and lentigines; the mother was mentally retarded. Two sibs were described with anterior chamber anomalies, corneal dermoids, and growth delay (16). Ruprecht and Majewski (36) reported on two sisters with Peters anomaly and arhinia, and Tabuchi et al (39) three sibs with Peters anomaly and cardiac malformations including Fallot's tetralogy. Alkemade (1) and Heon et al (21) described large series of patients with Peters anomaly, of whom several had solitary other symptoms, and Kivlin et al (26) and Holmstrom et al (22) reviewed the literature for symptoms additional to anterior chamber anomalies. Natarajan et al (32) published a case with facial features similar to Peters plus syndrome, but the boy had cataract and no short limbs or brachydactyly.

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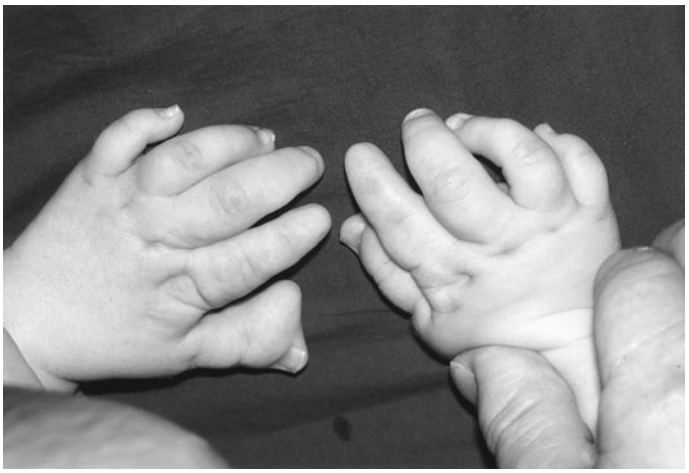
Phillips-Griffiths (macular coloboma, cleft palate, and abnormal finger mobility) syndrome

In 1969 Phillips and Griffiths (1) described a brother and sister with both bilateral macular coloboma, nystagmus, hypermetropia, cleft palate, diminished mobility in the fifth fingers, and bilateral hallux valgus. The girl was mentally retarded, had small canines and upper lateral incisors, delayed sexual maturation, bilateral genua valga and coxa valga, and recurrent patella dislocation. The boy had a sloping forehead, platybasia, hyperextensibility of the second and third finger, and irregularly implanted toes.

There is some resemblance with Sorsby syndrome, in which macular coloboma is found together with brachydactyly type B, and in some unilateral renal agenesis, uterine anomalies, and hearing loss (3), and the case described by Smith et al (2) with macular coloboma and short limbed dwarfism (Fig. 30–32).



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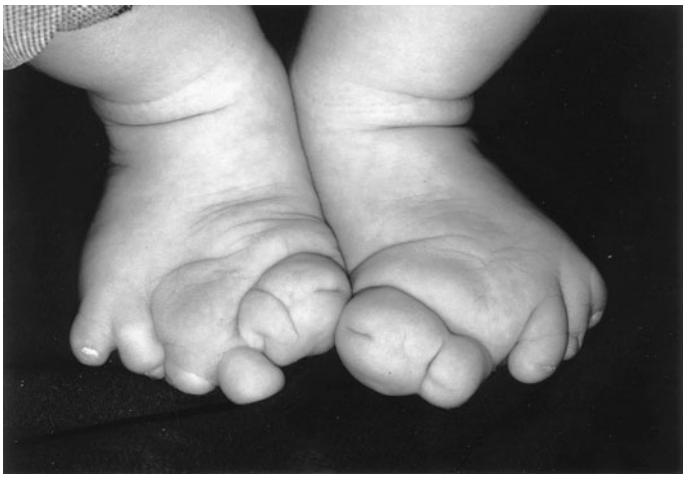

B

Fig. 30–32. *Phillips-Griffiths (macular coloboma, cleft palate, and abnormal finger mobility) syndrome*. (A,B) Note bifid thumbs and halluces, agenesis of nails. (Courtesy of M Baraitser and E Thompson. London, England.)

References [Phillips-Griffiths (macular coloboma, cleft palate, and abnormal finger mobility) syndrome]

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2. Smith RD et al: Congenital macular colobomas and short- limbed skeletal dysplasia. Am J Med Genet 5:365–371, 1980.
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Uncombable hair, retinal pigmentary disorder, oligodontia, and brachydactyly

Bork et al (1), in 1987, described hypotrichosis with uncombable properties, retinal pigmentary disorder, juvenile cataract, oligodontia, and brachydactyly with brachymetacarpalia. An additional patient was reported by Silengo et al (2) (Fig. 30–33).

Inheritance is autosomal dominant.

Uncombable hair may be seen in *tricho-dento-osseous syndrome, Rapp-Hodgkin (Hay-Wells) syndrome, EEC syndrome*, and in unusual facies, uncombable hair, mental retardation, postaxial polydactyly, phalangeal hypoplasia, and 2–3 toe syndactyly.

References (Uncombable hair, retinal pigmentary disorder, oligodontia, and brachydactyly)

1. Bork K et al: Familiäre kongenitale Hypotrichose mit "unkämmbaren Haaren," Retinapigmentblattdystrophie, juveniler Katarakt, und Brachymetakarpie; eine weitere Entität aus der Gruppe der ektodermalen Dysplasien. Hautarzt 38:342–347, 1987.
2. Silengo M et al: Uncombable hair, retinal pigmentary dystrophy, dental anomalies and brachydactyly. Am J Med Genet 47:931–933, 1993.

Wagner syndrome (hyaloideoretinal degeneration)

Wagner syndrome, an autosomal dominant hyaloideoretinal degeneration, was described in a Swiss family by Wagner (6) in 1938. Additional affected members were subsequently observed by several other authors (1,4). Other kindreds have been noted (3).

Empty vitreous with avascular strands is a constant feature. Chorioretinal atrophy and cataract are common features in those over 45 years. Peripheral retinal detachment and glaucoma were found in about 50% and 20%, respectively, in that group. Over 65% manifested elevation of rod and cone thresholds.

Inheritance is autosomal dominant with mapping to 5q13–q14 by Brown et al (2) in 1995. Fryer et al (3), in 1990, excluded a type 2 collagen defect, but a report by Korkko et al (5), in 1993, described a kindred with a type 2 collagen defect. Apparently there is genetic heterogeneity.

References [Wagner syndrome (hyaloideoretinal degeneration)]

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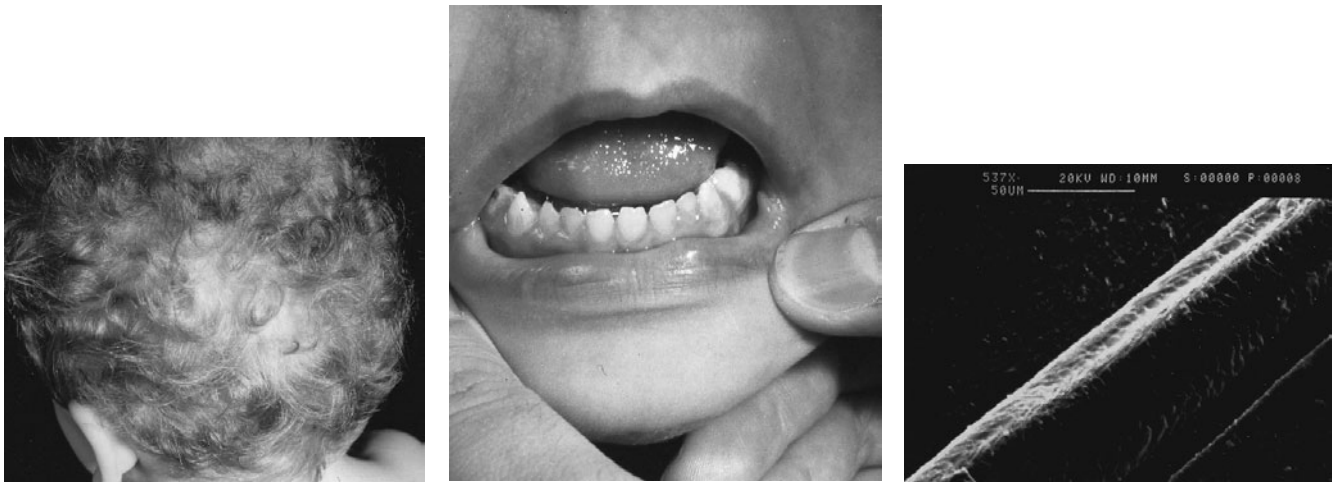

A B C

Fig. 30–33. *Uncombable hair, retinal pigmentary disorder, oligodontia, and brachydactyly*. (A) Four-year-old with uncombable hair. (B) Supernumerary lower lateral incisor reduction in crown form. (C) Hair showing longitudinal groove (pili canaliculi). (From M Silengo et al, Am J Med Genet 47:931, 1993.)

2. Brown DM et al: Genetic linkage of Wagner disease and erosive vitreoretinopathy to chromosome 5q13–14. Arch Ophthalmol 113:671–675, 1995.
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Weill-Marchesani (spherophakia-brachymorphism) syndrome

In 1932, Weill (23) described a patient with dislocated lenses, short stature, brachydactyly, and stiff joints, within a group of patients with Marfan syndrome. Marchesani (11), in 1939, recognized this to be a separate entity. About 125 cases have been described. Some families may in fact have autosomal dominant ectopia lentis in a generally short-statured family (12–14). The entity is especially frequent among the Amish (14).

Pattern of inheritance is unclear. In one of the original family of Marchesani (11) affected sibs born to unaffected, consanguineous parents pointed to autosomal recessive inheritance. Other similar families were reported (1,2,9,10,15,19,21,28). In several families it was noted that one or both parents had short stature with or without brachydactyly, suggesting mild heterozygote expression (2,8,15,17,18,24,28). On the other hand, families with clearly autosomal dominant inheritance have been published (5,7,8,16,22,25,27). Verloes et al (22) suggested that the latter entity be named glaucoma, ectopia, microspherophakia, stiff joints, short stature (GEMSS) syndrome. In the family originally described by Gorlin et al (7), possible linkage to chromosome 15q21.1, the localization of fibrillin-1 and microfibrillin-associated protein-1, was reported (25). Decreased fibrillin staining was found in the dermal-epidermal junctions and capillary dermis at immunohistochemical studies. Linkage to fibrillin-2 was excluded (25). Chromosome studies yielded normal results (14a). However, Mégarbané et al (14a) excluded 15q21.1 as the site for the autosomal recessive form.

Mental development is normal, although not in all cases (2,19,21).

Eye. There is congenital microspherophakia, that is, reduced horizontal and sagittal diameters of the lens giving it a spheric appearance. Severe myopia (5–20 diopters) is universally present. The anterior chamber is reduced. Glaucoma is a frequent complication in late childhood (4,6,8,24). In the absence of lens dislocation, the glaucoma is due to obstruction of the aqueous flow through the pupil (24). The lens dislocates usually forward or downward, either unilaterally or bilaterally, before the age of 10. Secondary features may be nystagmus, megalocornea, strands in the anterior chamber, fraying of the iris root, abnormal angle vessels, cataract, ablatio retina, and rupture of the globe (2,5,8,11,19,22,25,27,28). Microscopic studies of the lens are available (5).

Skeletal system. Proportionate short stature is the rule, varying in adults from 130 cm to 157 cm in females and 142 cm to 169 cm in males (6,7,11,22,23,25,27) (Fig. 30–34A,B). Hands are broad (2,4,6,19,28). Joint stiffness is especially prominent in the hands, but can be present in the shoulders (4,18,22,27), elbows (6,7,19,22,25,27), knees (4,27) (Fig. 30–34C), and ankles (4,27). Many patients have muscular build (2,11,19,28), as can be seen in hypochondroplasia. Scoliosis (6,22) and increased lumbar lordosis (4) occur. Adults with carpal tunnel syndrome have been reported (10,14,25). Radiological changes have included short and relatively wide phalanges, metacarpals and metatarsals, widening of other long bones (4), mild beaking of distal radii (27), wide ribs (4), thin cortex (4), and narrow spinal canal (4). A rare feature may be osteoporosis (6).

Other findings. The face may show brachycephaly, roundness, shallow orbits, narrow palpebral fissures, and maxillary hypoplasia. The palate may be highly arched and narrow. Ferrier et al (4) reported a patient with subvalvular fibromuscular aortic stenosis, another had mitral valve insufficiency (22), and two had pulmonic stenosis (19,28), but usually cardiac investigations have yielded normal results (2). The skin can be thick (2,22,25) and show stretch marks (22,27).

Differential diagnosis. The condition has to be differentiated from isolated autosomal dominant lens dislocation, *Marfan syndrome*, and Moore-Federman syndrome (22). The patients described by Feinberg (3) probably had *Gorlin-Chaudhry-Moss syndrome*.

References [Weill-Marchesani (spherophakia-brachymorphism) syndrome]

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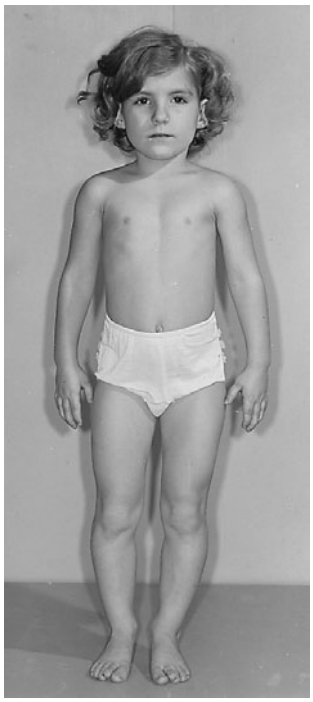

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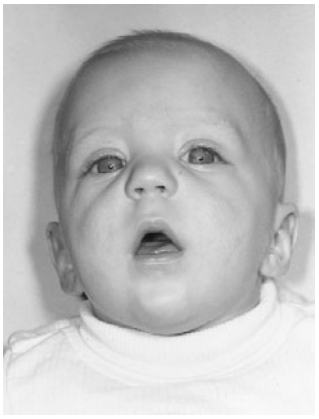

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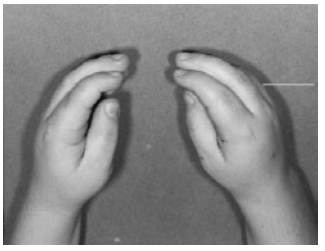

C

Fig. 30–34. *Weill-Marchesani (spherophakia-brachymorphism) syndrome*. (A) Proportionate short stature. Note contractures of digits. Her father, brother, and ultimately, son have the same condition. (B) Affected brother also had microspherophakia and severe (16 diopters) myopia. (C) Contractures of fingers. (From RJ Gorlin et al, J Pediatr Ophthalmol Strabismus 11:139, 1974.)

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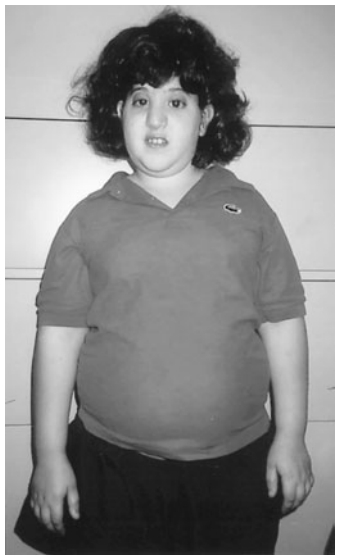
Fig. 30–35. *Fronto-ocular syndrome*. (A,B) Sibs with trigonocephaly, ocular hypotelorism, proptosis and ptosis, elevated nasal bridge, thin philtrum, and narrow bifrontal region. (From EN Schneider et al, Am J Med Genet 93:89, 2000.)



A

B

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Fronto-ocular syndrome

Schneider et al (1), in 2000, described an autosomal dominant disorder characterized by trigonocephaly due to coronal and metopic synostosis, ocular hypotelorism, proptosis and ptosis, epicanthic folds, hypoplastic supraorbital ridges, elevated nasal bridge, thin philtrum, and narrow bifrontal region (Fig. 30–35). Other possible components include glabellar capillary hemangiomas, congenital heart anomalies (pulmonary stenosis, atrial septal defect), and mild developmental disabilities.

Trigonocephaly may be an isolated finding or be part of other syndromes such as *holoprosencephaly, Frydman trigonocephaly syndrome, Opitz trigonocephaly syndrome* (*C syndrome*), and *Say-Meyer trigonocephaly syndrome*, but has been seen in *valproate embryopathy* and various chromosomal abnormalities [*del(9p)*, *del(11q)*, *del(13q)*, and *dup(13q)*].

Reference (Fronto-ocular syndrome)

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Appendix

Documentation of dysmorphic features is an essential part of clinical evaluation. Although some features can only be visualized, others require quantification to decide whether the feature in question deviates from the norm and, if so, by how much. Objective measurements often belie subjective clinical impression. For example, the patient with Down syndrome is sometimes described as having a highly arched palate. However, metric studies show that palatal height is normal, but palatal length is dramatically shorter than normal. Some features such as epicanthic folds cannot be precisely measured, but can be graded as being mild, moderate, or severe. Other features such as Brushfield spots are of the presence-absence type. Because some dysmorphic features defy measurement and even convincing verbal description, photographic documentation is very important in syndromology; phenotypic features may change with time. In some conditions, such as the de Lange syndrome, the phenotypic features, especially of the face, are usually constant enough at any age to impart the correct diagnostic impression, and the striking resemblance of affected individuals transcends the racial background of the patient. Occasionally, mild expression may render clinical diagnosis difficult, especially at birth. In some instances, for example, the characteristic phenotype of the de Lange syndrome may evolve with time. In other conditions, such as del(5p) syndrome, the phenotypic features tend to become less distinct with time (3).

This appendix provides a number of measurements of use in evaluating the face and cranium. The more practical and efficient but less accurate measures are most commonly used. Soft-tissue measurements take precedence over radiographic ones and the use of simple rather than sophisticated techniques is the rule. In this appendix, anthropometric measurements of the face and cranium are provided, but in addition there are a large number of radiographic and cephalometric standards. In some instances, several standards for the same measurement are provided. For example, inner and outer canthal distances suffice for clinical measurement of hypertelorism. However, when craniofacial surgery is contemplated, radiographic standards for interorbital distance are mandatory. An excellent study of bony interorbital distance has been provided by Costaras et al (5,6) and is highly recommended; their standards are not found here because their use of PA cephalometric landmarks and the indices they derive are too complex to present in this appendix. Finally, the canthal index is useful for evaluating possible hypertelorism in relatives of a proband who are not available for study but whose photographs are available.

The best general groups of growth references for dysmorphic conditions are found in the atlases of Saul et al (14) and Hall et al (8a). The reader is referred to the following references for special coverage: facial anthropometry (7), craniofacial anthropometric measurements in the newborn (27–41 gestational weeks) (1,9–11), anthropometric measurements of various syndromes and genetic conditions (8,8a,14–16), cephalometric atlases (2,12,13), cephalometric studies of syndromes and genetic conditions (4), and limitations of published metric studies for clinical use (3). Contents of the Appendix are listed on page 1216.

References (Appendix)

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Appendix Figures and Tables

Cranial measurements

Facial measurements

Intraoral measurements

Web sites and computerized database systems

Cranial measurements

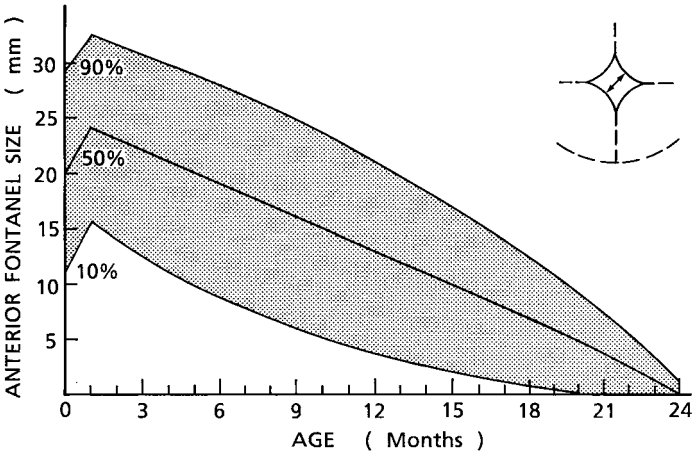

Fig. A–1. Anterior fontanel size. Percentiles from term to age of 24 months for both sexes. Inset, measurement of oblique diameter. (From G Duc and RH Largo, Pediatrics, 78:904, 1986.)

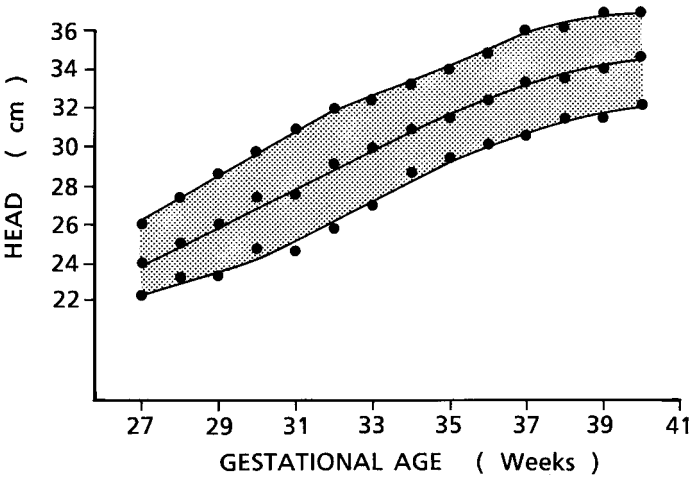

Fig. A–2. Head circumference from 27 to 41 gestational weeks. [From P Merlob et al, Birth Defects 20(7):1, 1984.]

Table A–1. Fontanel and suture closure

Closure	Time
Anterior fontanel	1 year ± 4 months
Posterior fontanel	Birth ± 2 months
Anterolateral fontanel	By third month
Posterolateral fontanel	During second year
Metopic suture	By third year (10 %, never)
Clinical closure of sutures	6–12 months
Anatomic closure of sutures	By thirtieth year

(From RJ Gorlin and JJ Pindborg, Syndromes of the Head and Neck, 1st ed, McGraw-Hill, New York, 1964.)

Table A–2. Detailed suture closure

Cranial suture	Closure begins (years)	Facial suture	Closure begins (years)
Interfrontal (metopic)[a]	2	Intermaxillary	
Interparietal (midsagittal)	22	(midpalatal)	30–35
Frontoparietal (coronal)	24	Frontomaxillary	68–71
Occipitoparietal (lambdoidal)	26	Frontonasal	68
Masto-occipital	26–30	Frontozygomatic	72
Sphenotemporal	28–32	Zygomaticotemporal	70–71
Temporoparietal (squamosal)	35–39	Zygomaticomaxillary	70–72
Sphenoparietal	29	Nasomaxillary	68
Sphenofrontal	22		

[a] Usually obliterated by third year; persists throughout life in 10%.

(From VC Kokich, The biology of sutures. In: Craniosynostosis: Diagnosis, Evaluation, and Management, MM Cohen Jr (ed), Raven Press, New York, 1986, p 94.)

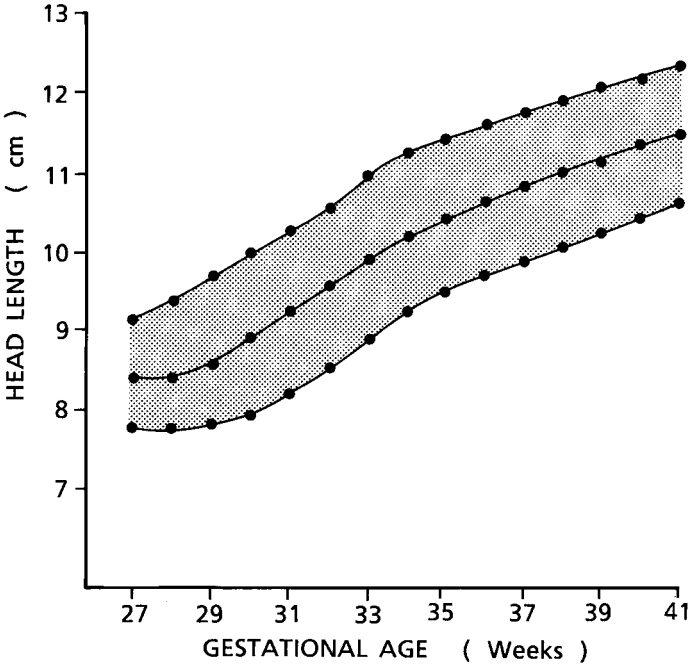

Fig. A–3. Head length from 27 to 41 gestational weeks. [From P Merlob et al, Birth Defects 20(7):1, 1984.]

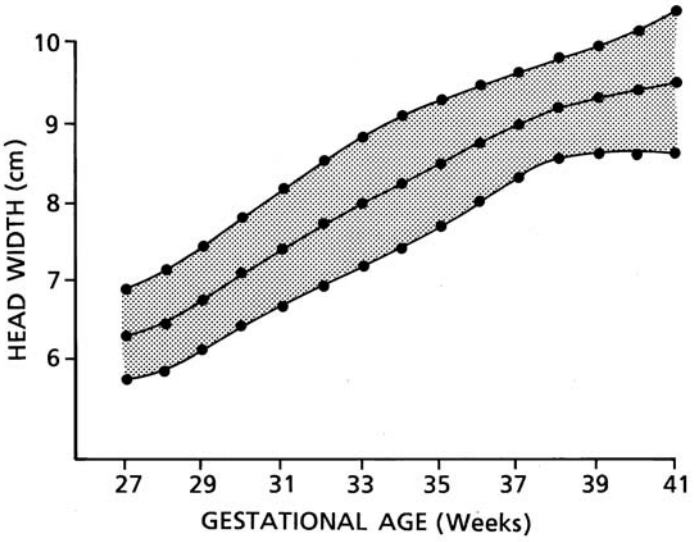

Fig. A–4. Head width from 37 to 41 gestational weeks. [From P Merlob et al, Birth Defects 20(7):1, 1984.]

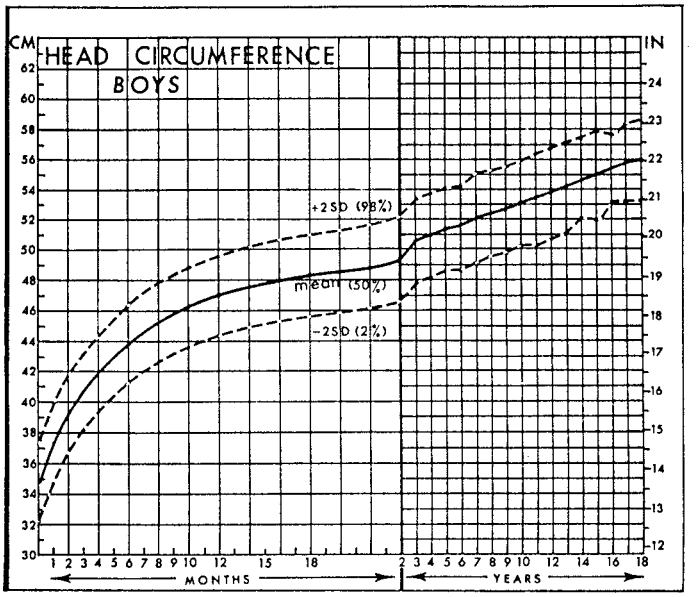

Fig. A–5. Head circumference to 18 years (males). (From G Nelhaus, Pediatrics 41:106, 1968.)

Table A–3. Cranial measurements and volume (males)[a]

Age	*N*	Head breadth		Head length		Head height		Mean cranial volume
		Mean	SD	Mean	SD	Mean	SD	
7 days	19	9.6	0.32	11.9	0.57	8.5	0.52	410
1 mo	24	10.1	0.45	12.7	0.70	9.2	0.57	522
2 mo	22	10.3	0.54	13.7	0.61	9.8	0.62	609
4 mo	20	11.3	0.50	14.4	0.81	10.5	0.60	766
6 mo	21	11.8	0.59	15.2	0.91	11.0	0.46	847
9 mo	19	12.0	0.71	15.4	0.93	11.1	0.59	896
12 mo	19	12.5	0.62	16.4	0.62	11.3	0.39	1010
18 mo	20	12.9	0.50	16.8	0.71	11.8	0.69	1078
2 yr	20	13.1	0.46	17.1	0.86	11.9	0.53	1129
3 yr	29	13.5	0.51	17.8	0.61	12.2	0.47	1206
4 yr	29	13.7	0.58	17.7	0.71	12.4	0.44	1267
5 yr	30	13.9	0.48	17.8	0.61	12.4	0.66	1281
6 yr	22	14.0	0.54	18.1	0.66	12.4	0.45	1309
7–8 yr	30	14.4	0.49	18.2	0.99	12.3	0.42	1354
9–10 yr	44	14.4	0.54	18.7	0.65	12.3	0.58	1384
11–12 yr	49	14.5	0.57	18.9	0.64	12.5	0.44	1424
13–14 yr	35	14.6	0.49	19.2	0.66	12.7	0.51	1480
15–16 yr	27	14.9	0.59	19.3	0.87	12.8	0.42	1492
17–18 yr	46	15.3	0.62	19.5	0.73	12.8	0.44	1533
19–20 yr	30	15.3	0.52	19.5	0.71	12.8	0.44	1548

[a]Linear measurements in centimeters, volume in milliliters.
(From AS Dekaban, Ann Neurol 2:285, 1977.)

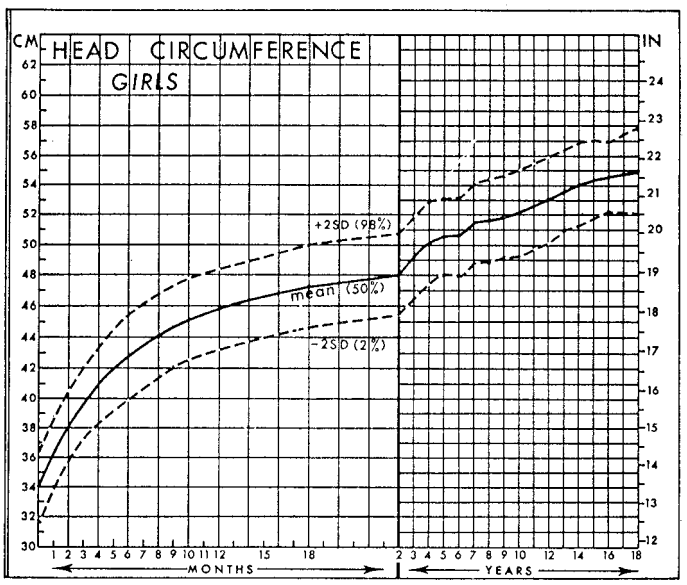

Fig. A–6. Head circumference to 18 years (females). (From G Nelhaus, Pediatrics, 41:106, 1968.)

Table A–5. Cephalic index[a]

Index	Skull type
x–75.9	Dolichocephaly
76.0–80.9	Mesocephaly
81.0–85.4	Brachycephaly
85.5–*x*	Hyperbrachycephaly

[a] Cephalic index = [(maximum head breadth)/(maximum head length)] 100.
(From MFA Montagu, An Introduction to Physical Anthropology, 3rd ed, Thomas, Springfield, 1960, p 570.)

Table A–4. Cranial measurements and volume (females)[a]

		Head breadth		Head length		Head height		Mean cranial volume
Age	*N*	Mean	SD	Mean	SD	Mean	SD	
7 days	19	9.3	0.41	11.6	0.30	8.3	0.57	398
1 mo	21	8.8	0.57	12.8	0.56	9.2	0.58	510
2 mo	20	10.3	0.68	13.4	0.88	9.5	0.57	529
4 mo	19	10.8	0.41	14.0	0.74	10.0	0.62	721
6 mo	23	11.4	0.45	14.7	0.56	10.4	0.44	748
9 mo	20	12.0	0.41	15.3	0.74	10.8	0.55	845
12 mo	19	12.3	0.65	15.6	0.59	11.0	0.50	913
18 mo	21	12.7	0.57	16.3	0.84	11.4	0.66	1012
2 yr	18	12.9	0.41	16.5	0.71	11.4	0.44	1033
3 yr	21	13.1	0.57	17.0	0.65	11.9	0.45	1148
4 yr	23	13.5	0.48	17.1	0.63	12.0	0.40	1180
5 yr	25	13.6	0.48	17.3	0.58	11.9	0.35	1198
6 yr	22	13.6	0.45	17.5	0.47	12.0	0.55	1218
7–8 yr	29	13.8	0.76	17.9	0.62	12.0	1.17	1260
9–10 yr	39	14.1	0.49	18.2	0.62	12.1	0.50	1310
11–12 yr	31	14.3	0.50	18.2	0.69	12.2	0.58	1339
13–14 yr	35	14.4	0.44	18.5	0.81	12.2	0.52	1371
15–16 yr	31	14.5	0.48	18.6	0.67	12.2	0.51	1386
17–18 yr	30	14.7	1.00	18.6	0.50	12.9	0.51	1402
19–20 yr	37	14.7	0.39	18.6	0.95	12.4	0.42	1425

[a] Linear measurements in centimeters, volume in milliliters.
(From AS Dekaban, Ann Neurol 2:285, 1977.)

Facial measurements

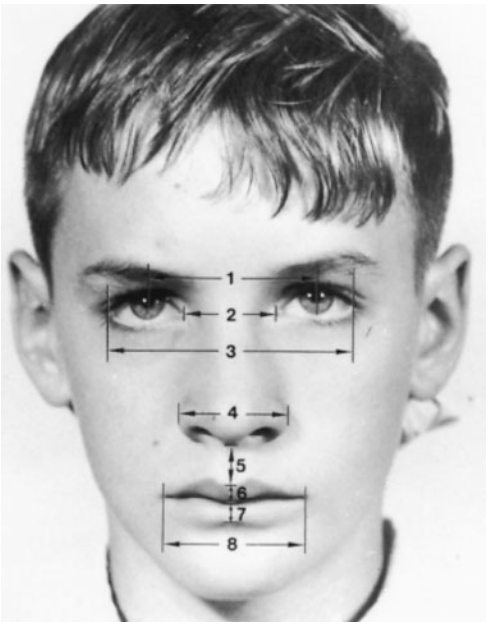

Fig. A–7. Common facial measurements. (1) Interpupillary distance, (2) inner canthal distance, (3) outer canthal distance, (4) interalar distance, (5) philtral length, (6) upper lip thickness, (7) lower lip thickness, and (8) intercommisural distance.

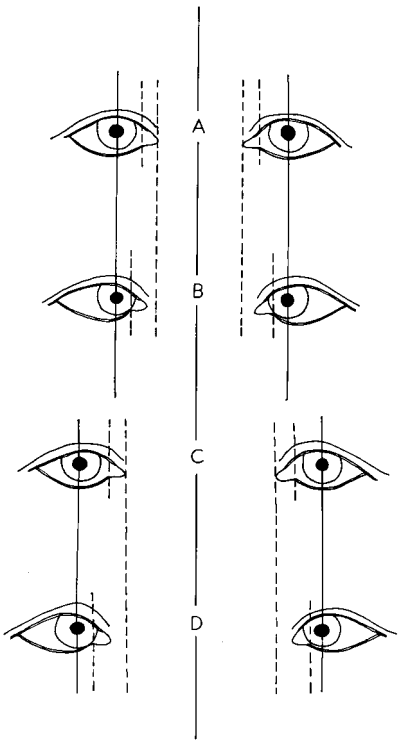

Fig. A–8. Primary telecanthus, secondary telecanthus, and hypertelorism. (A) Normal interocular distance. (B) Primary telecanthus. The inner canthi are far apart, although the outer canthi are normally spaced. Note how vertical line through lacrimal punctum cuts cornea. (LC) True ocular hypertelorism. Both inner and outer canthi are abnormally far apart. (D) True ocular hypertelorism toegether with secondary telecanthus. Note how vertical line through lacrimal punctum cuts cornea. [From MM Cohen Jr, Malformation syndromes. In: Surgical Correction of Dentofacial Deformities, WH Bell, WR Proffit, RP White (eds), W.B. Saunders, Philadelphia, 1980, pp 7–44.]

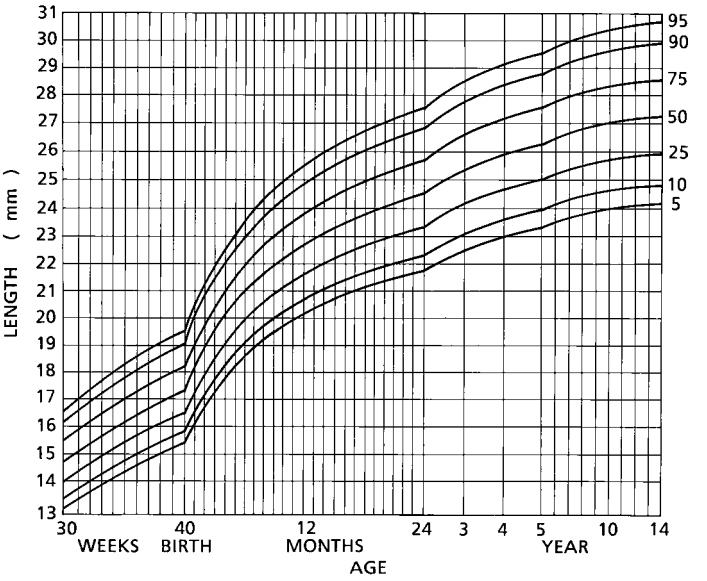

Fig. A–9. Palpebral fissure length. (From IT Thomas et al, J Pediatr 111:267, 1987.)

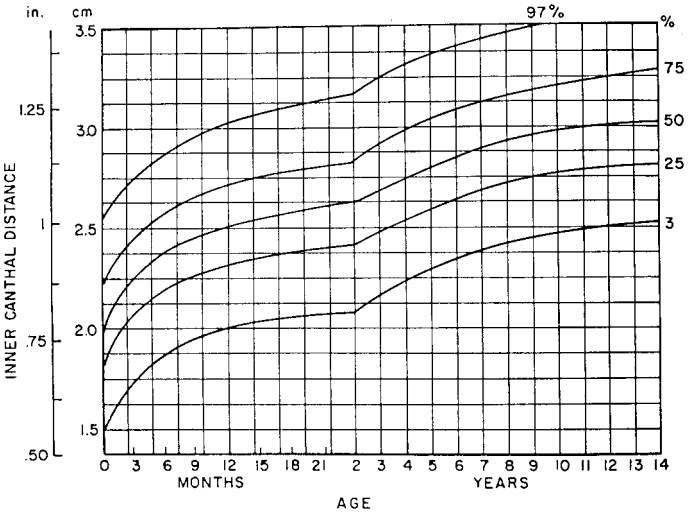

Fig. A–10. Inner canthal distance. [From M Feingold and WH Bossert, Birth Defects 10(13):1, 1974.]

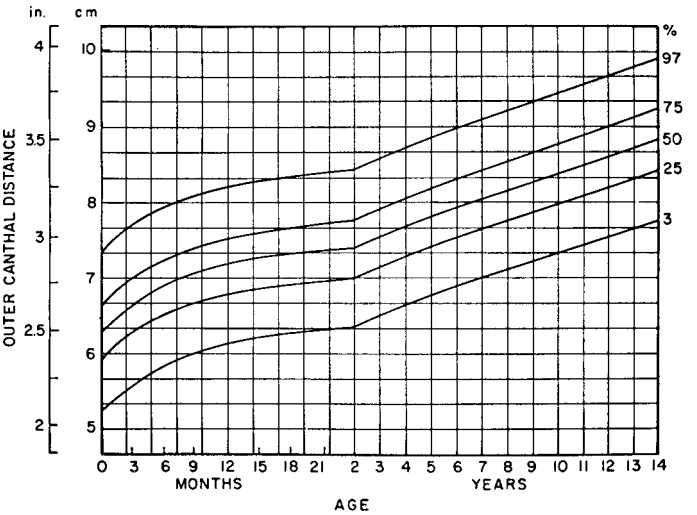

Fig. A–11. Outer canthal distance. [From M Feingold and WH Bossert, Birth Defects 10(13):1, 1974.]

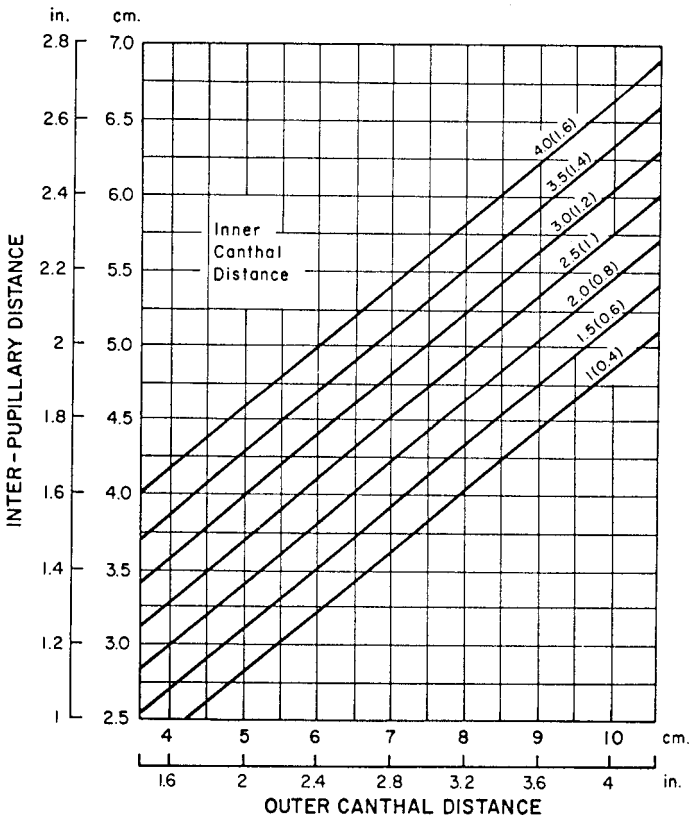

Fig. A–12. Interpupillary distance derived from inner and outer canthal distances. [From M Feingold and WH Bossert, Birth Defects 10(13):1, 1974.]

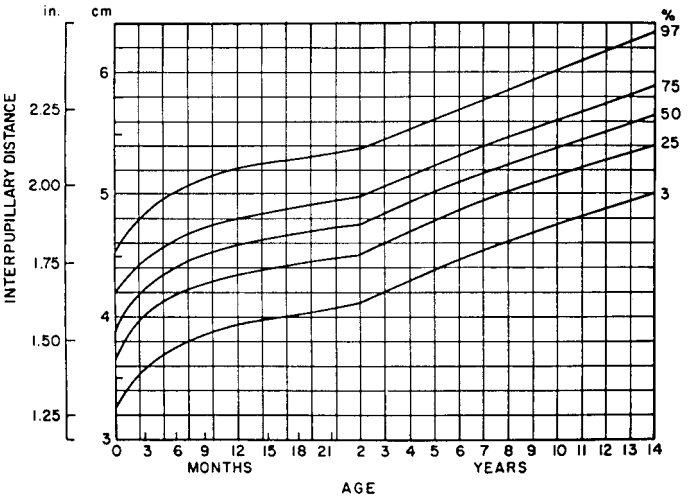

Fig. A–13. Direct interpupillary distance. [From M Feingold and WH Bossert, Birth Defects 10(13):1, 1974.]

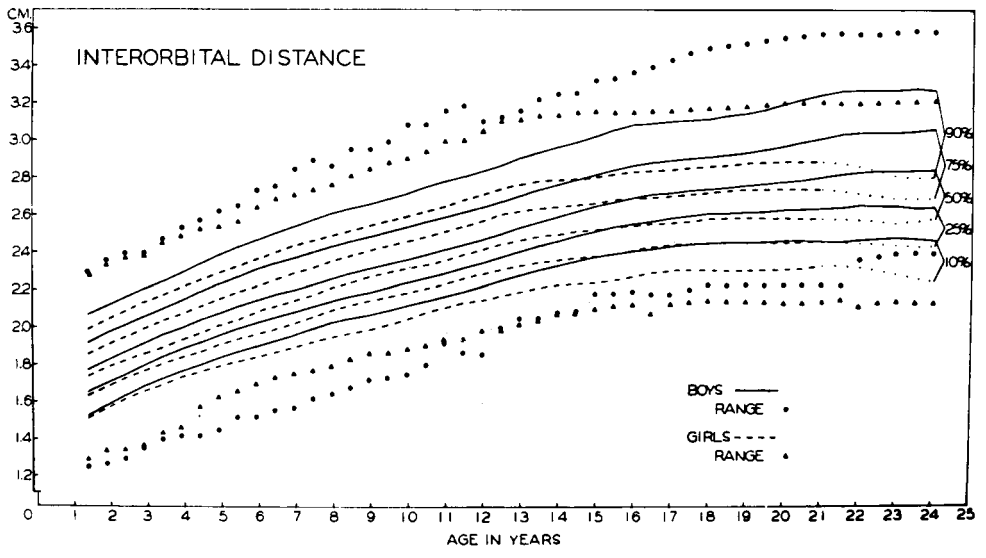

Fig. A–14. Bony interorbital distance. (From CF Hansman, Radiology 86:87, 1966.)

Table A–6. Canthal index

Definitions	Use
CI = canthal index IC = inner canthal distance OC = outer canthal distance	For approximate distance between the eyes from photographs by using a ratio measure

Canthal index formula

$$CI = \frac{IC}{OC} \times 100$$

Measurement	
38	Upper limit of normal
38–42	Euryopia
42 and above	Hypertelorism

(From H Günther, Virchows Arch Pathol Anat 290:373, 1933.)

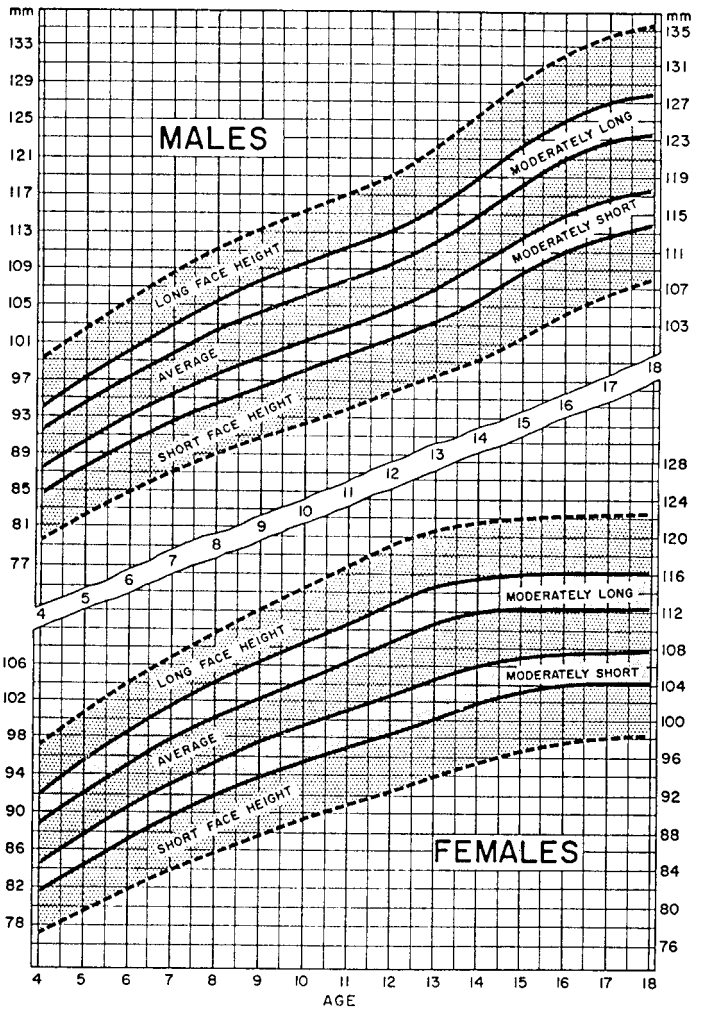

Fig. A–15. Face height based on North American white children. [From HV Meredith, Body size and form in childhood, with emphasis on the face. In: The Nature of Orthodontic Diagnosis, SL Horowitz and EH Hixon (eds), C.V. Mosby, St. Louis, 1966, pp 1–30.]

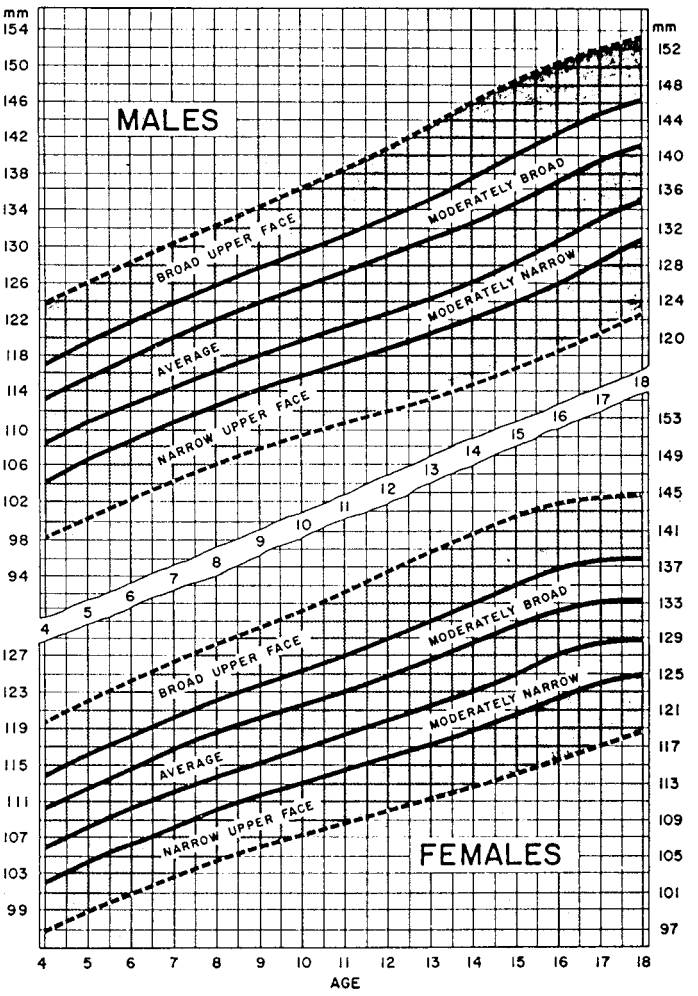

Fig. A–16. Face width based on North American white children. [From HV Meredith, Body size and form in childhood, with emphasis on the face. In: The Nature of Orthodontic Diagnosis, SL Horowitz and EH Hixon (eds), C.V. Mosby, St. Louis, 1966, pp 1–30.]

Table A–7. Philtrum length and intercommissural distance from 29 to 42 weeks gestation

Gestational age (weeks)	*N*	Philtral length (mm)		Oral intercommissural distance (mm)	
		Mean	±2 SD	Mean	±2 SD
28–29	7	6.0	0.3	21.4	4.0
30	11	7.3	2.4	20.3	1.8
31	12	6.7	0.6	22.8	2.9
32	10	7.3	1.4	23.7	4.2
33	18	7.8	1.8	24.4	2.8
34	19	8.3	2.0	24.8	4.0
35	13	8.1	1.6	24.5	3.7
36	15	8.5	0.8	25.0	5.1
37	20	9.0	1.5	26.2	4.0
38	20	9.1	1.8	29.0	5.6
39	28	9.5	1.1	27.5	3.2
40	41	9.8	1.4	27.9	3.1
41	25	9.6	1.2	28.0	4.2
42	13	9.5	2.0	28.9	5.2

(From K Mehes, J Craniofacial Genet Dev Biol 1:213, 1981.)

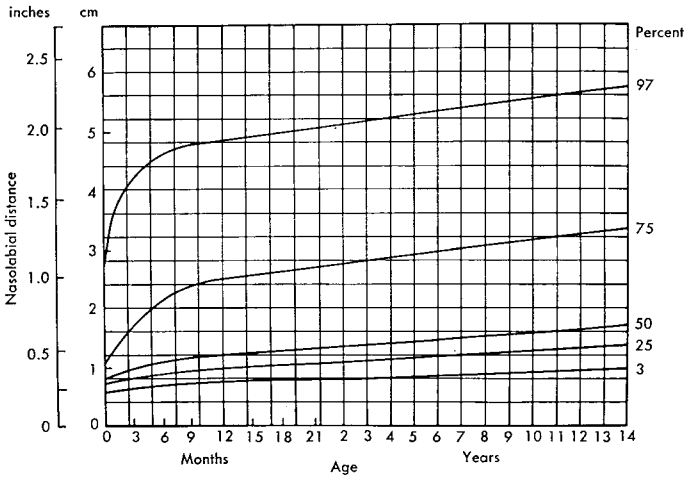

Fig. A–17. Philtrum length to age 14. (Courtesy of M Feingold, Boston, Massachusetts.)

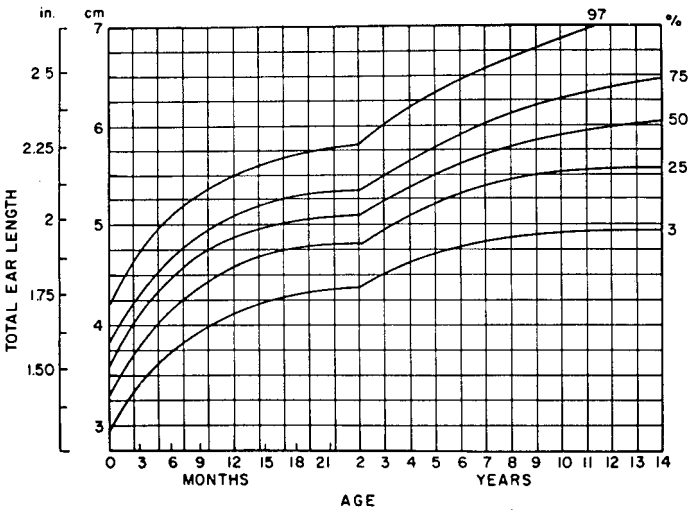

Fig. A–18. Ear length. [From M Feingold and WH Bossert, Birth Defects 10(13):1, 1974.]

Table A–8. Intercommissural distance from birth to adulthood

Age (years)	Males (mm)	Females (mm)
0–1	32	27
2–3	35	30
4–5	39	36
6–7	42	40
8–9	44	42
10–11	46	43
12–13	48	45
14–15	50	47
Adult	55	52

(From J Cervenka et al, Am J Dis Child 117:434, 1969.)

Intraoral measurements

Table A–9. Normal chronologic development of primary teeth

Tooth	Initiation, week *in utero*	Calcification begins, week *in utero*	Crown completed, month	Eruption, month	Root completed, year	Root resorption begins, year	Tooth shed, year
Central incisor	7	14 (13–16)	1–3	6–9	$1^1/_2$–2	5–6	7–8
Lateral incisor	7	16 ($14^1/_2$–$16^1/_2$)	2–3	7–10	$1^1/_2$–2	5–6	7–9
Canine	$7^1/_2$	17 (15–18)	9	16–20	$2^1/_2$–$3^1/_4$	6–7	10–12
First molar	8	$15^1/_2$ ($14^1/_2$–17)	6	12–16	2–$2^1/_2$	4–5	9–11
Second molar	10	$18^1/_2$ (16–$23^1/_2$)	10–12	20–30	3	4–5	11–12

(From WHG Logan and R Kronfeld, Development of the human jaws and surrounding structures from birth to the age of 15 years. J Am Dent Assoc 20:379–427, 1933; RC Lunt and DB Law, A review of the chronology of calcification of the deciduous teeth. J Am Dent Assoc 89:599, 1974; I Schour and M Massler, Studies in tooth development.The growth pattern of human teeth. J Am Dent Assoc 27:1918–1931, 1940.)

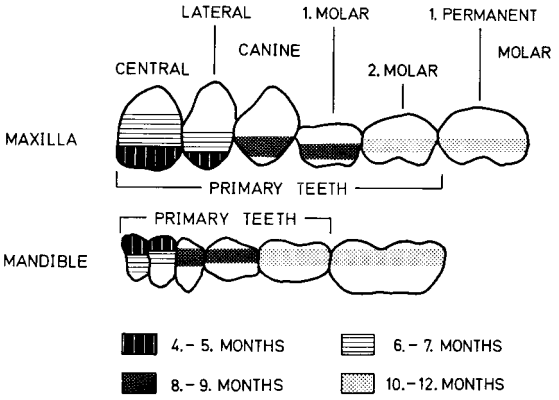

Fig. A–19. Chronology: Onset of pre- and postnatal enamel hypoplasia. (From WF Via and GA Churchill, JADA 59:702, 1959.)

Table A–10. Normal chronologic development of secondary teeth

Tooth	Initiation, month	Calcification begins	Crown completed, year	Eruption, year	Root completed, year
Maxilla					
Central incisor	5–$5^1/_4$ *in utero*	3–4 months	4–5	7–8	10
Lateral incisor	5–$5^1/_4$ *in utero*	1 year	4–5	8–9	11
Canine	$5^1/_2$–6 *in utero*	4–5 months	6–7	11–12	13–15
First premolar	Birth	$^1/_2$–$1^3/_4$years	5–6	10–11	12–13
Second premolar	$7^1/_2$–8	2–$2^1/_2$ years	6–7	10–12	12–14
First molar	$3^1/_2$–4 *in utero*	Birth	$2^1/_2$–3	6–7	9–10
Second molar	$8^1/_2$–9	$2^1/_2$–3 years	7–8	12–13	14–16
Third molar	$3^1/_2$–4 (yr)	7–9 years	12–16	17–25	18–25
Mandible					
Central incisor	5–$5^1/_4$ *in utero*	3–4 months	4–5	6–7	9
Lateral incisor	5–$5^1/_4$ *in utero*	3–4 months	4–5	7–8	10
Canine	$5^1/_2$–6 *in utero*	4–5 months	6–7	9–11	12–14
First premolar	Birth	$1^3/_4$–2 years	5–6	10–12	12–13
Second premolar	$7^1/_2$–8	$2^1/_4$–$2^1/_2$ years	6–7	11–12	13–14
First molar	$3^1/_2$–4 *in utero*	Birth	$2^1/_2$–3	6–7	9–10
Second molar	$8^1/_2$–9	$2^1/_2$–3 years	7–8	11–13	14–15
Third molar	$3^1/_2$–4 (yr)	8–10 years	12–16	17–25	18–25

(From WHG Logan and R Kronfeld, Development of the human jaws and surrounding structures from birth to the age of 15 years. J Am Dent Assoc 20:379, 1933; I Schour and M Massler, Studies in tooth development. The growth pattern of human teeth. J Am Dent Assoc 27:1918–1931, 1940.)

Table A–11. Dental anomalies and their frequencies

Teeth	Percentage
Congenitally missing, primary, white (9,19,22)	0.1–0.7
Congenitally missing, secondary, white	
Maxillary central incisors (24,27)	0.05
Maxillary lateral incisors (7,8,9,20,24,25,27)	1.0–2.0
Maxillary canines (7,24,27)	0.3
Maxillary first premolars (7,24,27)	0.3
Maxillary second premolars (7,8,9,24,27)	1.0–2.0
Maxillary first molars (24,27)	0.3
Maxillary second molars (7,24,27)	0.1
Mandibular central incisors (7,24,27)	0.3
Mandibular lateral incisors (7,24,27)	0.3
Mandibular canines (24)	0.1
Mandibular first premolars (7,24,27)	0.3
Mandibular second premolars (7,8,9,24,27)	1.2–2.5
Mandibular first molars (24,27)	0.3
Mandibular second molars (7,24,27)	0.3
Secondary teeth, other than third molars	
White (4,5,7,8,9,27)	3.0–7.5
Japanese (21,26)	5.8–9.2
Third molars, one or more absent (9,12,14)	2.5–35.0
One absent	7–10
Two absent	10–12
Three absent	4–6
Four absent	4–7
Defects, hereditary	
Dentin (32)	1 : 8,000
Enamel (32)	1 : 15,000
Dens invaginatus	
Maxillary lateral incisors (1,11,28)	1.2–6.6
Maxillary central incisors (13)	0.6
Dens evaginatus	
Japanese/Chinese (23,29)	1.0–2.0
Amerindian/Eskimo (23,29)	3.0–4.0
Enamel pearls	
Whites (31)	1.0–2.0
Double formations (fusion or gemination)	
Primary dentition	
White (5,10,13,15a,17,19,22)	0.2–0.7
Japanese (21,26)	2.5
Secondary dentition	
White (27)	0.2
Impacted	
Teeth, primary (6,18)	17.0
Maxillary canines, secondary (6)	0.9
Natal teeth (2)	0.03–0.05
Pegged	
Primary teeth (26)	0.2
Secondary maxillary lateral incisors	
White (27)	1.0–2.0
Japanese (30)	6.2
Shovel-shaped incisors	
Amerindian, Inuit, Oriental (15)	60–75
Supernumerary teeth	
Primary dentition (9,16,19,22)	0.3–0.8
Secondary dentition	
White (4,5,16,28)	1.0–3.5
Japanese (21)	2.2–5.3
Maxillary incisors, secondary (2,3)	0.3–0.5
Fourth molars, secondary (28)	0.2

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Table A–12. Nondental anomalies and their frequencies

Anomaly	Frequency in ostensibly normal population, approximate percentage
Cheek biting (39)	2
Cleft	
Lip–palate	
White (12,14)	0.06–0.15
Afro-American (3,4,10,24)	0.04
Japanese (20,33)	0.17
Amerindian (33,45)	0.3
Palate, isolated	
White (10,12)	0.04–0.05
Oriental (33)	0.06–0.07
Afro-American (3,4)	0.02–0.04
Uvula	
Amerindian (8,41)	10–20
Inuit (16)	3–6
Japanese (16)	1–2
White (30,44)	1–2
Afro-American (36,38)	0.25–0.50
Cysts, eruption (12)	0.2
Fordyce granules (sebaceous glands)	
Lips	
White (15,25,40)	50–80
Buccal mucosa	
White (15,25,40)	60–95
Afro-American (29)	55
Lip pits	
Paramedian (46)	1:200,000
Commissural	
Afro-American (5,38)	20
Caucasian (5)	12
Oriental (5)	6
Amerindian (8)	9
Inuit (19)	8
Tongue	
Ability to touch nose with (personal observation)	7–10
Ankyloglossia (7,28,48)	1:300 to 1 per 2000
Fissured	
5–18 years (9,35)	
Overall (1,15,48)	2–5
Folding of tip	
Within mouth	1–2
Outside mouth (47)	1 per 600
Geographic	
White (9,15)	1.0–2.5
Median rhomboid “glossitis”	
Caucasian (15,48)	0.2–0.3
Inuit (19)	0.6
Rolling or tubing	
White (13,42)	60–75
Afro-American (23)	80
Japanese (22)	25–30
Thyroid gland inclusion	
Microscopic evidence (6,37)	10
Clinical evidence (6)	1 per 10,000
Torus mandibularis	
White and Afro-American (17,21,43)	3–16
Inuit (17,18,19,26,27)	10–80
Oriental (38)	20–30
Torus palatinus	
White and Afro-American (21,31,38,43)	20(F-2, M-15)
American and Inuit (17,19,32)	25–75
Oriental (2,38)	40–90

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Web sites and computerized database systems

Table A–13. Web sites

American College of Medical Genetics	*www.faseb.org/genetics/acmg*
American Society for Human Genetics	*www.faseb.org/genetics/ashg/ashgmenu.htm*
Centers for Disease Control and Prevention	*www.cdc.gov/genetics/*
Dysmorphology Discussion Board	*genetics.ich.ucl.ac.uk/DDB/ddb./html*
Embryo Images: Normal and Abnormal Mammalian Development	*www.med.unc.edu/embryo_images/*
European Society for Human Genetics	*www.eshg.org*
Gene Expression in Tooth Database	*bite-it.helsinki.fi/*
GeneClinics	*www.geneclinics.org*
Genetic Alliance	*www.geneticalliance.org*
Genetics in Medicine	*www.lww.com/GIM*
GeneTests	*www.genetests.org*
Hereditary Hearing Loss Database	*dnalab-www.uia.ac.be/dnalab/hhh/*
Infobiogen	*www.infobiogen.fr*
Infogenetics	*www.infogenetics.org*
Muscular Dystrophy Association	*www.mdausa.org*
National Center for Biotechnology Information	*www.ncbi.nlm.nih.gov* and *www.ncbi.nlm.nih.gov/disease*
National Human Genome Research Institute	*www.nhgri.nih.gov*
National Organization for Rare Disorders	*http://www.rarediseases.org/*
NF Foundation	*www.nf.org*
Office of Rare Diseases	*rarediseases.info.nih.gov/ord/*
Online Mendelian Inheritance in Man	*www.ncbi.nlm.nih.gov/Omim*
Pedbase	*www.icondata.com/health/pedbase*

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Table A–14. Computerized database systems

Systems	Comments	References
BDIS (Birth Defects Information Services)	Coded anatomic description	Buyse (1)
LDDB (London Dysmorphology Database)	Coded anatomic description	Winter and Baraitser (11)
POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations)	Coded anatomic description	Marquet (5)
SYNDROC	Coded anatomic description	Schorderet (9)
OMIM (Online Mendelian Inheritance in Man). For web site, see left.	Key word searching	Schorderet (8)
Human Cytogenetic Database	Chromosomal abnormality or clinical features	Schinzel (7)
TERIS	To assess possible teratogens	Poliska (6)
REPROTOX	To assess possible teratogens	Scialli (10)
Radiologic Atlas of Skeletal Dysplasias	To assess skeletal dysplasias	Canepa (2) Hall (4)

[Based on MM Cohen Jr, The Child with Multiple Birth Defects, 2nd ed, Oxford University Press, New York, 1997 (2).]

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Index